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Expression and variation of lymphocyte scavenger receptors in inflammatory diseases and cancer

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EXPRESSION AND VARIATION OF LYMPHOCYTE SCAVENGER RECEPTORS IN INFLAMMATORY DISEASES AND CANCER

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Als meus pares

“I am still learning”

-Michelangelo

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ABBREVIATIONS

AAV	Adeno-associated virus
AIC	Akaike information criterion
AICD	Activation-induced cell apoptosis
ALCAM	Activated leukocyte adhesion molecule
ALL	Acute lymphocytic leukemia
ANA	Antinuclear antibody
APC	Antigen presenting cell
BCR	B cell receptor
Breg	Regulatory B cell
CARD	Caspase activation domain
CK2	Casein kinase 2
CD	Crohn's disease
CDCP-1	CUB domain-containing prtein-1
CFU	Colony forming unit
CIA	Collagen-induced arthritis
CLL	Chronic lymphocytic leukemia
DAMP	Damage-associated molecular pattern
DC	Dendritic cell
DP	Double positive
DSS	Dextran sulfate sodium
EAE	Experimental autoimmune encephalitis
ER	Endoplasmic reticulum
ESSDAI	EULAR Sjögren's syndrome disease activity index
GALT	Gut-associated lymphoid tissue
GO	Gene ontology
GvHD	Graft versus host disease
GWAS	Genome-wide association study
hCD5	Human CD5
HIV	Human immunodeficiency virus

IBD	Inflammatory bowel disease
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
ILC	Innate lymphoid cell
IMID	Immune-mediated inflammatory disease
i.p.	Intraperitoneal
IS	Immune synapse
i.v.	Intravenous
KO	Knock-out
LPS	Lipopolysaccharide
LRR	Leucine-rich repeat
LTA	Lipotheichoid acid
mAb	Monoclonal Antibody
MAMP	Microbial-associated molecular pattern
MAPK	Mitogen-activated protein kinase
MDSC	Myeloid-derived suppressor cell
MHC	Major histocompatibility complex
mLN	Mesenteric lymph node
MPO	Myeloperoxidase
MS	Multiple sclerosis
NK	Natural killer
NKT	Natural killer T
NLR	NOD-like receptor
NSCLC	Non-small cell lung cancer
PAMP	Pathogen associated molecular pattern
PBMC	Peripheral blood mononuclear cell
PBS	Phosphate buffered saline
PCa	Prostate cancer
PD-1	Programmed cell death 1

PD-L1	Programmed cell death ligand 1
PFA	Paraformaldehyde
PKC	Protein kinase C
PLC	Phospholipase C
PNS	Peripheral nervous system
PRR	Pattern recognition receptor
pSS	Primary Sjögren's syndrome
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RLR	RIG-I-like receptor
sCD5	Soluble CD5
sCD6	Soluble CD6
SF	Superfamily
shCD5	Soluble human CD5
shCD6	Soluble human CD6
SLE	Systemic lupus erythematosus
SNP	Single nucleotide polymorphism
SP	Single positive
SRCR	Scavenger receptor cysteine-rich
TCR	T cell receptor
TGF	Transforming growth factor
Th	T helper
TIL	Tumor-infiltrating lymphocyte
TLR	Toll-like receptor
TNF	Tumor necrosis factor
Treg	Regulatory T cell
UC	Ulcerative colitis
UTR	Untranslated region
WT	Wild type

I INTRODUCTION

1 The immune system

The immune system comprises a complex series of cellular and humoral components that protect the organism from aggressions coming from both the external (e.g., pathogens) and the internal (e.g., cancer) milieu. To this end, the immune system must be able to recognize and discriminate healthy, self structures from exogenous (non-self) or damaged host (altered-self) structures. This recognition is carried out through cell-membrane bound or soluble receptors from the innate (also named nonspecific or natural) and the adaptive (also named specific or acquired) immune system (**Figure I.1**).

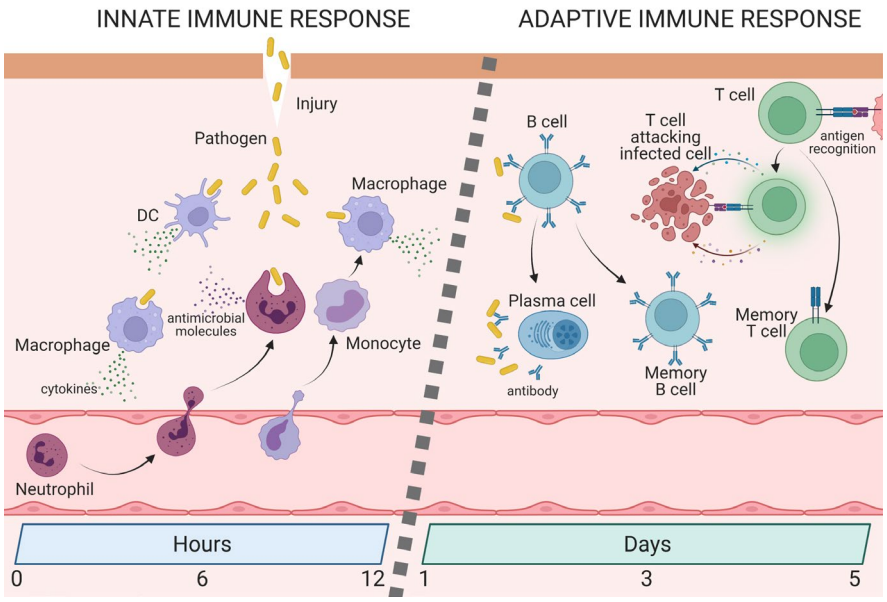


Figure I.1. Cellular and humoral components of the innate and adaptive immune responses. Adapted from CDC.

The innate immune system is phylogenetically the oldest and is operational in a few seconds (or at most within a few hours) after aggression, because it is already preformed. The cellular part of this system encompasses the mucocutaneous epithelial and the

endothelial barriers, myeloid phagocytic cells—polymorphonuclear leukocytes, monocytes, macrophages and dendritic cells (DC)—and cytotoxic cells—natural killer (NK) cells. The humoral part includes the complement and coagulation systems and other soluble mediators such as cytokines, chemokines or anaphylatoxins. The recognition in the innate system is carried out by germline encoded, non-clonally distributed and non-polymorphic receptors generically named **pattern-recognition receptors** (PRRs). These PRRs are specialized in the recognition of microbial-associated molecular patterns (MAMPs), which are conserved structural components of microbial surfaces, shared by multiple microbial species, essential for microbial survival and/or pathogenicity and non-shared by the host. Examples of MAMPs include the lipopolysaccharide from Gram-negative bacteria, lipoteichoic acid from Gram-positive bacteria, dsRNA or ssRNA from virus, mannan and β-glucans from fungi or chitin from parasites. PRRs also recognize the so-called damage-associated molecular patterns (DAMP), examples of which include heat-shock proteins, hyaluronic acid, ATP, high-mobility group box 1 protein (HMGB1) or uric acid.

The adaptive immune system is exclusive of vertebrates, having originated in ancestral jawed fish, and is operational several days or weeks after the aggression since it is not preformed—it is acquired upon first exposure to the antigens. Antigen recognition in the adaptive immune system is carried out by non-germline encoded, highly polymorphic and specific receptors exclusively expressed on B and T cells, named B cell receptors (BCR) and T cell receptors (TCR), respectively. They are generated through DNA recombination processes during B and T cell development in primary lymphoid organs (the bone marrow and thymus, respectively). Upon antigen-

specific recognition, naïve, mature B and T cells differentiate into short-life effector cells which mediate antibody production (plasma B cells), cytotoxicity (cytotoxic $CD8^+$ T cells) and cytokine secretion (helper $CD4^+$ T cells). Naïve B and T cells can also differentiate into quiescent long-life memory B and T cells, which will be available to develop faster and more efficient responses in case future encounters with the same antigen should happen.

While the innate and adaptive immune systems have their unique mechanisms of action, they are highly interrelated, working together and acting as a functional unit. The innate system is the first line of defense and delivers danger signals which engage the adaptive system. In turn, once activated the adaptive system potentiates the responses mediated by the innate system.

It is widely acknowledged that inborn or acquired defects in the function of the innate or the adaptive immune system can lead to immunodeficiency responsible for increased susceptibility to **infections** and **cancer**. Besides, deficiencies in the immune function may lead to diseases resulting from hyper-reactive immune responses, such as **autoimmunity** and **allergy**. These are consequences of functional defects involving regulatory and inhibitory molecules of either the innate or the adaptive immune system. To avoid host damage, the immune system is fitted with molecular mechanisms aimed at avoiding its over- or infra-activation. Within the adaptive immune system, this immunomodulatory role is played in part by a group of molecules referred to as **immune checkpoint receptors**.

1.2 Pattern recognition receptors

PRRs recognize highly conserved MAMPs and DAMPs, and they can be expressed as soluble forms present on bodily fluids or as receptors anchored to the cell membrane. The term PRR comprises receptors sharing a common function—pattern recognition—but with high structural heterogeneity. Therefore, PRRs are found among members of a great variety of structural protein families, which include Toll-like receptors (TLR), RIG-I-like receptors (RLR) NOD-like receptors (NLR), C-type lectin receptors (CLR) and scavenger receptors, among others (**Figure I.2**).

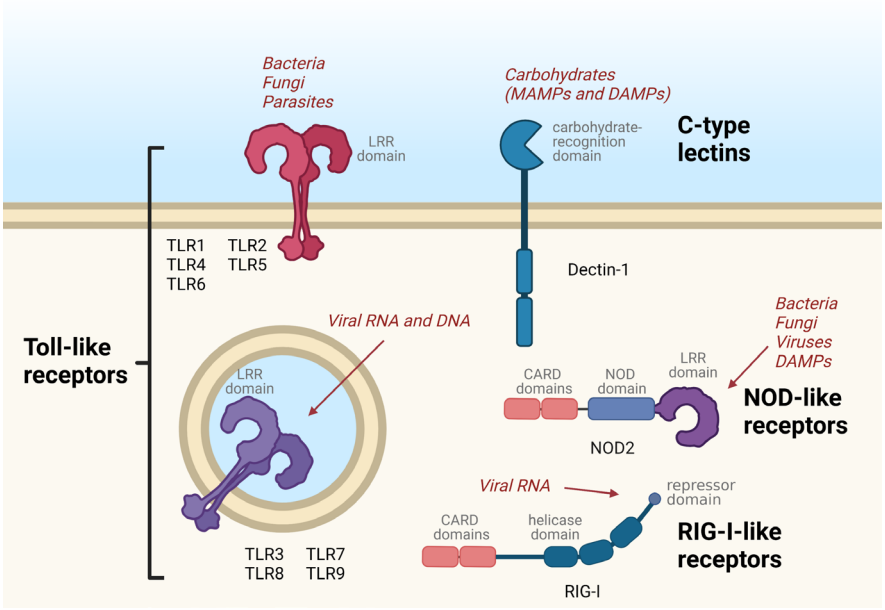


Figure I.2. Major PRR families. Representative examples of each family are shown. Grey: protein domains. Italics: main ligands. A more detailed representation of scavenger receptors is depicted in Figure I.3. Based on Kumar et al. 2011.

TLRs are the most studied PRRs. To date, 10 TLRs have been described in humans and 12 in mice (Kumar, Kawai, and Akira 2011). TLR1, TLR2, TLR4, TLR5 and TLR6 are present on the plasmatic membrane, and they are specialized in recognizing mainly MAMPs found on the surface of bacteria, fungi and parasites. As an example, TLR2 binds to β-glucans allowing fungal recognition, while TLR4 recognizes lipopolysaccharide from bacterial origin. On the other side, TLR3, TLR7, TLR8 and TLR9 are expressed on the membrane of endocytic vesicles, and they recognize viral nucleic acids. Structurally, TLRs are type-I transmembrane glycoproteins. In the extracellular part, they have leucine-rich repeat (LRR) domains that recognize MAMPs, while the intracellular domain of TLRs recruit intracellular effectors such as MyD88, TRIF and TRAM. In turn, they activate transcription factors like NF-κB and IRF3/7, and eventually induce secretion of proinflammatory cytokines and overexpression of major histocompatibility complex (MHC), adhesion and co-stimulatory molecules (Kumar et al. 2011).

The RLR family includes the cytoplasmic receptors RIG-I, MDA5 and LGP2, which recognize RNA from viral origin (Li and Wu 2021). Upon ligand binding, RIG-I and MDA5 expose caspase-recruiting domains (CARD), which engage signaling cascades (Satoh et al. 2010). LGP2 lacks such domains, and its signaling is probably mediated by interaction with RIG-I or MDA5 (Saito et al. 2007). RLR activation results in secretion of cytokines and chemokines that provide an anti-viral environment, enhancing apoptosis in infected cells, lytic capacity in NK cells and class-I MHC overexpression (Kumar et al. 2011).

NLRs are also cytoplasmic receptors and recognize both MAMPs such as peptidoglycan and DAMPs such as sodium urate crystals

(Mogensen 2009). They have a C-terminal domain consisting on LRR which binds to MAMPs or DAMPs, a central NOD domain allowing oligomerization, and an N-terminal protein interaction domain (Shaw et al. 2008). The latter can be a CARD, a pyrin domain, or a baculovirus inhibitor domain, and mediates signaling through the NF-κB and mitogen-activated protein kinase (MAPK) pathways (Kumar et al. 2011).

CLRs are transmembrane receptors mainly expressed on myeloid cells. They are characterized by their binding to carbohydrate residues, mainly from viruses, bacteria and fungi, and other MAMPs and DAMPs (Dambuza and Brown 2015). Two representative members of the CLR family, dectin-1 and dectin-2, are the main receptors for fungal β-glucans. In synergy with TLR2 and TLR4 they induce the secretion of cytokines like IL-12 and IL-23, conferring protection against fungal infections (Gantner et al. 2003; Robinson et al. 2009).

Scavenger receptors encompass a structurally diverse superfamily of PRRs characterized by their binding to a variety of DAMPs and PAMPs. Originally, they were defined by their ability to bind and remove modified low density lipoproteins, thus recognizing altered self structures (Brown and Goldstein 1979; Fogelman, Haberland, and Seager 1981). Over time, many receptors fitting the concept of scavenger receptor have been described and included in this superfamily. Today, the scavenger receptor superfamily includes a large number of members with great structural and functional diversity. Currently, scavenger receptors are defined as cell surface receptors typically binding multiple ligands, able to promote removal of non-self and altered-self structures (PrabhuDas et al. 2017). Thus,

they function as PRRs but, can also act as chaperones, immune modulators, lipid transporters and adhesion molecules (Canton, Neculai, and Grinstein 2013). The great structural diversity of scavenger receptors encouraged their classification according to the structure of their extracellular domains into 12 groups named A through L, as depicted in **Figure I.3** (PrabhuDas et al. 2017).

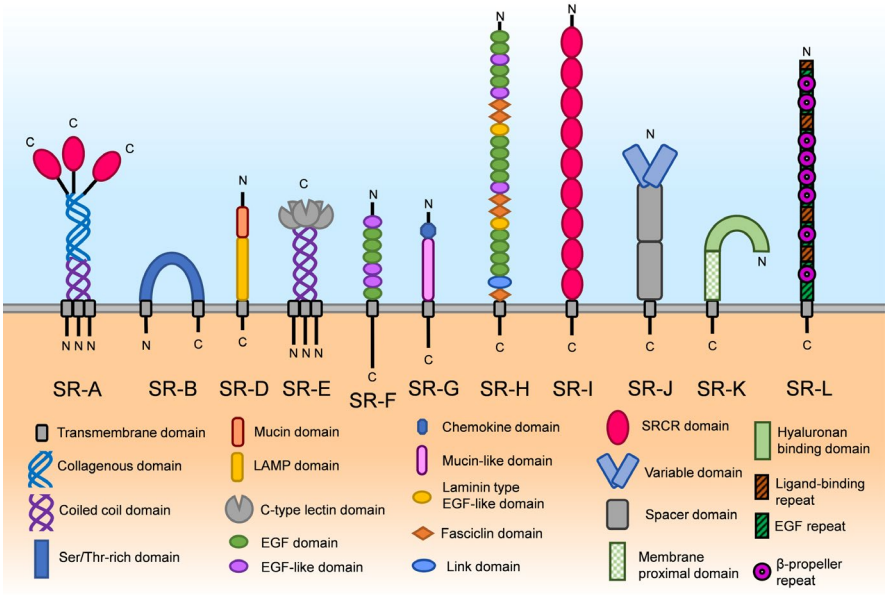


Figure I.3. Structure of different classes of scavenger receptors. SR stands for scavenger receptor, and the next capital letter represents the class. Class C is not present in mammals. Adapted from PrabhuDas 2017.

1.3 Immune checkpoints

The amplitude and duration of the adaptive immune response needs to be regulated. Immune checkpoints are accessory receptors able to trigger certain signaling pathways that eventually exert inhibitory or activating functions in the immune system (Baumeister et al. 2016). Consequently, they are crucial in minimizing possible damage to the host during immune responses, by either optimizing defensive

responses against infectious agents and cancer or attenuating overactive responses that would lead to autoimmune or allergic reactions. For instance, engagement of activating checkpoints such as CD28 during T cell activation is necessary to induce T cell proliferation and migration. However, if inhibitory checkpoints such as CTLA-4 are engaged, this process is suppressed and the T cell is driven into anergy or exhaustion (Qin et al. 2019). Some of the most studied activating and inhibitory immune checkpoints are depicted in **Figure I.4** (Mellman, Coukos, and Dranoff 2011; Wykes and Lewin 2017).

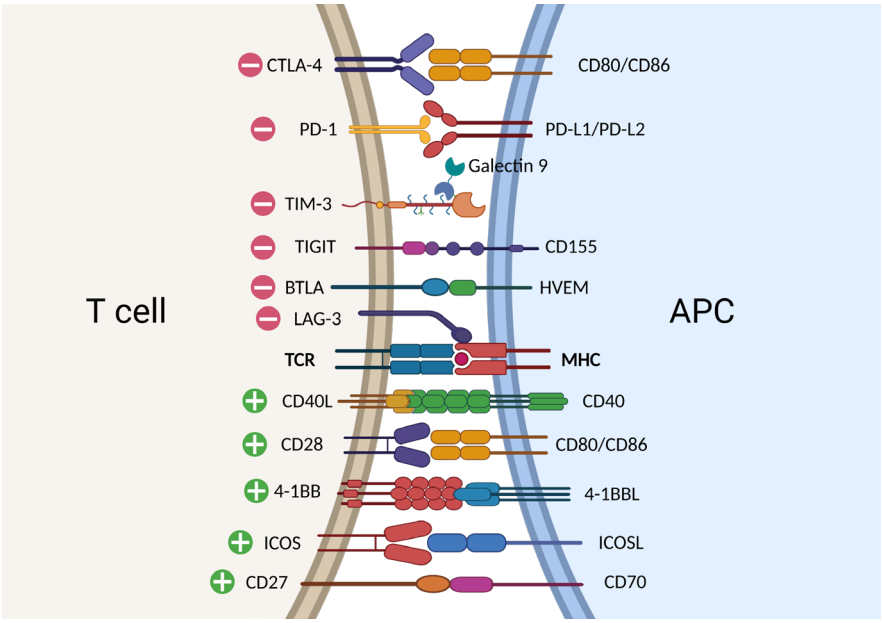


Figure I.4. Immune checkpoint receptors and their ligands. Minus and plus signs indicate inhibitory and activating functions, respectively. Adapted from Mellman 2011 and Wykes 2017.

The activating checkpoint CD28 is key in antigen presentation. It is constitutively expressed on naïve T and binds to CD80 and CD86 present on antigen presenting cells (APC) (Esensten et al. 2016). Combination of TCR stimulation and CD28 co-stimulation results in a

balance between activation of NFAT, AP-1 and NF-κB, which promote transcription of genes necessary for an immune response (e.g.: cytokines). However, in absence of CD28 co-stimulation, activation of NFAT is higher relative to AP-1, leading to a different gene expression pattern that eventually leads to T cell anergy (Macián et al. 2002). Other stimulatory immune checkpoints such as CD27 and CD40L are necessary for activation of T cells and generation of memory (Borst, Hendriks, and Xiao 2005; Tang et al. 2021).

The function of the inhibitory immune checkpoint receptors CTLA-4 and PD-1 is well known, and they are targets of currently used therapies. CTLA-4 is not expressed on naïve T lymphocytes, but its expression is induced during activation. It binds to CD80 and CD86 expressed on APC, so it competes with the co-stimulatory receptor CD28 and prevents excessive activation and damage (Chambers et al. 2001). In the case of PD-1, binding to its ligands (PD-L1/2) results in recruitment of the SHP1 and SHP2 phosphatases, which inhibits TCR-mediated cell proliferation and cytokine release (Chemnitz et al. 2004). Therefore, PD-1 plays a major role in peripheral tolerance. Other inhibitory immune checkpoint receptors such as LAG-3, TIM-3 and TIGIT are gaining interest as putative new therapeutical targets (Qin et al. 2019).

A balance between the function of inhibitory and activating immune checkpoints is necessary to provide an effective immune response while minimizing immune-mediated self-damage. Besides, immune checkpoint receptors can play a key role in cancer progression. Expression and engagement of inhibitory immune checkpoint receptors in the tumor microenvironment favors immune escape and tumor progression (Qin et al. 2019). Therapies based on blocking

immune checkpoints with monoclonal antibodies (mAb) have been developed and currently represent a therapeutic approach in cancer.

2 The lymphocyte receptors CD5 and CD6

CD5 and CD6 are lymphocyte surface receptors, closely related from a functional and a structural point of view. Both are signal-transducing type I transmembrane glycoproteins belonging to the scavenger receptor cysteine-rich superfamily (SRCR-SF). This is a structurally homologous but functionally diverse superfamily of innate immune receptors characterized by the presence of one or several repeats of the ancient and highly conserved SRCR domain. Both CD5 and CD6 proteins are composed by three tandem extracellular SRCR domains (from N- to C-terminal: SRCR1, SRCR2 and SRCR3), followed by a transmembrane domain and a cytoplasmatic tail devoid of intrinsic enzymatic activity but well adapted for Thr/Ser/Tyr phosphorylation and intracellular signaling.

2.1 Gene and protein structure of CD5 and CD6

The *CD5* and *CD6* genes lie less than 100 kb apart in the long arm of human chromosome 11—on the 11q12.2 band—, and in the orthologous region of mouse chromosome 19 (Lecomte et al. 1996; Padilla et al. 2000). *CD5* consists of 11 exons encompassing a 24.5 kb region located 82 kb in 3' direction to *CD6*, in a head-to-tail orientation (**Figure I.5**). This, together with the high structural, functional and tissue expression similarity between the CD5 and CD6 receptors, lead to the assumption that both genes arose from duplication of an ancestral gene (Lecomte et al. 1996; Padilla et al. 2000).

There is a good correlation between exon-intron organization and the structural domains of the CD5 protein: each SRCR domain is encoded by an individual exon (exons 3, 5 and 6). The interspacing Pro/Thr/Ser-rich region that connects SRCR1 and SRCR2 domains is encoded by exon 4. The transmembrane domain is encoded by exon 7 and the cytoplasmic tail by exons 8, 9 and 10 (Lecomte et al. 1996; Padilla et al. 2000) (**Figure I.5**). The signal peptide is encoded by exons 1 (18 aa) and 2 (6 aa). Exon 1 also contains the untranslated 5′ region (5′-UTR). Finally, exons 10 and 11 contain the stop codon and the 3′-UTR region, respectively (Lecomte et al. 1996; Padilla et al. 2000). There are two polyadenylation signals in exon 11 that could explain the identification of two species of *CD5* mRNA (2.7 and 3.6 kb each) (Jones et al. 1986). While for CD6 several isoforms have been described resulting from alternative mRNA splicing, a CD5 isoform encoding a protein with transmembrane region but no cytoplasmic tail has been detected from total peripheral blood mononuclear cell (PBMC) mRNA, for which no information is yet available on its expression pattern or function (Lecomte et al. 1996; Padilla et al. 2000). An alternate regulatory exon 1 (designated E1B) located ~8.2 kb upstream the ATG initiation codon of the conventional exon 1 (renamed E1A) of the human *CD5* gene has also been reported (Renaudineau et al. 2005). The E1B-containing transcripts exist exclusively in B lymphocytes and encode a truncated protein devoid of the leader peptide and retained intracellularly. As a consequence, the amount of E1A-containing transcripts is downregulated and the membrane CD5 expression is diminished in the presence of E1B-containing transcripts (Renaudineau et al. 2005).

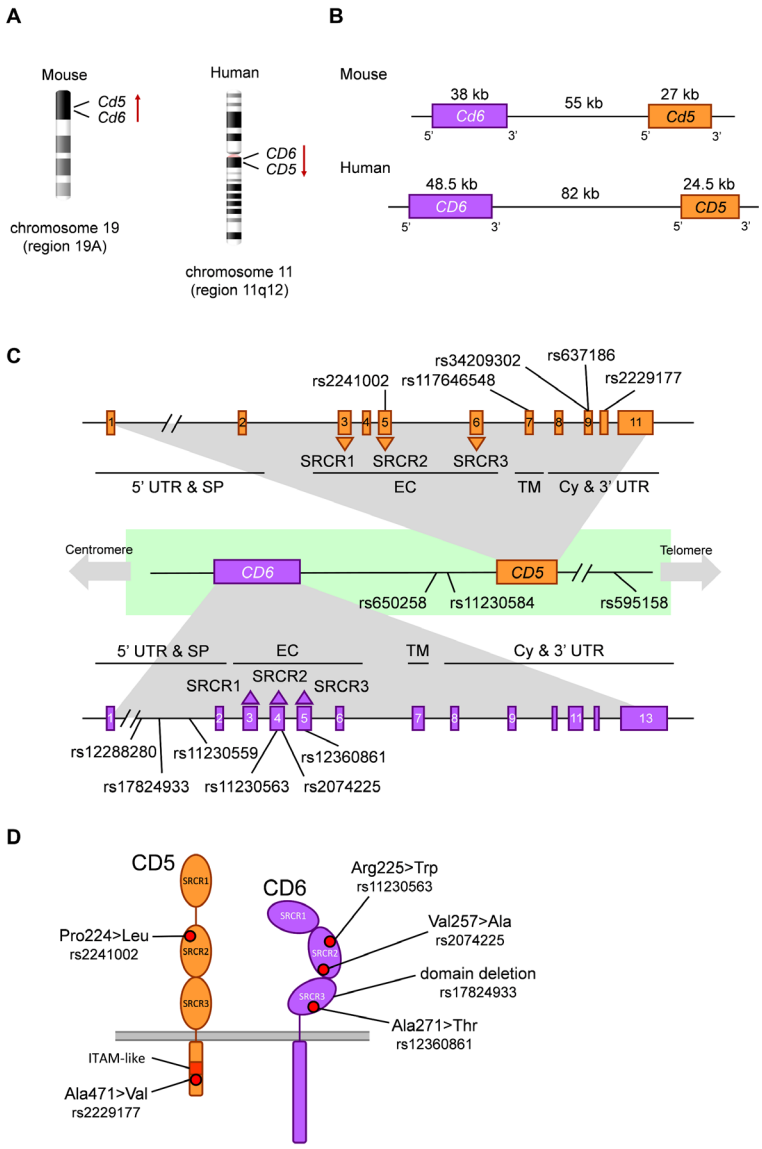


Figure I.5. Genomic location and arrangement of *CD5* and *CD6*. (**A**) Chromosome location of mouse and human genes coding for CD5 and CD6. Red arrows indicate 5' to 3' orientation. (**B**) Size, orientation and intergenic distance regarding CD5 and CD6 in mouse and human. (**C**) Exon/intron organization, protein coding regions and location of relevant SNPs in CD5 and CD6. (**D**) Structure of membrane CD5 and CD6 showing the impact of relevant SNPs. UTR, untranslated region; EC, extracellular region; Cy, cytoplasmic region; SRCR, scavenger receptor cysteine-rich domain; ITAM-like, immunoreceptor tyrosine-based activation motif-like.

The *CD6* gene consists of at least 13 exons, with the first 6 coding for the 5'-UTR, the signal peptide (exons 1 and 2), the three extracellular SRCR domains (exons 3–5) and the stalk region (exon 6) (Bowen et al. 1997). The transmembrane region is encoded by exon 7, the cytoplasmic region by exons 8–11 and the 3'-UTR region by at least exon 13 (**Figure I.5**). As mentioned above, *CD6* undergoes alternative RNA splicing that result in isoforms devoid of the SRCR3 extracellular domain (CD6Δd3) or certain intracytoplasmic signaling motifs (Bonet et al. 2013; Bowen et al. 1997; Castro et al. 2007), which are defective in binding to CD166/ALCAM and proper cytoplasmic tail phosphorylation and intracellular signaling, respectively.

Soluble CD5 and CD6 forms, consisting of their whole respective extracellular domains, can be shed by proteolytic cleavage of their membrane forms, a phenomenon enhanced after lymphocyte activation (J Calvo et al. 1999; Carrasco et al. 2017). Such soluble forms can be detected in sera from healthy individuals, and their concentration is increased in patients suffering from inflammatory conditions such as Sjögren's syndrome and systemic inflammatory response syndrome (Aibar et al. 2015; Ramos-Casals et al. 2001).

2.2 Tissue expression of CD5 and CD6

CD5 and CD6 are mainly expressed by all T cell subsets (Kamoun et al. 1981; Ledbetter et al. 1980; Reinherz et al. 1979), but also by few other small lymphoid and myeloid cell subsets. Although the expression pattern of CD5 and CD6 is similar, there are differences in certain cell subsets and maturation stages.

2.2.1 CD5 expression

CD5 is expressed by all circulating T cells and thymocytes, from early stages of their development—double negative (DN) thymocytes—and

its expression increases during T cell maturation—from the double positive (DP) thymocyte stage onwards—proportionally to the TCR signal strength (Azzam et al. 2001). The highest levels of CD5 expression are found in Treg ($CD4^+$ $CD25^+$ $FoxP3^+$) cells (Ordoñez-Rueda et al. 2009). CD5 is also expressed on a subset of B cells known as B1a cells (Berland and Wortis 2002), characterized by the production of natural antibodies independently of antigenic stimulation. Such antibodies are polyreactive and often autoreactive, providing innate protection against infections (Gommerman and Carroll 2000). CD5 expression has been reported in some myeloid and non-hematopoietic cells, including some macrophages (Borrello, Palis, and Phipps 2001; Moreau et al. 1999), endothelial cells in placentomes (Gogolin-Ewens et al. 1989), and DC subpopulations (Korenfeld et al. 2017; Li et al. 2019).

CD5 expression can be detected in certain B cell malignancies such as chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL) (Boumsell et al. 1980; Kamoun et al. 1981; Zukerberg et al. 1993). CD5 is also expressed by uncommon CLLs of T origin (T-CLL) and a few T cell lymphomas, but not by T cell acute lymphocytic leukemia (T-ALL) (Boumsell et al. 1980; Reinherz et al. 1979).

2.2.2 CD6 expression

As in the case of CD5, CD6 expression is detected in all circulating T cells and thymocytes, with its expression increasing during T cell maturation (Kamoun et al. 1981). Contrary to CD5, CD6 expression is low or negative in Treg cells (Garcia Santana, Tung, and Gulnik 2014). A fraction of mature B cells also expresses CD6. In humans, the highest expression of CD6 in B cells is found in tonsil B1a cells, which also express CD5, while in peripheral blood there is no correlation

between CD6 and CD5 expression (Alonso et al. 2010). In mice, CD6 expression is detected in spleen and peripheral blood B1a cells, but not in peritoneal B1a cells (Enyindah-Asonye, Li, Xin, et al. 2017). Unlike CD5, CD6 is also expressed on the major peripheral NK cell subset ($CD56^{dim}$ $CD16^{+}$), on a group of bone marrow hematopoietic cell progenitors and in some central nervous system regions (Braun et al. 2011; Cortés et al. 1999; Mayer et al. 1990).

Some B and T leukemias and lymphomas also express CD6. As in the case of CD5, CD6 is expressed by B-CLL and MCL cells (Boumsell et al. 1980; Kamoun et al. 1981; Zukerberg et al. 1993), but it is also weakly expressed by T-ALL cells (Kamoun et al. 1981).

2.3 Ligands of CD5 and CD6

Several endogenous ligands have been proposed for CD5, including CD72, the IgV_H framework region, gp200, gp40-80, gp150, IL-6 and CD5 itself (Biancone et al. 1996; Bikah et al. 1996; Brown and Lacey 2010; Javier Calvo et al. 1999; Haas and Estes 2001; Pospisil et al. 2000; Van De Velde et al. 1991; Zhang et al. 2016). Unfortinately, independent research groups have been unable to validate such proposed ligands, so the identity of CD5 endogenous ligands is still controversial.

Conversely, CD6 has a well characterized ligand: CD166/ALCAM (for activated leukocyte cell adhesion molecule), also known as MEMD (for melanoma metastasis clone D) (Bowen et al. 1995; Degen et al. 1998; Patel et al. 1995). CD166/ALCAM is a type I transmembrane adhesion protein of the immunoglobulin superfamily, consisting of five extracellular Ig domains (two N-terminal of the V type and three C-terminal of the C2 type), a transmembrane domain, and a short cytoplasmic domain that binds to the actin cytoskeleton (**Figure I.6**)

(te Riet et al. 2014). CD166/ALCAM is broadly distributed among many healthy and diseased tissues, including activated lymphocytes, several epithelia (thymic, epidermal, intestinal, mammary, pancreatic and renal), endothelia, neurons, fibroblasts, and malignant melanoma and prostate cancer (PCa) cells. (Bowen et al. 1995; Donizy et al. 2015; Kristiansen et al. 2003; Levin et al. 2010; Patel et al. 1995). CD166/ALCAM can establish low-affinity homophilic (ALCAM–ALCAM) and high-affinity heterophilic (ALCAM–CD6) adhesive interactions (te Riet et al. 2007). Protein structure studies have mapped the CD6–CD166/ALCAM interaction, which involves the SRCR3 domain of CD6 and the most N-terminal Ig domain (V1) of CD166/ALCAM (**Figure I.6**) (Chappell et al. 2015).

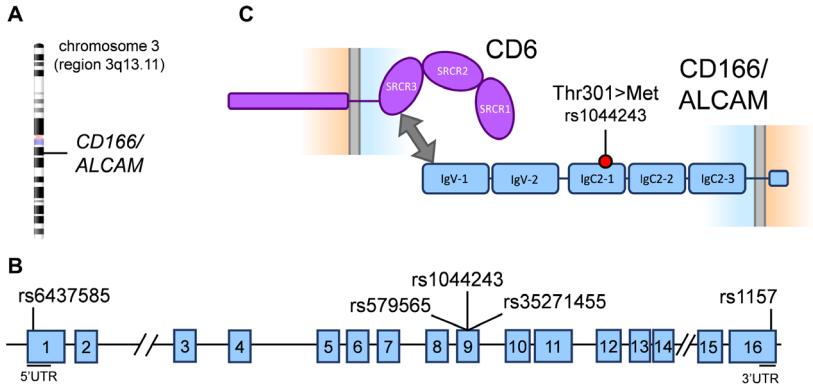


Figure I.6. Genomic location and arrangement of *CD166/ALCAM*, and interaction with CD6. (**A**) Chromosome location of the human gene coding for ALCAM. (**B**) Exon/intron organization and location of relevant SNPs in *ALCAM*. (**C**) Structure of membrane ALCAM showing interaction with CD6 and the impact of the rs1044243 SNP. Grey arrow shows areas involved in the CD6-ALCAM interaction. UTR, untranslated region; SRCR, scavenger receptor cysteine-rich domain; IgV, immunoglobulin variable-like domain; IgC2, immunoglobulin constant 2-like domain.

Other endogenous molecules reported to interact with CD6 include galectins 1 and 3 (Escoda-Ferran et al. 2014) and CD318 (Enyindah-Asonye, Li, Ruth, et al. 2017). Galectins are soluble proteins that recognize glycans containing galactose linked with β-glycosidic bonds to other monosaccharides. They are synthesized by several immune cell types as cytosolic proteins, and can be released to the extracellular medium independently of the secretory pathway, acting as PRRs and regulators of the immune response (Liu 2005; Sato et al. 2009). CD318, also known as CUB domain-containing protein-1 (CDCP-1), TRASK or SIMA135 is a transmembrane protein with three extracellular CUB domains and an intracellular region with five Tyr residues that can be phosphorylated by kinases of the Src family, and is involved in regulation of cell adhesion (Spassov et al. 2011). CD318 is expressed on epithelial, hematopoietic and mesenchymal cells, as well as in several tumors (Bühring et al. 2004; Casar et al. 2012; Uekita and Sakai 2011).

Apart from binding to endogenous ligands, both CD5 and CD6 act as PRRs. It has been reported that CD5 interacts with β-glucan from fungal cell walls (Vera et al. 2009), the hepatitis C virus (Sarhan et al. 2012), and structures present in the tegument of the parasite *Echinococcus granulosus* (Mourglia-Ettlin et al. 2018). In line with this PRR function, mouse data indicate that CD5 is a non-redundant integral component of host's immune response to fungal infection (Velasco-de-Andrés et al. 2020). In the case of CD6, it interacts with integral components of Gram-positive and Gram-negative bacterial cell walls (lipopolysaccharide, lipoteichoic acid and peptidoglycan) (Sarrias et al. 2007), gp120 of the human immunodeficiency virus (HIV)-1 (Carrasco et al. 2014) and *E. granulosus* tegument molecules different from those recognized by CD5 (Mourglia-Ettlin et al. 2018).

The dual properties of CD5 and CD6 as immune modulators and PRRs position them as potential mediators of microbial-host immune crosstalk. As it will be explained in sections I.2.4.1 and I.2.4.4, CD5 and CD6 can negatively modulate TCR signaling, which helps avoid AICD in lymphocytes with high affinity TCRs and maintain their response. Therefore, ligation of CD5 and CD6 by their microbial ligands can help in developing a high affinity response against pathogens, which in turn can have consequences in autoimmune diseases and other immune-mediated disorders (Lenz 2009; Vera et al. 2009).

2.4 Function of CD5 and CD6

2.4.1 CD5 in health

CD5 is physically associated with the TCR or the BCR in lymphocytes, and co-localizes with them at the center of the immunological synapse (IS) (Beyers, Spruyt, and Williams 1992; Brossard et al. 2003; Gimferrer et al. 2003). This allows CD5 to modulate activation or cell death signals in lymphocytes during antigenic recognition. Early *in vitro* research performed with anti-CD5 mAbs pointed to co-stimulator function for CD5 (Alberola-Ila et al. 1992; Ceuppens and Baroja 1986; Ledbetter et al. 1985). However, later *in vivo* studies in *Cd5*$^{-/-}$ mice evidenced an indubitable co-inhibitory function for CD5. They showed that *Cd5*$^{-/-}$ thymocytes are hyperresponsive to CD3 crosslinking, presenting increased Ca^{2+} mobilization and phosphorylation of phospholipase C (PLC)-γ1, CD3ζ and Vav (Tarakhovsky et al. 1995). Also, CD5 expression levels correlate with higher inhibition of phosphorylation and Ca^{2+} release without affecting CD3 expression, T-APC contact, or stabilization of the IS (Brossard et al. 2003). Similarly, B-1a cells from *Cd5*$^{-/-}$ mice display increased proliferation and Ca^{2+} mobilization after anti-IgM stimulation, indicating that CD5 has a negative modulator role not

only in T but also in B cells (Bikah et al. 1996). Such role is provided by recruitment of multiple interactors with negative regulatory function (Cbl-b, UBASH3A, ANKRD13A) to the CD5 signalosome as depicted in **Figure I.7**, which end up down-modulating lymphocyte activation (Axtell et al. 2006; Demydenko 2010; Dennehy et al. 1998; Mori et al. 2021; Soldevila, Raman, and Lozano 2011). Consequently, CD5 is supposed to play an important role in several physiologic and pathologic processes, including lymphocyte development and survival, tolerance, autoimmunity, infection and cancer.

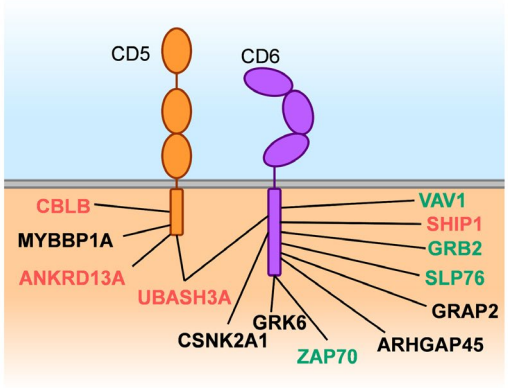


Figure I.7. Signalosome of CD5 and CD6. Recruiting of several mediators with negative (CBLB, ANKRD13A, UBASH3, SHIP1) or positive (ZAP-70, SP76, VAV1, GRB2) regulatory functions confers CD5 and CD6 a co-stimulatory and/or co-inhibitory function. Adapted from Mori et al. 2021.

During T-cell development, selection of thymocytes depends on TCR signal intensity (Jameson and Bevan 1995). *Cd5*$^{-/-}$ mice display reduced single positive (SP) thymocyte population, suggesting that CD5 is necessary to prevent their apoptosis (Tarakhovsky et al. 1995). Indeed, further studies have shown that CD5 expression increases during transition from the DP to the SP stage, and that CD5 expression positively correlates with TCR signaling intensity and

avidity. This way, CD5-mediated negative modulation of TCR signaling allows immature T cells with higher TCR avidities to survive negative selection in the thymus and prevents excessive autoreactivity while allowing a more effective response in the periphery (Azzam et al. 1998, 2001; Fulton et al. 2014).

Direct signaling through CD5 has been shown to enhance lymphocyte survival. In thymocytes, this is achieved through activation of the MAPK pathway, which induces expression of the anti-apoptotic protein Bcl-2 (Zhou et al. 2000). This helps prevent AICD events in T cells. For instance, damage in experimental autoimmune encephalitis (EAE) is dampened in *Cd5*$^{-/-}$ mice, because in lack of CD5 effector T cells mediating neuronal damage undergo increased AICD (Axtell et al. 2004). It was later shown that the casein kinase 2 (CK2)-binding domain at the C-terminal cytoplasmic endo of CD5 is necessary for this anti-apoptotic function, and it has been proposed that CK2 mediates these effects through activation of anti-apoptotic mediators such as Bcl-2 and Bcl-xl and inhibition of pro-apoptotic mediators such as caspases and Bid (Axtell et al. 2006; Soldevila et al. 2011). Similarly, CD5 mediates survival of B cells thanks to activation of protein kinase C (PKC), which induces expression of the anti-apoptotic protein Mcl-1, and secretion of IL-10 (Perez-Chacon et al. 2007). Autocrine Il-10 signaling decreases Ca^{2+} mobilization, further preventing apoptosis (Gary-Gouy et al. 2002).

The regulatory properties of CD5 support its role in tolerance. This would be achieved by downmodulating the activity of autoreactive effector T cells and/or by modulating natural and induced Treg cells (nTreg and iTreg, respectively). It has been described that T cell activation leads to further CD5 overexpression, preventing excessive

lymphocyte activation (Hawiger et al. 2004; Sestero et al. 2012; Stamou et al. 2003). Also, *Cd5*$^{-/-}$ mice have increased production of nTregs, although their suppressive functionality is debatable (Dasu et al. 2008; Ordoñez-Rueda et al. 2009). Additional studies showed that a CD5-dependent mechanism promotes conversion of self-reactive peripheral CD5^{hi} T cells into extrathymic iTreg cells in response to autoantigens presented by peripheral tolerogenic DCs. This would be achieved by CD5-mediated blockade of mTOR (Henderson et al. 2015; Henderson and Hawiger 2015). Similarly, anergization of autoreactive B cells due to continuous exposure to self antigens is achieved through CD5 overexpression (Hippen, Tze, and Behrens 2000).

2.4.2 CD5 in autoimmunity

Due to the immunomodulatory function of CD5, its role in autoimmune diseases has been extensively researched. Increased numbers of circulating CD5^{+} B lymphocytes correlating with presence of circulating autoantibodies, risk or severity have been described in different autoimmune diseases, including systemic lupus erythematosus (SLE), Sjögren's syndrome, multiple sclerosis (MS), rheumatoid arthritis (RA), spondylarthritis, type I diabetes mellitus and autoimmune nephropathies (Böhm 2004; Burastero et al. 1990; Cantaert et al. 2012; Correale et al. 1991; Dauphinée, Tovar, and Talal 1988; Hara et al. 1988; Lorini et al. 1993; Mix et al. 1990; Morbach et al. 2006; Muñoz et al. 1991; Villar et al. 2011; Wang et al. 2014; Wu et al. 2011). Some of these results, however, are controversial, with studies showing no correlation between CD5^{+} cells and RA (Sowden, Roberts-Thomson, and Zola 1987) or even association between CD5^{+} cell presence and improved therapy response in autoimmune nephropathies (Nagatani et al. 2013).

Other studies have dug deeper into the mechanistic role of CD5 in autoimmune disease. In SLE, IL-21 induces granzyme B expression in $CD5^+$ B cells with regulatory function, and reduces their survival (Hagn et al. 2010). Also, IL-6 induces expression of the E1B isoform of CD5, which is retained in the cytoplasm thus reducing expression of membrane CD5 in B cells. (Garaud et al. 2008, 2009). As a result, the negative regulatory function of CD5 is reduced, and maintenance of B cell anergy is deregulated in SLE patients. In MS, presence of $CD5^+$ B cells in circulation and in the cerebrospinal fluid positively correlates with the development of the disease and its severity during the relapsing-remitting phase—the earliest manifestation of MS (Seidi, Semra, and Sharief 2002). However, $CD5^+$ B cells are reduced during the secondary-progressive phase—a more advanced stage of MS—, and their presence is associated with decreased anti-myelin antibody production (Niino et al. 2012; Sellebjerg et al. 2002). Other studies have found the opposite: increased $CD5^+$ B cell proportions in secondary-progressive MS (Bongioanni et al. 1996). Interestingly, studies in *Cd5*$^{-/-}$ mice showed delayed onset and decreased disease activity in the EAE model, which was mediated by increased AICD (Axtell et al. 2006). Intriguingly, similar studies with anti-CD5 mAbs showed decreased activity if administered earlier and increased activity when administered later in a rat neuritis model (Strigård et al. 1988). In an inflammatory bowel disease (IBD) model induced by dextran sulphate sodium (DSS), *Cd5*$^{-/-}$ mice were protected, correlating with an increase of the Treg function (Dasu et al. 2008).

Apart from T and B cells, CD5 is expressed in subsets of epidermal and dermal DC subsets. Such $CD5^+$ DCs prime cytotoxic T lymphocytes and polarize $CD4^+$ T cells to Th1 and Th22 phenotypes. These effector populations are involved in psoriasis, and in fact $CD5^+$ DCs have been

found increased in inflamed tissue compared with normal skin in psoriasis patients (Korenfeld et al. 2017).

Pre-clinical and clinical studies targeting CD5 in autoimmune diseases have also been performed. Treatment with the mouse IgG_1 anti-rat CD5 OX-19 IgG1 mAb (Dallman, Thomas, and Green 1984) protected rats from T cell-dependent diabetes models (Ellerman et al. 1996; Like et al. 1986), and reduced proteinuria and mesangial injury in a rat glomerulonephritis model (Ikezumi et al. 2000). These changes correlated with a decrease in circulating T lymphocytes and would agree with depletion of autoreactive T cells. However, treatment with OX-19 was also reported to increase relapse in an experimental allergic neuritis model concomitant with down-regulation of CD5 expression on T lymphocytes, together with its suppressive function (Strigård et al. 1988). Therefore, anti-CD5 mAbs may have a dual effect, by inducing both internalization of membrane bound CD5 and T cell depletion, and the balance between these effects can lead to increased or decreased autoimmunity.

The use of checkpoint inhibitor therapies has the downside of excessive immune activation, which can lead to immune-related adverse events (autoimmunity) (Bajwa et al. 2019). Given the negative immunomodulatory role of the CD5 receptor in lymphocyte activation, therapies targeting CD5 would also be expected to have similar potential adverse effects. Nevertheless, loss of CD5 function can lead to excessive T cell activation and eventually to AICD) (Axtell et al. 2004). Considering this evidence, the use of soluble CD5 (sCD5) proteins as a decoy receptor has been explored in autoimmunity models, pursuing attenuation of inflammation. Indeed, administration of chimerical human CD5-Fc (hCD5-Fc) protein abrogated the

formation of granular immunoglobulin deposits in peripheral capillaries and reduced production of anti-rabbit antibodies in a T-cell dependent antibody-mediated membranous glomerulonephritis mouse model (Biancone et al. 1996). Given that putative CD5 ligands are expressed on T and B cells, the authors hypothesized that the effect was based on interference of T-B cell co-stimulation (Biancone et al. 1996). In another work, adenoviral expression of chimerical mouse CD5-Fc (mCD5-Fc) protein arrested the development of EAE, while hCD5-Fc did not (Axtell et al. 2004). Treatment with mCD5-Fc also correlated with a lower number of activated T cells, as a result of increased AICD. The latter prompts the assumption that blockade of CD5 interaction with endogenous ligands would induce apoptosis of hyper-activated autoreactive T cells. In contrast, transgenic mice expressing shCD5 have been reported to develop more severe forms of EAE and collagen-induced arthritis (CIA) (Fenutría et al. 2014). Though several experimental differences may account for the contradicting results (*e.g.*, use of WT *vs* transgenic mice, human *vs* mouse protein, Fc-based *vs* non-chimerical soluble proteins, etc.) one of them could be the different serum protein levels, and consequently of functional CD5 blockade, achieved with the respective transgenic (10-100 ng/mL shCD5) and adenoviral (1700 ng/mL mCD5-Fc) expression systems used (Axtell et al. 2004; Fenutría et al. 2014). Consequently, the extent of CD5-ligand interference could be a relevant factor to sufficiently activate T lymphocytes to induce AICD in autoimmune settings.

In summary, the role of CD5 in autoimmune diseases might depend on its pattern expression, the disease, and timing. Therefore, knowledge on the role of $CD5^+$ cells must be expanded to provide insights into the conflicting results reported to date.

2.4.3 CD5 in cancer

The negative regulatory properties of CD5 position this molecule as an immune checkpoint receptor, with a putative role in tumor immunosurveillance. Indeed, an inverse correlation between CD5 expression levels and antitumor activity has been described in T cells with identical TCR specificity from lung carcinoma (Dorothée et al. 2005). This would lower the activation threshold and allow T lymphocytes to respond in a context of MHC class I downregulation. In line with this findings, *Cd5*$^{-/-}$ mice show slower tumor growth in a mouse melanoma model (Tabbekh et al. 2011). On the other side, CD5 protects T cells from AICD, so at more advanced stages of the model this phenomenon prevailed. In line with these results, high CD5 expression in non-small cell lung cancer (NSCLC) and melanoma has been associated with improved prognosis (Moreno-Manuel et al. 2020).

Targeting of CD5 has been explored as an immunotherapy for cancer. *Ex vivo* treatment with a blocking anti-CD5 (53-7.3) mAb increased the capacity of CD8^{+} T lymphocytes to kill mouse breast cancer cells concomitant with increased expression of markers for both T cell activation (*i.e.*, CD69) and AICD (*i.e.*, Fas, FasL) (Alotaibi et al. 2020). The latter would indicate that targeting additional T cell molecules in combination with CD5 blockade may be necessary to prevent CD8^{+} T cell exhaustion and sustain CD8^{+} T cell function. Also, a transgenic mouse line was developed to assess the *in vivo* use of sCD5 as a decoy receptor in cancer therapy. This mouse line (shCD5) constitutively expresses the soluble portion of human CD5 (shCD5EμTg) under control of the non-tissue specific SV40 promoter and immunoglobulin μ heavy chain enhancer (Eμ) (Fenutría et al. 2014), achieving serum concentrations of shCD5 in the range of 10-

100 nM. Major B and T cell compartments were normal, though percentage changes were observed in some minor lymphocyte subsets: decreased spleen transitional 1 and 2 B cells and increased spleen marginal zone B cells; decreased peritoneal and spleen regulatory B (Breg) cells; decreased lymph node Treg cells; and increased spleen natural killer T (NKT) cells. Similar phenotypes were observed after repeated (every-other-day) injections of recombinant shCD5 protein for two weeks (Fenutría et al. 2014). The functional relevance of such phenotypic lymphocyte changes was supported by the demonstration of slower melanoma tumor growth in transgenic mice compared with wild type (WT) controls. Similarly, shCD5 treatment (*i.p.*) in combination with chemotherapy (doxorubicin plus vincristine) of WT mice implanted with melanoma cells, decreased tumor growth compared with mice treated with chemotherapy alone. These results highlight the potential of sCD5 as a treatment in cancer.

Validation and mechanistic studies were further performed in a similar transgenic mouse line (shCD5LckEμTg) expressing shCD5 under the control of lymphoid-specific *lck* promoter and the Eμ enhancer to ensure preferential expression in lymphoid tissues (Simões et al. 2017). Challenge of such transgenic mice with different tumor (melanoma and thymoma) cell lines again led to slower tumor growth compared with WT controls. Analysis of tumor-draining lymph nodes (TdLN) from transgenic mice showed higher cellularity at the expense of both $CD4^+$ and $CD8^+$ T cells, but with a lower percentage of Treg cells (Simões et al. 2017). Intra-tumor mRNA analyses showed reduced IL-6 and increased IL-15 expression levels, which are known to inhibit and potentiate NK function, respectively (Cifaldi et al. 2015; Rautela and Huntington 2017). The possibility that NK cells could be involved in the anti-tumor effect of transgenic

shCD5 was confirmed by its reversion following treatment with the NK cell-depleting anti-NK1.1 antibody (Simões et al. 2017). Importantly, all the above mentioned findings in transgenic mice could be reproduced in tumor-challenged WT mice administered with exogenous shCD5 protein (Simões et al. 2017). Moreover, *ex vivo* assays showed that shCD5 interfered with polarization of naïve $CD4^+$ T lymphocytes from WT mice to Treg, while favored polarization to Th1 (Simões et al. 2017). Taken together, these studies position shCD5 administration as a potential therapeutic strategy in cancer. These treatments would work as immune checkpoint inhibitors, therefore enhancing anti-tumor immune responses, and by shifting immune populations towards a more pro-inflammatory status (increased effector T and NK cell and decreased T and B cell regulatory populations).

A role for $CD5^+$ B lymphocytes in cancer has also been proposed, with controversial results. CD5-expressing Breg cells have been identified as one of the suppressive cell subtypes recruited into pancreatic ductal adenocarcinoma (Das et al. 2020). Circulating $CD5^+$ B cells were decreased in patients with bladder cancer, probably due to either infiltration of these cells into the tumor or to the effect of T cells or cytokines (Roudafshani et al. 2019). Also, the presence of $CD5^+$ B cells in tumor-draining lymph nodes correlated with lower staging in head and neck squamous cell carcinoma patients (Norouzian et al. 2019). In samples of tumor, lymph node and surrounding tissue of various cancer types (prostate, ovarian, and NSCLC), $CD5^+$ B cells are present, and display phosphorylated STAT3 (Zhang et al. 2016). The authors also showed that administration of $CD5^+$ B cells promote growth of a melanoma mouse model and suggest that this is mediated by interaction of IL-6 with CD5, which

would generate a positive feedback through phosphorylation of STAT3 and subsequent CD5 overexpression.

As commented in section I.2.2.1, CD5 is also expressed by certain leukemias and lymphomas. Therefore, preclinical and clinical trials have been performed targeting CD5 with various mAbs, with partial but transient responses (Dillman et al. 1984; Foss et al. 1998; Hollander 1984). CD5 expression promotes survival of CLL cells thanks to autocrine IL-10 production and induces a differential gene expression pattern characteristic of CLL cells (Gary-Gouy et al. 2002, 2007). In diffuse large B cell lymphoma, a CD5-associated gene signature has been identified in a subset of $CD5^+$ tumors, associated with poor prognosis (Suguro et al. 2006). It can be therefore inferred that not only CD5 is a phenotypic marker of certain malignancies, but also plays a role in their pathophysiology.

2.4.4 CD6 in health

Like CD5, CD6 is physically associated with the TCR-CD3 complex and co-localizes with it at the center of the IS (Gimferrer et al. 2003). Thanks to this, CD6 is well positioned to modulate TCR signaling during specific antigen recognition. CD6 also interacts with CD166/ALCAM expressed on the surface of APCs (Gimferrer et al. 2004), likely playing a role in the formation and stabilization of the IS. This is sustained by the impairment of IS formation observed following blockade of the CD6–CD166/ALCAM interaction with soluble CD6 and CD166/ALCAM proteins (sCD6, CD6-Fc, or ALCAM-Fc), galectins 1 and 3 or blocking mAbs against CD6 or CD166/ALCAM (Escoda-Ferran et al. 2014; Gimferrer et al. 2004; Zimmerman et al. 2006). However, steric effects cannot be ruled out in the observed disruption of the IS. Additional evidence shows that the

CD6–CD166/ALCAM interaction is relevant in lymphocyte adhesion to epithelial and endothelial surfaces, and in transmigration to inflamed tissues (Bowen et al. 1995; Cayrol et al. 2008; Patel et al. 1995).

Early studies showed that CD6 crosslinking with mAbs and with its ligand CD166/ALCAM leads to T cell activation, measured as increased MAPK phosphorylation, IL-2 production, and cell proliferation. Moreover, TCR crosslinking induced phosphorylation of the CD6 intracellular tail (Gangemi et al. 1989; Ibáñez et al. 2006; L. M. Osorio et al. 1998; Wee et al. 1993). Thus, a co-stimulatory role was attributed to CD6. However, later studies with CD6-positive and -negative cell lines and *Cd6*$^{-/-}$ mice found that CD6 expression inhibits T cell activation (Hassan et al. 2006; Li et al. 2017; Oliveira et al. 2012; Orta-Mascaró et al. 2016). This effect depended on the interaction of phosphorylatable Tyr residues in the cytoplasmic tail (Y622 and Y629) with intracellular interactors like syntenin-1 (Gimferrer et al. 2005), GADS (Breuning and Brown 2017) and TSAd (Hem et al. 2017). More recently, a proteomic analysis of the CD6 signalosome has reported a series of intracellular interactions with both positive (SLP-76, ZAP-70, VAV1) and negative (UBASH3A, SHIP1) regulators (Mori et al. 2021), as depicted in **Figure I.7**. This might explain the conflicting results on the co-stimulatory or -inhibitory nature of CD6 obtained so far.

During human and mouse thymocyte development, CD6 expression increases from a minimal expression in DN cells to the maximal expression in CD4^{+}SP cells (Singer et al. 2002). Available data from *Cd6*$^{-/-}$ mice in C57BL/6 background eventually positioned CD6 as a negative modulator of TCR signaling during negative selection of

immature thymocytes (Orta-Mascaró et al. 2016). Such observation led to the conclusion that CD6 raises the activation threshold in DP thymocytes, preventing negative selection. Another *Cd6*$^{-/-}$ mouse line, in DBA-1 backgorund, showed that CD6 acts as a negative regulator of activation and AICD in peripheral T cells (Li et al. 2017).

The first study on the role of CD6 in cell survival showed that CD6^{+} B-CLL cells stimulated with anti-IgM were protected against apoptosis when in presence of anti-CD6 mAbs (Osorio et al. 1997). Such effect was mediated by an increased the bcl-2/bax ratio. Later, it was described that CD6 expression correlates positively with thymocyte resistance to apoptosis (Singer et al. 2002). Signaling pathways induced by the CD6–CD166/ALCAM interaction include three MAPK cascades, eventually inducing p38 and Janus kinase (JNK), which are involved in cell survival (Ibáñez et al. 2006). Although the exact mechanism by which CD6 promotes cell survival is still unknown, it is hypothesized that it involves Tyr phosphorylation in its cytoplasmic tail and interaction with CK2, like it happens with CD5 (Axtell et al. 2006; Bonet et al. 2013). Moreover, CD6 expression protects T lymphocytes from Galectin-1 and Galectin-3 induced apoptosis (Escoda-Ferran et al. 2014).

Regarding tolerance, early studies showed that donor bone marrow T cell depletion with anti-CD6 mAbs before allogeneic bone marrow transplantation lead to reduced graft versus host disease (GvHD) (Soiffer et al. 1992). Later, it was observed that CD6^{-} T cells present reduced alloreactivity (Rasmussen et al. 1994), and that anti-CD6 mAbs inhibit T cell autoreactive responses (Singer et al. 1996). More recently, it was described that T cells from *Cd6*$^{-/-}$ mice have reduced alloreactive responses, and that such mice present higher induction of

FoxP3$^+$ Treg cells, although with reduced functionality (Consuegra-Fernández et al. 2017).

2.4.5 CD6 in autoimmunity

Several lines of evidence support a role for CD6 in autoimmune disorders. In MS lesions, CD166/ALCAM is overexpressed and facilitates lymphocyte transmigration thanks to its interaction with CD6 (Cayrol et al. 2008), and MS patients express less CD6 mRNA (Wagner et al. 2014). In mouse EAE models, blockade of CD6–CD166/ALCAM interaction with anti-CD166/ALCAM mAbs leads to less severe disease and reduced immune infiltrates (Cayrol et al. 2008). EAE models in *Cd6*$^{-/-}$ mice also show decreased severity compared with *wt* counterparts (Li et al. 2017), while the disease is exacerbated in *Alcam*$^{-/-}$ mice (Lécuyer et al. 2017). Such differences can be attributed to a dual role for CD6 as a modulator of the immune response and as a mediator of lymphocyte migration.

Aside from decreased EAE, *Cd6*$^{-/-}$ mice show decreased imiquimod-induced psoriasis (Consuegra-Fernández et al. 2018), autoimmune uveitis (Zhang et al. 2018), intestinal ischemia-reperfusion (Enyindah-Asonye, Li, Xin, et al. 2017) and bovine type II collagen-induced arthritis (CIA) (Li et al. 2020), but increased chicken type II collagen CIA (Orta-Mascaró et al. 2016) and GvHD-induced lupus-like disease (Consuegra-Fernández et al. 2017). These conflicting results probably arise from the particular pathophysiology of the models and the different genetic background of the mouse lines used, which may favor certain CD6 functions and interactors.

Availability of mouse and humanized anti-CD6 mAbs has provided valuable information regarding the potential targeting of CD6 for the treatment of RA, psoriasis and potentially other T cell–driven

autoimmune conditions (Hernández et al. 2016). Indeed, ALZUMAb® (Itolizumab), a humanized anti-human CD6 mAb developed from its parent murine antibody IOR-T1, has been approved by the Drugs Controller General of India in January 2013 to treat psoriasis (Dogra, Shabeer, and Rajagopalan 2020; Jayaraman 2013). A randomized phase III clinical trial was carried out in India in a cohort of 225 patients with moderate to severe chronic psoriasis plaques in which Itolizumab was effective and well-tolerated (Krupashankar et al. 2014).

In the light of the above, the use of sCD6 could provide an effective alternative. Indeed, preliminary observations made with shCD6*lck*EμTg mice and WT mice treated with soluble human CD6 (shCD6) reveal improved outcomes (lower clinical score) in two different experimental autoimmune diseases (CIA and EAE) (Simões et al. 2020) and warrant further clinical validation.

2.4.6 CD6 in cancer

The ability of CD6 to modulate important physiological lymphocyte processes warrants exploration of its immunomodulatory potential in cancer therapy. Indeed, CD6 expression was early reported in CLL and in some lymphosarcoma cell leukemia cells (Kamoun et al. 1981), despite CD6 expression did not correlate with disease progression (Sembries et al. 1999). However, it is known that CD6 ligation induces expression of anti-apoptotic proteins and prevents apoptosis of leukemic B cells following IgM cross-linking (Lyda M. Osorio, Jondal, and Aguilar-Santelises 1998). Thus, prevention of CD6 ligation or down-modulation of CD6 expression on leukemic cells would increase their sensitivity to apoptosis and limit their abnormal expansion.

The CD6 ligand CD166/ALCAM is involved in the maintenance of tissue architecture, immune responses and tumor progression (Swart 2002). A number of studies support the association of CD166/ALCAM expression with aggressiveness in a variety of cancers, including melanoma, prostate, breast, ovarian, esophageal, bladder and intestinal cancers (likely as a result of homophilic ALCAM–ALCAM interactions), thus constituting an oncology-related target and prognostic marker (Darvishi et al. 2020; Weidle et al. 2010).

Blockade of CD6–CD166/ALCAM interactions has been explored in experimental cancer models. *In vitro* studies showed that shCD6, CD6-blocking mAbs and chimerical CD166/ALCAM-Fc proteins similarly inhibit T-cell proliferation, suggesting to be, at least in part, the result of interfering heterophilic CD6–CD166/ALCAM interactions (*e.g.*, APC–T-cell interactions) (Gimferrer et al. 2004; Kim et al. 2018). Furthermore, shCD6 inhibits proliferation and migration of tumor cell lines expressing high CD166/ALCAM surface levels (B16-F0, EL-4, and MC-205) (Simões et al. 2020).

Recent work provides proof-of-concept on the immunotherapeutic potential of sCD6 in cancer and its translatability to the clinical practice (Simões et al. 2020). This was explored by challenging genetically modified (shCD6LckEμTg) or WT mice expressing high circulating levels of shCD6 with subcutaneous or metastatic syngeneic cancer cells of different lineage origins (B16-F0 melanoma, MCA-205 sarcoma and RMA-S lymphoma cells). The results showed significantly delayed *in vivo* growth of tumor cells constitutively expressing high CD166/ALCAM surface levels in transgenic shCD6*lck*EμTg mice compared with WT controls (Simões et al. 2020). Moreover, significantly lower number of lung metastases and

improved survival was observed when WT mice transduced with hepatotropic AAV expressing soluble mouse CD6 (AAV-smCD6) were challenged (*i.v.*) with B16.F0 melanoma cells. Importantly, both delayed local growth and lower metastasization results were observed in tumor-challenged WT mice infused with shCD6 protein (Simões et al. 2020). *In vitro* studies showed that mechanisms operating at the level of lymphocyte effector function and tumorigenicity were engaged in the presence of shCD6 such as defective Treg generation and function, decreased CD166/ALCAM-mediated tumor cell proliferation/migration and impaired galectin-induced T-cell apoptosis (Simões et al. 2020). Similarly, an anti-CD6 mAb increased *in vitro* and *in vivo* killing of several tumor lines, an effect that was attributed to increased NK activity (Ruth et al. 2021).

3 Functionally relevant *CD5*, *CD6* and *CD166/ALCAM* polymorphisms

To date, no *CD5*, *CD6* or *CD166/ALCAM* deficiencies have been reported in humans. A long list of SNPs has been identified in the *CD5*, *CD6* and *CD166/ALCAM* loci, with several of them showing functional relevance. Selected functionally relevant SNPs from the *CD5* locus and the *CD5*–*CD6* intergenic region are listed in **Table I.1**, from the *CD6* locus in **Table I.2** and from the *CD166/ALCAM* locus in **Table I.3**. Also, the effect of relevant SNPs on the protein structure is depicted in **Figures I.5** and **I.6**.

3.1 CD5 polymorphisms

Table I.1. Reported frequency and relevance of *CD5* and intergenic SNPs.

Gene	SNP	Alleles	Change	CADD	AFR	EUR	EAS	SAS	AMR	Functional/clinical relevance
CD5	rs2241002	C>T	Pro224> Leu	11.06	0.31	0.15	0.06	0.15	0.14	T allele associated with lower risk of lupus nephritis and higher melanoma mortality. Haplotypic combinations with rs2229177 associated to lupus nephritis, and survival in melanoma and chronic lymphocytic leukemia (CLL).
	rs117646548	G>A	Ala377> Thr	11.86	0.00	0.01	0.00	0.00	0.01	
	rs34209302	C>T	His461> Tyr	0.092	0.08	0.01	0.00	0.08	0.01	
	rs637186	G>A	Arg461> His	0.014	0.01	0.08	0.00	0.04	0.05	
	rs2229177	C>T	Ala471> Val	25.2	0.51	0.55	0.99	0.80	0.66	T allele associated with more signaling upon CD5 stimulation, stronger TCR inhibition, decreased lupus nephritis risk, and lower survival in melanoma and CLL.
Inter-genic	rs650258	T>C		0.051	0.65	0.63	0.88	0.76	0.76	C allele associated with increased multiple sclerosis (MS) risk.
	rs11230584	G>A		1.789	0.25	0.15	0.13	0.18	0.11	Modulation of *CD5* and *CD6* expression.
	rs595158	C>A		2.165	0.55	0.54	0.99	0.79	0.67	Risk locus in rheumatoid arthritis.

Alleles are depicted as ancestral > derived. CADD: Combined annotation-dependent depletion. Derived allele frequencies in populations from 1000 Genomes Project Phase 3 (AFR: African, EUR: European, EAS: East Asian, SAS: South Asian, AMR: American).

Regarding *CD5*, the two most relevant SNPs reported to date are rs2241002 (C>T) and rs2229177 (C>T), which result in amino acid substitutions at the SRCR2 domain (Pro224>Leu) and just next to an ITAM-like cytoplasmic motif (Ala471>Val), respectively (Carnero-Montoro et al. 2012; Cenit et al. 2014). Human population data

analyses provided evidence for a recent selective sweep in East Asia and suggested the nonsynonymous substitution at position 471 (Ala471>Val; rs2229177) of the cytoplasmatic region of the CD5 receptor as the most plausible target of selection. As illustrated in **Figure I.8**, the ancestral (Ala471; C) and the newly derived (Val471; T) *CD5* variants were found in similar proportions in African and European populations, while the newly derived (Val471; T) variant was much more abundant East Asian and native American populations.

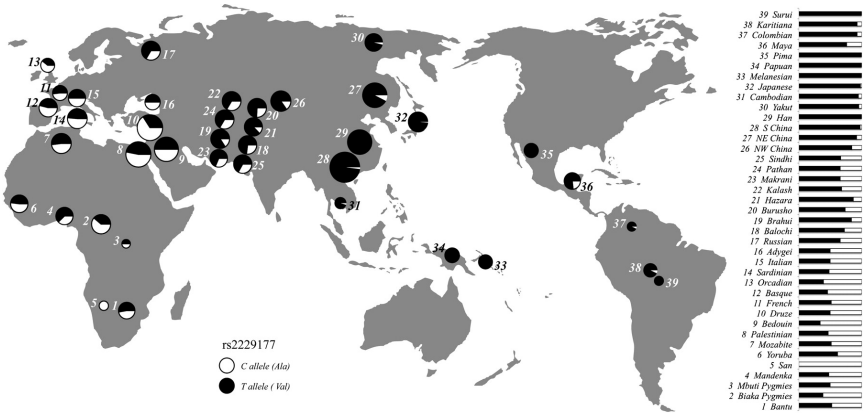


Figure I.8. Geographical distribution of the ancestral *CD5* rs2229177^{C} (Ala471, white) and the derived rs2229177^{T} (Val471, black) alleles into the Human Genome Diversity Panel. Populations, numbered 1–39, are listed in the allele frequency bar plot at the right. Source: Carnero-Montoro et al. 2012.

Further studies showed that cell transfectants expressing the Ala471 variant (rs2229177^{C}) show lower MAPK activation and IL-8 production when either crosslinked with anti-CD5 mAbs or exposed to the fungal β-glucan-rich particle Zymosan, respectively, with regard to the Val471 variant (rs2229177^{T}) (Carnero-Montoro et al. 2012). This would be compatible with the Ala471 variant having a lower signaling capability and, consequently, lower ability to negatively modulate the activation signals delivered by the clonotypic

antigen-specific receptor complex—TCR and BCR. Accordingly, PBMCs from homozygous Ala471 (rs2229177^{CC}) individuals show higher T-cell proliferative responses than homozygous Val471 (rs2229177^{TT}) ones (Cenit et al. 2014). An interpretation for these observations is that the ancestral *CD5* variant Ala471 has a lower negative modulatory capacity of the TCR than the Val471 variant.

Functional relevant *CD5* SNPs have been investigated as putative susceptibility or disease modifier markers in autoimmune and neoplastic disorders. Accordingly, a genome-wide association study (GWAS) has shown association of *CD5* variation (rs595158) with RA susceptibility (Eyre et al. 2012). Association studies of *CD5* variation in SLE show that the rs2241002^{C} (Pro224) and rs2229177^{C} (Ala471) alleles are associated with the development of lupus nephritis (Cenit et al. 2014), which represents a severe form of the disease. The same study showed that the rs2241002^{C}-rs2229177^{C} haplotype (Pro224-Ala471) is overrepresented in SLE patients with nephritis. This finding agrees with the reported lower negative immunomodulatory properties of the *CD5* Pro224-Ala471 variant.

The inhibitory function of CD5 in T and B1a cell activation has positioned this receptor as a relevant player in the immune response against cancer (Consuegra-Fernández et al. 2015; Tabbekh et al. 2013). This is illustrated by a few studies on *CD5* variation in human malignancies. Thus, the rs2229177^{C} (Ala471) and the rs2241002^{C} (Pro224) alleles correlate with better outcome and increased melanoma-associated mortality, respectively (Potrony et al. 2016). This could be attributed again to the lower capacity of the rs2229177^{C} (Ala471) allele to downregulate activating TCR-mediated intracellular

signals, which would potentiate T-cell anti-melanoma immune responses.

Aside from tumor-infiltrating lymphocytes (TILs), CD5 can also be expressed on certain malignant cells. There, the different signaling capabilities of *CD5* variants might play a role in their biological and/or clinical behavior. This is the case of chronic lymphocytic leukemia (CLL), the most frequent hematological malignancy in western countries (Tamura et al. 2001). Clinical association studies show that CLL patients either homo- (rs2229177^{CC}) or heterozygous (rs2229177^{CT}) for the ancestral Ala471 allele present higher progression-free survival in the most prevalent but less aggressive subgroup of IGVH-mutated CLL (Delgado et al. 2017). This would indicate that CD5 is not only a phenotypical marker but a relevant player in the biological or clinical behavior of CLL.

3.2 *CD6* polymorphisms

Regarding *CD6*, the list of identified SNPs includes the non-synonymous rs11230563 (C>T) and rs2074225 (T>C) SNPs causing amino acid substitutions at the SRCR2 domain (Arg225>Trp and Val257>Ala, respectively) and the rs12360861 (G>A) at SRCR3 domain (Ala271>Thr). Intronic *CD6* SNPs include rs12288280 (G>T), rs17824933 (C>G) and rs11230559 (T>C) in intron 1, together with the 3′ intergenic SNP rs650258 (T>C) (Swaminathan et al. 2013). Efforts to unveil the effect of these variants in the CD6 function show that the rs17824933^{G} allele is associated to skipping of exon 5, resulting in increased expression of a CD6 isoform lacking the SRCR3 domain (CD6Δd3), in which the CD166/ALCAM-binding site is located (Castro et al. 2007; Kofler et al. 2011). Although this does not result in a change of the total CD6 amount on the cell surface, increased

Δd3/full-length CD6 ratio results in lower activation of $CD4^+$ lymphocytes (Kofler et al. 2011). No direct impact on CD6 expression or function has been described yet for rs11230559, but it has been shown to be in linkage disequilibrium with rs17824933 and the non-synonymous SNPs rs11230562 in SRCR2 (C>T; Thr217>Met) and intracellular rs2074233 (G>A, Gly606>Ser) (Swaminathan et al. 2013). The *CD6* haplotype involving $rs11230563^C$ and $rs2074225^C$ SNPs (Arg225 and Ala257) results in higher CD6 surface expression on $CD4^+$ and $CD8^+$ naïve T cell and NKT cell subsets (Swaminathan et al. 2013). Quantitative trait loci studies have shown that the rs11230584 SNP in the intergenic region between *CD5* and *CD6* modulates expression of both genes under certain pathological circumstances (Peters et al. 2016).

Several *CD6* SNPs have been associated to immune-mediated inflammatory disorders (IMIDs), including MS, psoriasis and Behçet's disease. *CD6* is a consolidated risk locus for MS as stated by a meta-analysis of six GWAS (De Jager et al. 2009). This study identified the *CD6* rs17824933 SNP as a risk marker for MS in cohorts of European origin, with the $rs17824933^G$ allele being associated to greater MS risk (De Jager et al. 2009). Further gene-specific approaches were then performed to confirm this observation. Association of $rs17824933^G$ allele with increased MS risk was confirmed in twelve independent European cohorts (Leppä et al. 2011; Swaminathan et al. 2010). A study aiming at fine mapping the *CD6* locus in MS in a European cohort (Swaminathan et al. 2013) found an association of the $rs2074225^T$ (Val257) allele with higher MS risk.

Table I.2. Reported frequency and relevance of *CD6* SNPs.

SNP	Alleles	Change	CADD	AFR	EUR	EAS	SAS	AMR	Functional/clinical relevance
rs12288280	G>T	Intronic	2.973	0.50	0.10	0.10	0.05	0.14	T allele associated with decreased neuromyelitis optica risk in an Asian cohort.
rs17824933	C>G	Intronic	7.58	0.01	0.23	0.03	0.07	0.12	G allele associated with increased expression of CD6Δd3, increased MS risk in European cohorts, increased psoriasis severity.
rs11230559	T>C	Intronic	4.239	0.01	0.25	0.04	0.07	0.12	In linkage disequilibrium with rs17824933.
rs11230563	C>T	Arg225> Trp	22.4	0.61	0.36	0.17	0.21	0.30	Haplotypic combinations with rs2074225 associated with differential *CD6* expression. T allele associated with decreased MS risk in an African American cohort, decreased psoriasis severity and increased Behçet's disease risk in Han population. Involvement in IBD.
rs2074225	T>C	Val257> Ala	17.66	0.33	0.38	0.59	0.54	0.56	Haplotypic combinations with rs11230563 associated to differential CD6 expression. T allele associated with increased MS risk in a European cohort.
rs12360861	G>A	Ala271> Thr	0.001	0.04	0.19	0.00	0.05	0.12	A allele associated with decreased MS risk in a European cohort and increased psoriasis severity.

Alleles are depicted as ancestral > derived. CADD: Combined annotation-dependent depletion. Derived allele frequencies in populations from 1000 Genomes Project Phase 3 (AFR: African, EUR: European, EAS: East Asian, SAS: South Asian, AMR: American).

Haplotypic analyses also found similar strong association for the *CD6* rs11230563^{T}-rs2074225^{T} haplotype (Trp225-Val257), which involves non-synonymous substitutions at CD6 SRCR2. In a mechanistic exploration, the risk rs11230563^{T}-rs2074225^{T} haplotype correlated with lower CD6 expression in various lymphocyte subsets (Swaminathan et al. 2013). The same study also found association of rs11230559^{C} with higher MS risk and confirmed the risk alleles rs17824933^{G} and rs650258^{C} (Sawcer et al. 2011). In another study,

the *CD6* rs12360861^{G} (Ala271) allele was also associated to increased MS risk in a European cohort (Wagner et al. 2014).

CD6 association studies in MS have also been performed in non-European cohorts. An African American cohort did not confirm association with the intronic rs17824933 SNP, but found the *CD6* rs11230563^{C} allele (Arg225) as a risk marker for MS (Johnson et al. 2010). A replication study in an Asian cohort did not show any association of *CD6* SNPs with MS risk but found association of the intronic rs12288280^{G} allele with neuromyelitis optica, a similar demyelinating disease with distinct pathophysiology (Park et al. 2013).

Regarding other inflammatory diseases, the *CD6* rs12360861^{G}, rs17824933^{G} and rs11230563^{C} alleles have been found associated to increased Ps severity in a European cohort (Consuegra-Fernández et al. 2018). In Chinese Han population, rs11230563^{T} was found associated to increased risk of Behçet's disease (Zheng et al. 2016). GWAS and meta-analyses have also shown association between *CD6* rs11230563 SNP and susceptibility to IBD (Ellinghaus et al. 2016; Jostins et al. 2012).

To date, there is no current evidence linking *CD6* expression and/or variation with susceptibility or prognosis to malignancies. This contrasts with the high number of studies reporting association of CD166/ALCAM expression with grade, stage and invasiveness of different carcinomas (Darvishi et al. 2020). The known relevance of CD6-CD166/ALCAM interaction in cell-to-cell adhesive contacts established between T cells and other immune (B cells, macrophages, DCs) and non-immune (endothelial, epithelial) cells warrants future studies of CD6 variation in cancer.

3.3 *CD166/ALCAM* polymorphisms

Relevant *CD166/ALCAM* polymorphisms include rs6437685 (C>T) in the 5'UTR, rs1044243 in exon 9, and rs1157 in the 3' UTR. *In vitro* studies with a reporter gene showed that the CD166/ALCAM promoter and 5'UTR containing the rs6437685^{T} allele has higher transcriptional activity than the rs6437685^{C} allele (Zhou et al. 2011). Authors of the same study also observed that the *CD166/ALCAM* mRNA expression in breast cancer tissue was higher in patients homozygous for the rs6437685^{T} allele. The rs1044243 SNP causes an amino acid substitution at the central Ig domain of CD166/ALCAM (C>T; Thr301>Met). Although the molecular impact of this change has not been reported, an *in silico* evaluation with the *Sorting Intolerant From Tolerant* (SIFT) tool revealed a damaging impact (Varadi et al. 2012). Interestingly, rs1044243 lies in a 7 bp SNP hotspot, with the synonymous SNPs rs579565 (G>A) 2 bp upstream and rs35271455 (T>C) 4 bp downstream. Similarly, the rs1157 (G>A) lies at the 3'UTR region and no impact has been empirically shown for such change, but an *in silico* test with the microRNA.org tool predicted changes in miRNA binding (Varadi et al. 2012).

There is evidence for association between risk and progression of MS with variation at *CD166/ALCAM*. Specifically, individuals carrying the rs6437585^{T} allele showed higher risk of MS and earlier age of onset (Wagner et al. 2013). *In vitro* studies showed that the rs6437585^{T} allele is associated with increased *CD166/ALCAM* transcriptional activity (Zhou et al. 2011), which would agree with investigations showing upregulated CD166/ALCAM expression on central nervous system vessels in active MS lesions (Cayrol et al. 2008).

Table I.3. Reported frequency and relevance of *CD166/ALCAM* SNPs.

SNP	Alleles	Change	CADD	AFR	EUR	EAS	SAS	AMR	Functional/clinical relevance
rs6437585	C>T	5'UTR	13.89	0.11	0.07	0.13	0.13	0.05	T allele associated with higher transcriptional activity, earlier MS onset, increased breast cancer risk and decreased bladder cancer risk.
rs579565	G>A	Syn	11.89	0.30	0.24	0.15	0.18	0.31	
rs1044243	C>T	Thr301> Met	24.40	0.01	0.11	0.05	0.06	0.05	T allele associated with increased breast cancer mortality.
rs35271455	T>C	Syn	9.587	0.00	0.02	0.00	0.02	0.00	
rs1157	G>A	3'UTR	0.239	0.01	0.18	0.15	0.22	0.21	A allele associated with increased breast cancer mortality, colon cancer recurrence and gallbladder cancer risk, and decreased bladder cancer risk.

Alleles are depicted as ancestral > derived. CADD: Combined annotation-dependent depletion. Derived allele frequencies in populations from 1000 Genomes Project Phase 3 (AFR: African, EUR: European, EAS: East Asian, SAS: South Asian, AMR: American).

CD166/ALCAM variation also has been shown to impact several malignancies. The rs6437585^{T} allele was shown to be associated with increased risk of breast cancer (Zhou et al. 2011). Another study also showed that rs1044243^{T} allele homozygosity associates with increased mortality risk in breast cancer patients (Varadi et al. 2012). The same study and two others showed a damaging effect of the minor allele of rs1157 in cancer, including increased breast cancer mortality, increased colon cancer recurrence, and increased gallbladder cancer risk (Gerger et al. 2011; Varadi et al. 2012; Yadav et al. 2016). Later, the study of a much smaller cohort showed association of rs6437585^{C} and rs1157^{G} with increased bladder cancer susceptibility (Verma, Kapoor, and Mittal 2017). This data points to a role for genetic variation of *CD166/ALCAM* in several autoimmune and malignant disorders.

4 The immune system in disease

In the present thesis the function of CD5 and CD6 will be explored through the study of their relevance in diseases in which the immune system plays a role: IMIDs and cancer. The following is a brief summary of the immune system role in these disorders.

4.1 Immune-mediated inflammatory diseases

Together with recognition and elimination of "non-self" and "altered-self" antigens, a main feature of the immune system is the lack of reactivity against autoantigens, known as tolerance (Mackay 2008). This is achieved thanks to central and peripheral tolerance. Central tolerance is the process occurring in the bone marrow and thymus that eliminates B and T lymphocytes presenting strong affinity for self-antigens. Peripheral tolerance counteracts autoreactive B and T cells that migrate to secondary lymphoid organs. In B cells it can be achieved by anergy, in T cells it occurs as anergy in presentation without co-stimulation or in presence of CTLA-4, or activation-induced cell death (AICD) after overactivation with high antigen concentrations (Romagnani 2006). Normally, the immune system recognizes self-antigens but does not react against them, in what is called homeostatic autoimmunity. An example is the production of natural antibodies—antibodies that are produced without antigenic activation. Most natural antibodies are polyreactive and autoreactive, and play physiological roles in healthy individuals (Avrameas et al. 2007). However, in autoimmune diseases a disbalance in immune response leads to loss of tolerance and persistent immune responses against self-antigens, causing tissular damage and loss of physiological homeostasis.

Autoimmune diseases are part of the so called immune-mediated inflammatory diseases (IMID), a term that refers to a heterogeneous group of conditions resulting from a deregulation of the immune response. They are usually caused by the interaction of genetic predisposition and environmental factors, including infectious and non-infectious agents (Wang, Wang, and Gershwin 2015). However, the precise etiology of many autoimmune diseases is poorly known. Autoimmune diseases can be mediated by autoantibodies, auto-reactive B cells and/or auto-reactive T cells. Their prevalence is between 3 and 5% of the general population (Eaton et al. 2007; Jacobson et al. 1997), and some of the most frequent ones are inflammatory bowel disease, multiple sclerosis (MS), type 1 diabetes, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), ankylosing spondylitis, and psoriasis and psoriatic arthritis (Agrawal et al. 2019).

4.2 Cancer immunology

The ability of the immune system to recognize stressed and damaged tissues also allows recognition and elimination of potential cancerous cells, a process known as immune surveillance (Burnet 1970). In fact, evasion of immune destruction was classified as an emerging hallmark of cancer by Hanahan and Weinberg (Hanahan and Weinberg 2011). Briefly, this means that immune surveillance can eliminate incipient cancerous cells and only those able to evade this detection and elimination can further proliferate and generate a tumor. However, the immune system can also facilitate tumor progression. The ability of the immune system to shape the phenotype of tumors towards either regression or progression is known as cancer immunoediting and consists of three phases: elimination, equilibrium and escape (Dunn, Old, and Schreiber 2004).

The elimination phase consists of an anti-tumor response that might be able to eliminate cancerous cells. It is based on an initial recognition of tissue remodeling and damage by the innate system, including macrophages, NK cells, NKT cells and/or γδ T cells, followed by secretion of pro-inflammatory cytokines such as interferon (IFN)-γ. Next, this pro-inflammatory environment and the release of tumor-associated antigens—antigens exclusively found in cancer cells—can induce an adaptative response, via DC presentation of these antigens and activation of specific $CD4^+$ and $CD8^+$ T lymphocytes, eventually killing tumor cells. Alternatively, less immunogenic variants of tumor cells may arise, reaching the equilibrium phase. In this case, the anti-tumor immune response can contain tumor growth but is not able to eliminate it completely. Finally, in the escape phase new genetic and epigenetic variations confer tumor cells resistance to the immune system and the tumor mass can grow and become clinically detectable. Escape mechanisms include secretion of anti-inflammatory cytokines (TGF-β, IL-10), recruiting cells with a suppressor phenotype such as regulatory T cells (Treg), myeloid derived suppressor cells (MDSC) and tumor associated macrophages, decreased recognition by the immune system (down-regulation of HLA class I and NKG2D ligands), and engagement of immune checkpoints (CTLA4–CD80/CD86 and PD-1–PD-L1 axes) (Dong et al. 2002; Dunn et al. 2004; Leach, Krummel, and Allison 1996).

Cancer cells interaction with the tumor microenvironment can shape tumor progression. The tumor microenvironment consists of immune, stromal, and endothelial cells. The immune microenvironment is formed by a variety of cell types, including T and B lymphocytes, macrophages, neutrophils, and MDSCs, which can either suppress or promote tumor growth. Depending on the degree of CD3 and CD8

infiltration, cancers can be classified according to the immunoscore, which is a predictor of prognosis and response to treatment. Generally, tumors with low immunoscores are referred to as “cold” tumors and tumors with high immunoscores are referred to as “hot” (Galon and Bruni 2019).

Knowledge on cancer immunology has led to the development of a family of cancer therapies based on the blockade of checkpoint axes such as the CTLA4–CD80/CD86 and the PD-1–PD-L1, known as immune checkpoint inhibitors. Several immune checkpoint inhibitor therapies have been approved by regulatory agencies such as the EMA and the FDA, and they include anti-CTLA4 (ipilimumab), anti-PD-1 (pembrolizumab, nivolumab, cemiplimab) and anti-PD-L1 (atezolizumab, avelumab, durvalumab) mAbs (Hargadon, Johnson, and Williams 2018). These treatments have been an advance in cancer therapy, having long term responses in certain cases. For instance, treatment with ipilimumab can increase 5-year survival from 10% to 20% in advanced-stage melanoma (Schadendorf et al. 2015). Nevertheless, many patients do not respond to these treatments, with varying response rates among different tumor types. Factors determining response to immune checkpoint inhibitors are not completely understood, but they include tumor mutational burden and, more importantly, the degree of T cell infiltration in tumors, with T-cell-inflamed tumors being more likely to respond (Maleki Vareki 2018).

II HYPOTHESIS AND OBJECTIVES

CD5 and CD6 are signal transducing lymphocyte receptors involved in the fine tuning of activation and differentiation events following specific antigen recognition by T and B1a cells. This is mainly based on their physical association with the clonotypic antigen-specific receptor complexes present on T (TCR) and B1a (BCR) cells, and their ability to recruit downstream molecular effectors either inhibiting or potentiating lymphocyte responses (Blaize et al. 2020; Cho and Sprent 2018; Mori et al. 2021). Besides, CD5 and CD6 are scavenger receptors involved in the recognition of different MAMPs. This makes them good candidates for natural selection pressure exerted by pathogens. Accordingly, CD5 has been identified as one of the genetic loci targeted by natural selection in recent evolution of human populations. There is compelling evidence showing that positively selected gene variants conferring increased resistance to infectious agents today are associated with increased risk for IMIDs but decreased risk of cancer, opposite sides of the same coin.

On this basis, we hypothesize that changes in the expression level or the amino acid sequence of CD5 and CD6 will also impact the susceptibility to or the phenotypical characteristics of immune mediated disorders such as IMIDs and cancer.

The general objective of the present thesis is to assess the immunomodulatory effect of *CD5* and *CD6* gene expression and variation in immune-mediated diseases.

The specific objectives of this thesis are the following:

- To evaluate the effects of *CD5* and *CD6* gene expression in experimental models of immune-mediated disorders.
- To evaluate the effects of genetic polymorphisms of *CD5* and *CD6* in patients undergoing immune-mediated disorders.

III MATERIALS AND METHODS

1 Mice

CD5 deficient mice (*Cd5*$^{-/-}$) (Tarakhovsky, Müller, and Rajewsky 1994) backcrossed for 12 generations into the C57BL/6 background were kindly provided by Dr. Chander Raman (Department of Medicine, University of Alabama in Birmingham). CD6 deficient mice (*Cd6*$^{-/-}$) in C57BL/6 background (Orta-Mascaró et al. 2016) were obtained through a development agreement with the Knockout Mouse Project (KOMP), an international consortium promoted by the National Institutes of Health (NIH; https://www.komp.org). Wild-type mice of the C57BL/6 background were purchased from Charles River Laboratories (France). Colonies of all genetically modified and wild-type mouse lines were bred in the animal facilities at Facultat de Medicina from Universitat de Barcelona. All mouse procedures were approved by the Animal Experimentation Ethical Committee from University of Barcelona.

2 Experimental colitis models

2.1 DSS-induced mouse colitis model

Colitis was induced by administration of 2% (w/v) 36-50 kDa dextran sulfate sodium (DSS) (MP Biomedicals) in drinking water for 5 days to 11- to 19- week-old wild-type, *Cd5*$^{-/-}$ or *Cd6*$^{-/-}$ female mice weighing >20 g. Body weight and disease activity index (DAI) were monitored every day. DAI was scored as follows: rectal bleeding (absent=0, present=1), animal motility (normal=0, reluctant=1, hunched=2), fur appearance (normal=0, ruffled=1, spiky=2) and body weight loss (none=0, 0-5%=1, 5-10%=2, 10-15%=3, >15%=4). At day 8, mice were euthanized by cervical dislocation for collection of blood and organ samples. Colons were measured and weighted, and pieces of ~2

mm were cut from the terminal part of the colon and submerged in RNA later (Sigma) o/n at 4 °C before being stored dry at -80 °C for further RNA analysis or fixed in phosphate-buffered saline (PBS) containing 4% paraformaldehyde (PFA) during 48 h for histological studies.

2.1.1 Measurement of hematological parameters

EDTA-anticoagulated blood was centrifuged in heparinised capillaries for 30 min at 1000 xg and haematocrit was calculated as the length of packed red blood cells (RBC) divided by the total blood length (RBC + serum) multiplied by 100. For RBC count, blood was diluted in PBS and RBC were counted with a haemocytometer.

2.1.2 Determination of microbial load in DSS-treated mice

Mesenteric lymph nodes (mLN) and liver were collected under sterile conditions and disaggregated through a 40 μm nylon mesh for overnight (o/n) seeding at 37 ºC on Columbia agar plates with 5% sheep blood (Becton-Dickinson) and colony forming units (CFU) counting.

2.1.3 RNA analysis

RNA was extracted from terminal colon pieces using the TRIzol® Reagent (Life Technologies) and the PureLink™ RNA Mini Kit (Ambion, Life Technologies) following manufacturer's instructions, with the aid of a QIAGEN TissueLyser. RNA was quantified and retrotranscribed into cDNA by using the High-capacity cDNA Kit (Life Technologies). Cytokine mRNA levels were assessed by real-time quantitative PCR (RT-qPCR) with the TaqMan™ Fast Universal PCR Master Mix No AmpErase™ UNG (Life Technologies) using a 7900HT fast real-time PCR system (Applied Biosystems, Foster City, CA, US) and the FAM gene expression assays listed in **Table III.1**, from

Thermo Fisher Scientific. Relative cytokine mRNA expression normalized to *Gapdh* (Mm99999915_g1) expression was calculated as $2^{-\Delta\Delta Ct}$, where $\Delta\Delta Ct = (CT_{Gene\ of\ interest\ sample} - CT_{GAPDH\ sample}) - (CT_{Gene\ of\ interest\ basal} - CT_{GAPDH\ basal})$.

2.1.4 Histological analyses

PFA-fixed samples were included in paraffin and 3 µm sections were obtained and stained with haematoxylin-eosin. Histology was scored by two independent evaluators according to the following parameters: degree of inflammation (0-3), goblet cell loss (0-2), abnormal or hyperproliferative crypts (0-3), abscesses (0-1), architectural damage (0-2), transmural damage (0-3). Images were obtained with an Eclipse 50i microscope, using a Pan Fluor 10x/0.30 objective and a Digital Sight DS-5M camera, all from Nikon.

2.2 Adoptive T-cell transfer colitis model

Spleen cells from euthanized mice were removed aseptically and disaggregated 70 µm nylon cell strainer. The resulting splenocyte suspension was used to obtain untouched $CD4^+$ cells by using the MojoSort™ Mouse CD4 Naïve T Cell Isolation Kit (BioLegend) according to the manufacturer's protocol. Naïve $CD4^+$ T cells were further purified by fluorescence-activated cell sorting (FACS). To this end, the cell suspension was stained with Fixable Viability Dye eFluor 450 (Thermo Fisher Scientific) at 1:1000, anti-CD45RB-FITC (clone C363-16A, BioLegend) at 1:100, and anti-CD4-BV510 (clone RM4-5, BioLegend) at 1:100. Labelled cells were sorted with a FACSAria III cell sorter (BD) to obtain $CD4^+CD45RB^{high}$ cells, following the gating strategy shown in **Figure III.1**.

Table III.1. TaqMan probes for RNA quantification

Gene	Protein	Assay number
Cd3e	T-cell surface glycoprotein CD3ε chain	Mm01179194_m1
Pdcd1	Programmed cell death protein 1 (PD-1)	Mm00435532_m1
Cd79a	B-cell antigen receptor complex-associated protein α chain (CD79A)	Mm00432423_m1
Ncr1	Natural cytotoxicity triggering receptor 1 (NKp46)	Mm01337324_g1
Klrc1	Natural killer cell receptor NKG2A	Mm00516111_m1
Mpo	Myeloperoxidase (MPO)	Mm00447885_m1
Lcn2	Neutrophil gelatinase-associated lipocalin (NGAL)	Mm01324470_m1
Nos2	Nitric oxide synthase, inducible (iNOS)	Mm00440502_m1
Ifng	Interferon-γ (IFN-γ)	Mm00801778_m1
Il17a	Interleukin-17A (IL-17A)	Mm00439619_m1
Il4	Interleukin-4 (IL-4)	Mm00445259_m1
Il10	Interleukin-10 (IL-10)	Mm00439614_m1
Il22	Interleukin-22 (IL-22)	Mm00444241_m1
Tnf	Tumor necrosis factor (TNF)	Mm00443260_g1
Il1b	Interleukin-1β (IL-1β)	Mm00434228_m1
Il6	Interleukin-6 (IL-6)	Mm00446190_m1
Tgfb1	Transforming growth factor β-1 (TGF-β-1)	Mm01178820_m1
Ccl3	C-C motif chemokine 3 (CCL3)	Mm00441259_g1
Cxcl1	C-X-C motif chemokine ligand 1 / Growth-regulated α protein (CXCL1)	Mm04207460_m1
Tbx21	T-box transcription factor TBX21 / T-bet	Mm00450960_m1
Rorc	Nuclear receptor ROR-γ	Mm01261022_m1
Gata3	Trans-acting T-cell-specific transcription factor GATA-3	Mm00484683_m1
Foxp3	Forkhead box protein P3 (FOXP3)	Mm00475162_m1

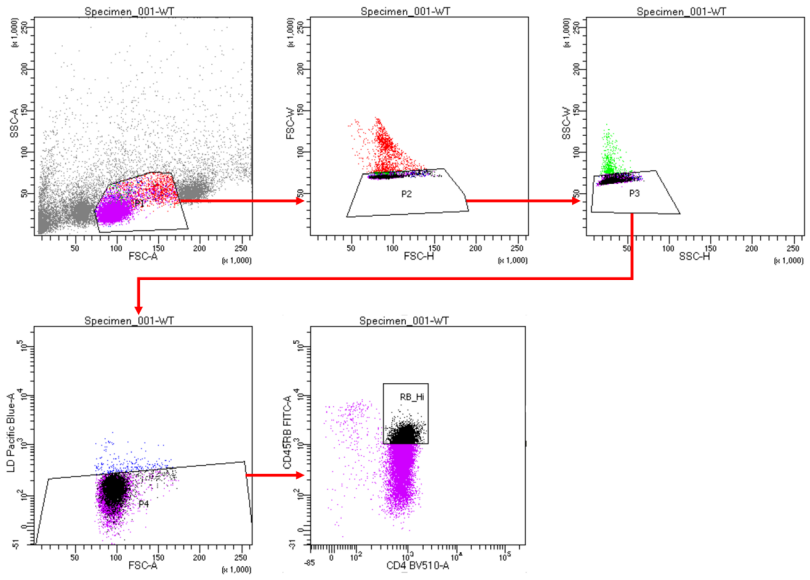


Figure III.1. Gating strategy for naïve CD4⁺ T-cell sorting. First a SSC-A vs FSC-A gating was used to select the lymphocyte population. Then, consecutive FSC-W vs FSC-H and SSC-W vs SSC-H gatings were used to select single cells. Next, live cells were selected as cells with low staining for the Viability Dye eFluor 450. Finally, CD4⁺ CD45RB^{high} cells were selected.

To induce colitis, $3 \cdot 10^5$ CD4⁺CD45RB^{low} cells obtained from either *Cd6*$^{-/-}$ mice or wild-type controls were intra-peritoneally injected into each Rag2$^{-/-}$ mouse. Body weight and disease activity index (DAI) were monitored every other day. DAI was scored as follows: rectal bleeding (absent=0, present=1), stool consistency (normal=0, loose=1, diarrhea=2), animal motility (normal=0, reluctant=1, hunched=2), fur appearance (normal=0, ruffled=1, spiky=2) and body weight loss (none=0, 0-5%=1, 5-10%=2, 10-15%=3, >15%=4). At day 8, mice were euthanized by CO_2 inhalation for collection of organ samples. Colons were measured, weighted, and used for lamina propria cell isolation.

2.2.1 Cell isolation from the lamina propria

Colons from euthanized mice were longitudinally opened and washed with Dulbecco's PBS. Epithelial cells were removed by 5 consecutive steps of 10-minute incubation in PBS + 5 mM EDTA at 37 °C, vortexing, and discarding supernatant. The remaining tissue (lamina propria) was cut into small pieces and digested for 20 min at 37 °C in RPMI 1640 (Gibco) containing 0.5 mg/mL collagenase VIII (Sigma) and 10 U/mL DNase I (Roche). Next, cells were isolated by passing through a 18G needle and a 70 μm nylon cell strainer. The obtained cell suspension was stained with Alexa Fluor 700-labeled anti-CD3 (clone 17A2, BioLegend), BV510-labeled anti-CD4 (clone RM4-5, BioLegend), and SuperBright 645 anti-CD45 (clone 30-F11, BioLegend) Abs.

3 Patient cohorts

Crohn's disease patients (n=1352) and ulcerative colitis patients (n=1013) were from the ENEIDA registry. The ENEIDA registry was developed and maintained by the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU) and consists of a genomic DNA biobank and an associated clinical database. The samples included in the present study were from patients attending the following hospitals, all in Spain: Hospital Clínic de Barcelona, Hospital de la Princesa, Hospital del Mar, Hospital la Paz, Hospital Universitari Mútua de Terrassa, Hospital San Jorge, Hospital Reina Sofía, Hospital Dr. Josep Trueta, Hospital Universitari Germans Trias i Pujol, Hospital Universitari de Bellvitge, Hospital Parc Taulí, Hospital de la Santa Creu i Sant Pau, Consorci Sanitari de Terrassa, and Hospital General de Tomelloso.

Consecutive primary Sjögren's syndrome (pSS) patients (n=212) attending to Hospital Clínic de Barcelona were included in the study. Patients fulfilled the 2002 criteria approved by the American-European Consensus Group (Shiboski et al. 2017; Vitali et al. 2002). Exclusion criteria for considering Sjögren's syndrome as a primary disease were chronic HCV/HIV infection, previous lymphoproliferative processes, and associated systemic autoimmune diseases. Diagnostic tests for pSS (ocular tests, parotid scintigraphy and salivary gland biopsy) were administered according to the European Community Study Group recommendations (Vitali et al. 1993).

PCa patients (n=376) attending the Urology Department of the Hospital Clínic de Barcelona, Spain. All patients were diagnosed with a prostate adenocarcinoma and were treated by means of radical prostatectomy, radiotherapy or prostate cryotherapy.

Unrelated healthy volunteers from the Banc de Sang i Teixits (BST) of Generalitat de Catalunya were included as controls for disease susceptibility analyses. A cohort of n=305 volunteers was used in the pSS study, and it was broadened to a sample size of n=604 in the IBD study to balance the case:control ratio.

All the studies were approved by the local Hospital Ethics Committees and written consent was obtained from all participants before inclusion.

3.1 Clinical data and definitions in the IBD cohort

Age of IBD onset was calculated as date of diagnosis − date of birth. The following extraintestinal manifestations were included: peripheral arthritis/arthralgia, ankylosing spondylitis, sacroiliitis, sclerosing cholangitis, cutaneous manifestations (pyoderma

gangrenosum or erythema nodosum), and ocular manifestations (uveitis or iritis). Requirement of biological treatments included treatment with adalimumab, certolizumab, golimumab, infliximab, natalizumab, vedolizumab, and ustekinumab. Prognosis was calculated as previously described: patients not requiring any immunomodulatory nor surgical treatment during at least 4 years of follow-up from diagnosis were classified as "good prognosis" while patients requiring two or more immunomodulatory treatments and/or two or more abdominal surgeries were described as "poor prognosis" (Lee et al. 2017).

Location (terminal ileum, colon, ileocolon, and upper gastro-intestinal) and behaviour (nonstricturing and nonpenetrating, structuring, and penetrating) of CD were classified according to the Montreal classification (Silverberg et al. 2005). For statistical analysis of location, a value of 1 was assigned to patients with colonic disease, 2 to patients with ileocolonic disease and 3 to patients with ileal disease, independently of upper gastro-intestinal tract involvement. Upper gastro-intestinal tract involvement (presence *vs*. absence) was assessed independently of distal ileal and colonic involvement. To generate stenosis-free survival and fistulae-free survival curves, time between enrolment and complication (patients with stenosis or fistulae) or between enrolment and last follow-up (patients without stenosis or fistulae) was calculated.

For statistical analysis of extent in UC patients, a value of 0 was assigned to patients with ulcerative proctitis (Montreal classification E1) and a value of 1 was assigned to patients with left-sided UC or extensive UC (Montreal classification E2 and E3). Description of the IBD cohorts is shown in **Table III.2**.

Table III.2. Clinical characteristics of the IBD study cohorts. Number of patients is shown for categorical parameters. Median and interquartile range is shown for numerical parameters.

Parameter	CD (n=1352)	UC (n=1013)	IBD (n=2365)
Sex			
Male	661 (48.9 %)	530 (52.3 %)	1191 (50.3 %)
Female	691 (51.1 %)	483 (47.7 %)	1174 (49.6 %)
Ethnicity			
Caucasian	1173	856	2029
Arab	13	10	23
Asian	6	3	9
African	5	3	8
Jew	4	1	5
Gipsy	3	3	6
Other	11	6	17
Smoking*	380 (28.1 %)	108 (10.7 %)	488 (20.6 %)
Age at diagnosis (years)	29.7 (22.4, 41.2)	35.2 (26.8, 47.8)	32.0 (23.7, 44.2)
Follow-up (years)	12.0 (7.4, 19.2)	12.4 (7.4, 19.2)	12.2 (7.4, 19.2)
Extra-intestinal manifestations			
Peripheral arthritis			287 (12.1 %)
Ankylosing spondylitis			73 (3.1 %)
Sacroiliitis			68 (2.9 %)
Sclerosing cholangitis			22 (0.9 %)
Cutaneous			158 (6.7 %)
Ocular			56 (2.4 %)
Location			
Colonic	234 (17.3 %)		
Ileocolonic	631 (46.7 %)		
Ileal	355 (26.3 %)		
Phenotype			
Stricturing	342 (25.3 %)		
Penetrating	251 (18.6 %)		
Perianal disease	361 (26.7 %)		
Extent			
Proctitis		153 (15.1 %)	
Left or extensive colitis		828 (81.7 %)	
Biological treatments	809 (59.8 %)	282 (27.8 %)	1091 (46.1 %)
Prognosis			
Good	137 (10.1 %)	441 (43.5 %)	578 (24.4 %)
Poor	577 (42.7 %)	232 (22.9 %)	809 (34.2 %)

(*) persistent habit at the last follow-up

3.2 Clinical data and definitions in the pSS cohort

Disease diagnosis was defined as the time when the attending physician confirmed fulfillment of the 2002 revised European criteria proposed by the American-European Consensus Group (Vitali et al. 2002). The main disease features were retrospectively collected and analyzed. The following clinical variables were selected for harmonization and further refinement: age, gender, ethnicity, country of residence, fulfillment of the 2002 criteria items, antinuclear antibodies (ANA), rheumatoid factor (RF), C3 and C4 levels, cryoglobulins. The epidemiological variables included in this study were age at diagnosis, gender and ethnicity according to Food and Drug Administration (FDA) definitions (Anon 1997). Systemic involvement at diagnosis was retrospectively classified and scored according to the EULAR Sjögren's syndrome disease activity index (ESSDAI) (Seror et al. 2010), which evaluates 12 domains or organ systems, and the ClinESSDAI (Seror, Meiners, et al. 2016), which evaluates the same domains but excluding the last (biological) domain. Each domain is divided into 3-4 levels according to the degree of activity and scored as 0 (no activity), 1 (low activity), 2 (moderate activity) or 3 (high activity) (Seror et al. 2015). Disease activity states (DAS) were calculated as: no activity (global score = 0), low activity (global score 1-4), moderate activity (global score 5-13) and high activity (global score ≥14) (Seror, Bootsma, et al. 2016).

Additionally, cumulative systemic involvement was also classified and scored according to the ESSDAI. Cumulative systemic involvement was defined as the systemic activity present since diagnosis of pSS to the last medical visit. Death and cause of death related to cancer were collected through the medical records. General characteristics of the pSS patient cohort are shown in **Table III.3**.

Table III.3. General characteristics of the cohort of pSS patients.

Variables	**n (%)**
Gender (Female)	202 (95.3)
Ethnicity (Caucasian)	201 (94.8)
Age at diagnosis	54 (14.4)
Dry mouth	212 (100)
Dry eyes	205 (96.7)
Schirmer's test (abnormal)	185/194 (95.4)
Salivary scintigraphy (abnormal)	163/180 (90.6)
Minor salivary gland biopsy (positive)	103/113 (91.2)
ANA (positive)	181/211 (85.8)
RF (positive)	98/208 (47.1)
Anti-Ro/La antibodies (positive)	151 (71.2)
Anti-Ro (SSA)	143 (67.5)
Anti-La (SSB)	103/211 (48.8)
Monoclonal gammopathy	25/142 (17.6)
Low C3 levels (<0.82 g/L)	19/210 (9)
Low C4 levels (<0.11 g/L)	13/207 (6.3)
Cryoglobulins (positive)	17/201 (8.5)
Cytopenias	
Anemia (Hb < 110 g/L)	43/211 (20.4)
Leukopenia (<4000/mm^3)	57/211 (27)
Thrombocytopenia (<150000/ mm^3)	23/211 (10.9)
Neutropenia (<1500/mm^3)	53/211 (25.1)
Lymphopenia (<1000/mm^3)	21/211 (10)
ESSDAI domains	
Constitutional	28 (13.2)
Lymphadenopathy	27 (12.7)
Glandular	60 (28.3)
Articular	93 (43.9)
Cutaneous	37 (17.5)
Pulmonary	41 (19.3)
Renal	5 (2.4)
Muscular	1 (0.5)
Peripheral nervous system	23 (10.8)
Central nervous system	8 (3.8)
Hematological	159 (75)
Biological	141 (66.5)
Total ESSDAI (baseline)	7.4 (6.8)
Total ESSDAI (cumulative)	10.2 (8.5)

3.3 Clinical data and definitions in the PCa cohort

Clinical data, including age, ISUP grade group, therapies (radical prostatectomy, cryotherapy, radiotherapy), biochemical recurrence (BR), metastases, and PCa-related death, was retrospectively collected from medical records. BR was defined as increase of prostate-specific antigen (PSA) >0.2 ng/mL after radical prostatectomy or increase of PSA >2 ng/mL over nadir after radiotherapy or cryotherapy. General characteristics of the PCa patient cohort are shown in **Table III.4**.

Table III.4. Characteristics of the PCa patient cohort (n=376).

Age (years). Mean (SD)	68.7 (7.3)
PSA at diagnosis (ng/mL). Mean (SD)	8.4 (4.6)
ISUP grade group, *n* (%)	
1	126 (33.5 %)
2	149 (39.6 %)
3	67 (17.8 %)
4	17 (4.5 %)
5	13 (3.5 %)
Unknown/missing	4 (1.1 %)
Treatment	
Radical prostatectomy	287 (77.2 %)
Radiotherapy	9 (2.4 %)
Cryotherapy	76 (20.4 %)
Pathology after radical prostatectomy, *n* (%)	
pT2	237 (82 %)
pT3	47 (16 %)
Positive margins	70 (24 %)
Follow-up (months). Median (interquartile range)	62.00 (31.00, 77.00)
BR, *n* (%)	119 (31.6 %)
Time to BR (months). Median (interquartile range)	25.00 (12.00, 48.00)
Metastases, *n* (%)	5 (1.3 %)
PCa related death, *n* (%)	6 (1.6 %)

4 Genomic DNA analyses

Genomic DNA samples from the patient cohorts were provided by the respective organizations: ENEIDA/GETECCU for CD and UC, and the Autoimmune Diseases and Urology Departments of the Hospital Clínic de Barcelona for pSS and PCa patients, respectively. Genomic DNA samples from BST controls were purified by using the MagNA Pure 96 DNA and Viral NA Large Volume Kit (Roche Diagnostics) and the High-throughput robotic workstation MagNA Pure 96 (Roche Diagnostics).

Genomic DNA samples (20 ng) were subjected to real-time PCR (RT-PCR) in a LightCycler® 480 Instrument (Roche) using the TaqMan Genotyping Master Mix and the TaqMan genotyping probes listed in **Table III.5**, and all from Thermo Fisher Scientific, and following manufacturer's instructions.

Table III.5. TaqMan probes for SNP genotyping

Gene	SNP	Assay number
CD5	rs2241002	C__25472293_20
	rs2229177	C___3237272_10
CD6	rs17824933	C__33967506_10
	rs11230563	C__31727142_10
	rs12360861	C__25922320_10
CD166/ALCAM	rs6437585	C__29281365_20

The *CD166/ALCAM* rs579565, rs1044243 and rs35271455 SNPs, which lie in a SNP hotspot spanning 7 bp at exon 9, were PCR amplified for further sequence-based typing (PCR-SBT) using the Hs00666884_CE assay from Thermo Fisher Scientific.

5 *CD5* variants expression and transcriptome analysis of Daudi cells

The Ala471 or Val471 variants of CD5 were stably expressed on Daudi cells for further transcriptomic analyses. To this end, codon-optimized versions of cDNA encoding the Ala471 or the Val471 variants were synthesized by GenScript (Leiden, Netherlands) and cloned into the lentiviral pLVX-Puro expression vector. The packaging cell line HEK293T was co-transfected with such pLVX-Puro vectors and the packaging plasmids pCMV-VSV-G and psPAX with the Lipofectamine2000 kit (Thermo Fisher Scientific). After 3 days in culture with complete DMEM medium (**Table III.6**), lentiviral particle rich supernatants were collected and purified by centrifugation and 0.45 µm filtration.

Table III.6. Composition of complete media.

Medium	Component	Concentration	Provider
Complete DMEM	Dulbecco's modified Eagle's medium (DMEM) with glutamine	Base	Gibco
	Fetal bovine serum	10%	Sigma-Aldrich
	Penicillin	100 UI/mL	Laboratorios ERN
	Streptomycin	100 µg/mL	Laboratorios Normon
Complete RPMI	RPMI 1640	Base	Sigma-Aldrich
	Fetal bovine serum	10%	Sigma-Aldrich
	Penicillin	100 UI/mL	Laboratorios ERN
	Streptomycin	100 µg/mL	Laboratorios Normon

For lentiviral transduction, Daudi cells were incubated for 48 h with lentiviral particles coding for either Ala471 or Val471 CD5 variants in presence of polybrene (Merck Millipore). Transduced cells were first selected in complete RPMI (**Table III.6**) containing puromycin (1 µg/µL; Gibco) and further subjected to cell sorting in a BD FACSAria

after staining with a PerCP-Cy5.5 anti-human CD5 antibody (clone 53-7.3, BioLegend).

Daudi cells stably expressing CD5 were incubated in complete RPMI medium with for 24 h in presence of either 10 μg/mL of anti-IgM $F(ab')_2$ antibody (Jackson ImmunoResearch) or 1 μg/mL anti-CD5 mAb (CRIS-1, Exbio), or in absence thereof. Then, expression of surface markers was determined by flow cytometry with the mAbs from **Table III.7** and RNA was extracted for RNAseq.

Table III.7. mAb cocktail used for assessment of Daudi cell activation.

Specificity	Fluorochrome	Clone	Provider
CD40	BV421	5C3	BD Pharmigen
CD69	PE-Cy7	L78	BD Biosciences
CD80	FITC	MEM-233	ImmunoTools
CD83	PE	HB15e	BioLegend
CD86	APC	FUN-1	BD Biosciences

RNA extraction was carried out with the RNeasy Mini Kit (Qiagen). cDNA libraries for sequencing were prepared with the NEBNext rRNA Depletion Kit and the NEBNext Ultra II Directional RNA Library Prep Kit for Illumina (New England BioLabs) for sequencing in a MiSeq platform (Illumina). Sample processing for library preparation was performed by the Translational Genomics facility at IGTP, sequencing was performed at the CRG Genomics facility, and data analysis was performed with support from the High Content Genomics and Bioinformatics Facility at IGTP.

Initial exploratory analysis and data normalization was performed using the DESeq2 package. Then, a gene ontology enrichment analysis for biological processes was performed with the GOrilla web tool, using default settings (Eden et al. 2009). Results with padj<0.05 for the mHG test were selected.

6 Statistical analyses

In the mouse model studies, normality of data was assessed with the D'Agostino & Pearson normality test. When data was normally distributed, differences were assessed by t-tests, otherwise Mann-Whitney tests were performed. In multiple comparisons, P values were corrected for false discovery rate (FDR).

Statistical analysis in patient/donor cohort studies was performed with R 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria), with the packages 'SNPassoc', 'survival', and 'haplo.stats' available at the Comprehensive R Archive Network (CRAN) repository. The 'association' function included in the 'SNPassoc' package was used to assess linkage between each SNP and desired clinical variables with generalized linear models. For each analysis, 4 models were generated (codominant, dominant, recessive, log-additive), and the model with lowest Akaike information criterion (AIC) was chosen. Overdominant models were not considered. P values were corrected for FDR with the 'p.adjust' function (Q values). Cox proportional hazards regression was used in survival analyses. For haplotypic analyses, putative haplotypes were inferred with the expectation-maximization (EM) algorithm. The 'haplo.glm' function included in the 'haplo.stats' package was then used to assess linkage between haplotypes and binary clinical variables with generalized linear models. Odds ratio (OR) and confidence intervals (CI) for such associations were obtained with the 'haplo.cc' function.

IV RESULTS

1 CD5 and CD6 deficiency in immune-mediated experimental disorders

1.1 CD5 and CD6 deficiency in DSS-induced colitis

The putative role of CD5 and CD6 lymphocyte co-receptors in the pathophysiology of immune-mediated disorders was first explored by subjecting *Cd5*$^{-/-}$ and *Cd6*$^{-/-}$ mice to the DSS-induced colitis, a well-accepted experimental model for IBD studies (Kiesler, Fuss, and Strober 2001). *Cd5*$^{-/-}$ mice showed a less aggressive disease than WT *Cd5*$^{+/+}$ controls (**Figure IV.1A**), as deduced from lower body weight loss and DAI, in agreement with a previously published result (Dasu et al. 2008). In contrast, *Cd6*$^{-/-}$ mice showed an exacerbated

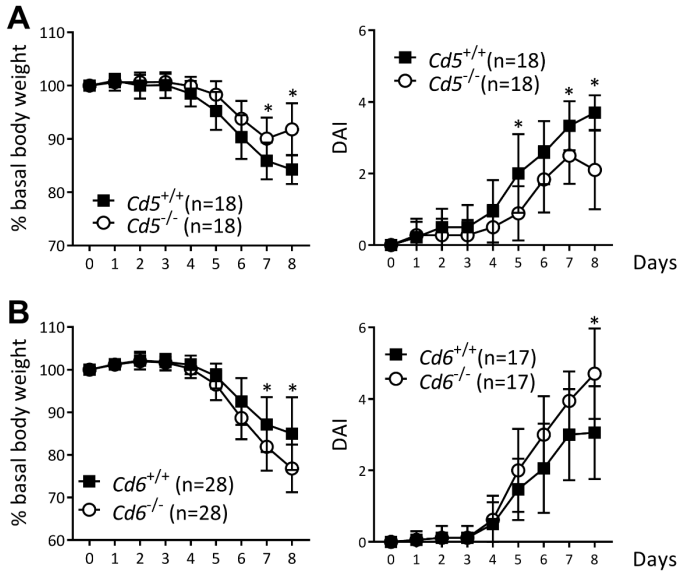


Figure IV.1. DSS-induced colitis in *Cd5*$^{-/-}$ and *Cd6*$^{-/-}$ mice *vs.* wild-type controls. Percentage of basal body weight (left) and DAI (right) of *Cd5*$^{-/-}$ mice *vs. Cd5*$^{+/+}$ controls (**A**) and *Cd6*$^{-/-}$ mice *vs. Cd6*$^{+/+}$ controls (**B**). Mean ± SD values are depicted. Statistical differences were assessed by multiple t-tests (one per day) controlled with the FDR approach. *, q<0.01.

phenotype with regard to WT *Cd6*$^{+/+}$ controls. Particularly, *Cd6*$^{-/-}$ mice presented increased body weight loss (**Figure IV.1B, left**) and DAI (**Figure IV.1B, right**). The latter was influenced at the expense of body weight loss and rectal bleeding.

It is worth mentioning that severity of DSS-induced colitis was season-dependent; *Cd6*$^{-/-}$ mice lost more weight than the *Cd6*$^{+/+}$ controls when DSS colitis was induced during the spring/summer but not during the autumn/winter (**Figure IV.2**), a situation reminiscent of that reported for other mouse models of human diseases (e.g.: EAE) (Teuscher et al. 2004), and for the onset of symptoms IBD in patients, which occurs more commonly in the spring or summer (Peng, Ran, and Shen 2015).

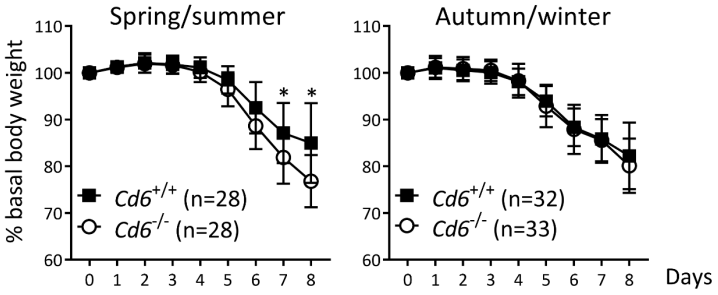
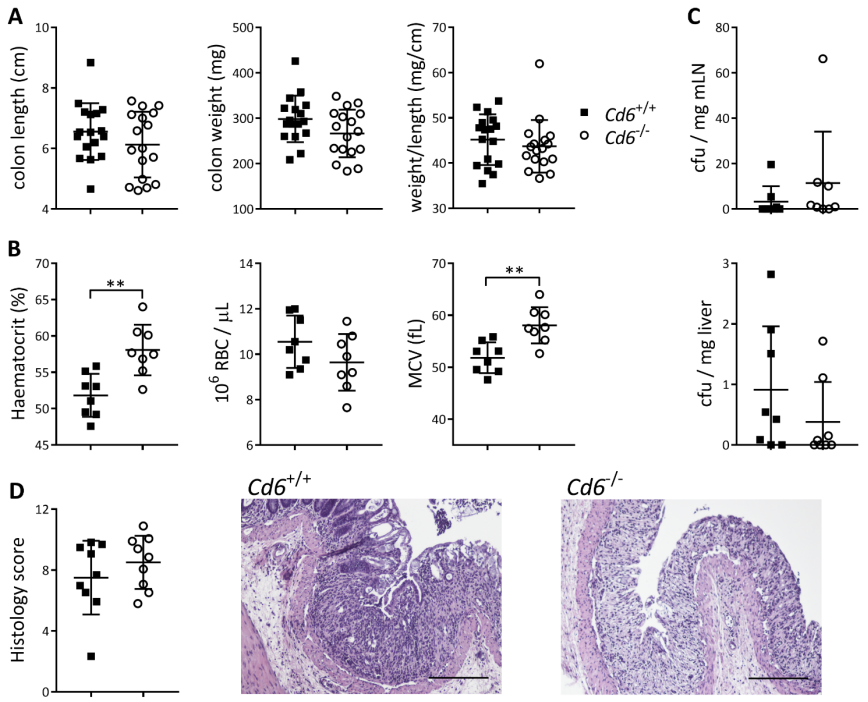


Figure IV.2. Seasonal effect on DSS-induced colitis. Percentage of basal body weight of *Cd6*$^{-/-}$ mice *vs*. *Cd6*$^{+/+}$ controls during spring/summer (same mice as in B) or autumn/winter. In each graph is depicted the mean ± SD of four independent experiments. Statistical differences were assessed by multiple t-tests (one per day) controlled with the FDR approach. *, q<0.01.

The lack of published information on the DSS-induced colitis model in *Cd6*$^{-/-}$ mice encouraged a deeper evaluation of different experimental parameters at the end of disease follow-up (day 8). No differences were observed in colon length, weight, or weight/length ratio relative to *Cd6*$^{+/+}$ controls (**Figure IV.3A**). As illustrated in **Figure IV.3B**,

Cd6$^{-/-}$ mice presented increased haematocrit (consistent with higher diarrhoea-induced fluid loss), and a trend to lower RBC counts together with increased MCV (consistent with moderate rectal bleeding and erythroblast production (Kirby et al. 2020)), respectively. No CFU count differences were observed in mLN and liver (**Figure IV.3C**), arguing against increased bacterial translocation to draining organs as responsible for the differences observed in disease severity. Histological analyses showed noticeable crypt architectural distortion in colon samples from both *Cd6*$^{+/+}$ and *Cd6*$^{-/-}$ mice, though no significant differences between their histology scores could be observed (**Figure IV.3D**).

Gene expression analyses of a wide panel of mRNA transcripts was performed, including pro-/anti-inflammatory cytokines and chemokines, transcription factors, and cell surface markers (see **Table III.1** from Materials and Methods section). Decreased levels of *Ifng*, *Cd3e*, *Ncr1* and *Gata3* transcripts together with increased expression of *Il6* and *Cxcl1* were observed in *Cd6*$^{-/-}$ mice with regard to WT controls (**Figure IV.4**). A trend towards increased expression of *Ncr1* was also observed. Expression of *Il4*, a target of GATA3, was also analyzed but is not depicted because it was undetectable in a high proportion of samples. In general, these results point towards a decreased Th1, Th2 and NK responses, a conserved Th17 response, and increased neutrophil function in *Cd6*$^{-/-}$ mice. However, these are not accompanied by detectable differences in macroscopic or histological damage.



↑ Figure IV.3. Monitoring of DSS-induced colitis parameters from *Cd6*$^{-/-}$ mice *vs.* *Cd6*$^{+/+}$ controls at day 8 post-induction. (**A**) Dot plot showing colon length, weight and weight/length ratio of *Cd6*$^{-/-}$ (n=17) and *Cd6*$^{+/+}$ control (n=17) mice. Mean ± SD values are depicted. Statistical differences were assessed by t-test. (**B**) Haematocrit, RBC count and mean corpuscular volume (MCV) at day 8 from *Cd6*$^{-/-}$ (n=8) and *Cd6*$^{+/+}$ (n=8). Mean ± SD values are depicted. Statistical differences were assessed by t-test. *, p<0.05; **, p<0.01. (**C**) Analysis of microbial translocation into mesenteric lymph nodes (mLN; top) and liver (bottom) from the same mice as in **B**. Depicted are mean ± SD of CFU/mg. Statistical differences were assessed by Mann-Whitney tests. (**D**) Histology score (mean ± SD, left) and representative haematoxylin-eosin stain of the terminal colon from *Cd6*$^{+/+}$ (left) and *Cd6*$^{-/-}$ (right) DSS-treated mice. Scale bar: 200 µm. Statistical differences were assessed by t-test.

→ Figure IV.4. mRNA expression in colon samples from mice undergoing DSS-induced colitis. Expression of mRNA transcripts in colon samples from *Cd6*$^{-/-}$ mice and *Cd6*$^{+/+}$ controls (the same mice as in Figure IV.3B). Depicted are mean ± SD of mRNA fold increase (DSS/basal). Statistical differences were assessed by Mann-Whitney tests. *, p<0.05.

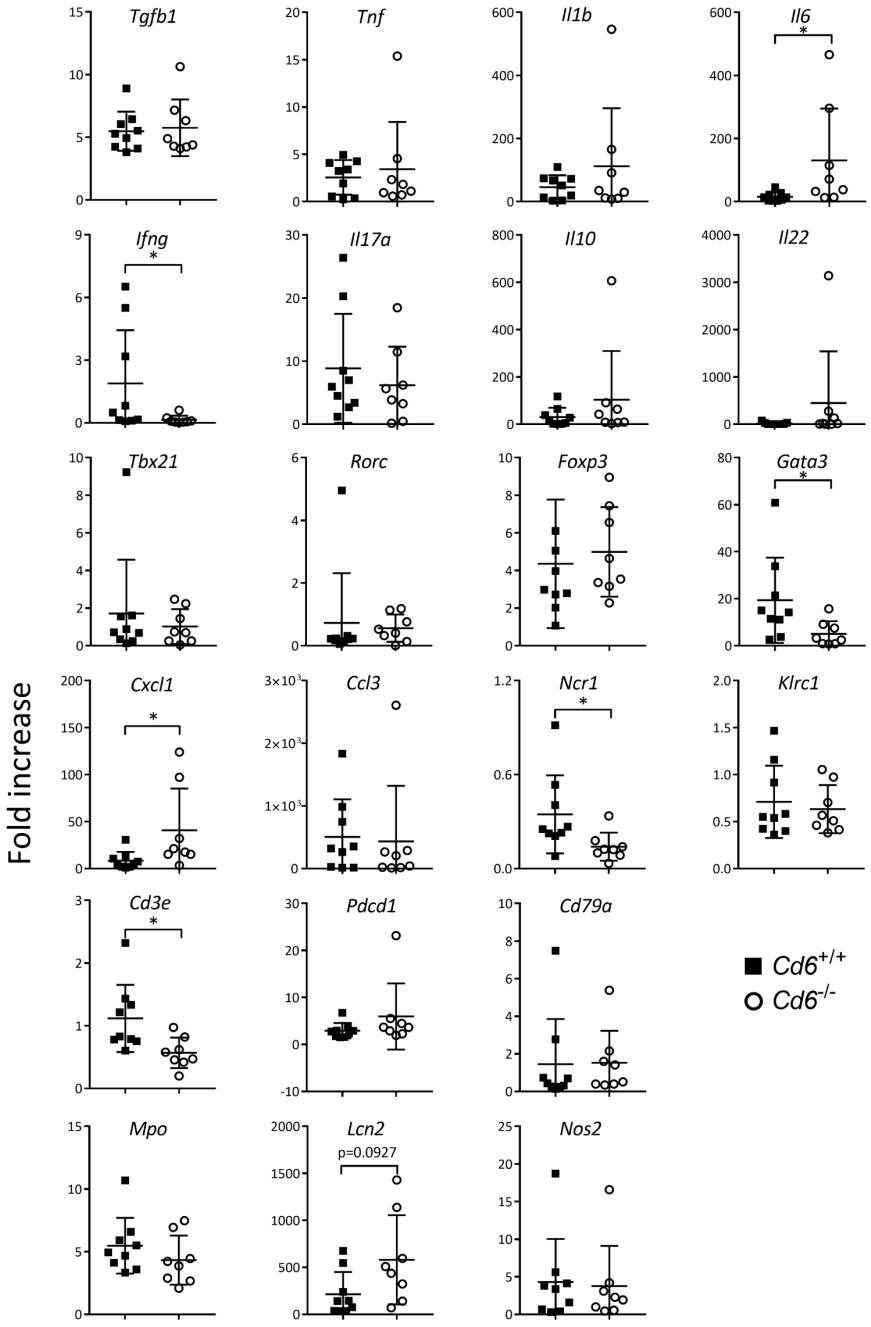

Fold increase
Tgfb1
Tnf
Il1b
Il6
Ifng
Il17a
Il10
Il22
Tbx21
Rorc
Foxp3
Gata3
Cxcl1
Ccl3
Ncr1
Klrc1
Cd3e
Pdcd1
Cd79a
Mpo
Lcn2
p=0.0927
Nos2
Cd6+/+
Cd6-/-

Figure IV.4.

1.2 CD6 deficiency in naïve CD4+ T cell adoptive transfer colitis

To test the relevance of CD6 in the colitogenic capacity of naïve T CD4+ cells, *Rag2*$^{-/-}$ mice were injected *i.p.* with naïve T CD4+ cells from either *Cd6*$^{-/-}$ mice or *Cd6*$^{+/+}$ controls. Upon follow-up, mice did not show any significant differences in terms of weight loss or DAI (**Figure IV.5A**). No differences were observed in the colon weight, length, and weight/length ratio of these mice (**Figure IV.5B**). As

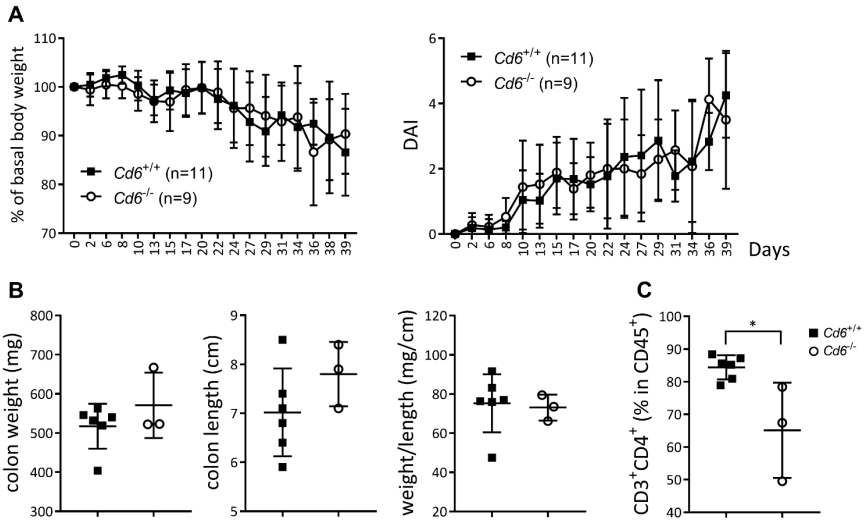


Figure IV.5. Experimental colitis model induced by adoptive transfer of naïve CD4+ T cells from *Cd6*$^{-/-}$ or wild-type (*Cd6*$^{+/+}$) mice into immunodeficient R*ag2*$^{-/-}$ mice. (**A**) Percentage of basal body weight (left) and DAI (right) of *Rag2*$^{-/-}$ mice injected *Cd6*$^{-/-}$ *vs. Cd6*$^{+/+}$ naïve CD4+ T cells. Mean ± SD values of two independent experiments are depicted. Statistical differences were assessed by multiple t-tests (one per day) controlled with the FDR approach. *, q<0.01. (**B**) Dot plot showing colon length, weight, and weight to length ratio of *Cd6*$^{-/-}$ (n=6) and *Cd6*$^{+/+}$ control (n=3) mice. Mean ± SD values are depicted. Statistical differences were assessed by Mann-Whitney tests. (**C**) Dot plot showing percentage of CD3+CD4+ cells in the CD45+ population of the colonic lamina propria from the same mice as in B. Mean ± SD values are depicted. Statistical differences were assessed by Mann-Whitney tests. *, p<0.01.

shown in **Figure IV.5C**, flow cytometry staining of the lamina propria cells showed decreased $CD3^+CD4^+$ infiltration among the immune ($CD45^+$) population. This argues against differences in the colitogenic capacities of naïve T $CD4^+$ cells from *Cd6*$^{-/-}$ mice and *Cd6*$^{+/+}$ controls.

2 *CD5* and *CD6* gene variation in immune-mediated clinical disorders

2.1 Impact of *CD5* and *CD6* gene variation on clinical expression of IBD

CD (n=1352) and UC (n=1013) patients from the ENEIDA registry and volunteer blood donor controls (n=604) from BST were genotyped for functionally relevant *CD5* (rs2229177, rs2241002) and *CD6* (rs12360861, rs11230563, rs17824933) SNPs. The study also included a functionally relevant SNP (rs6437585) located at the 5'UTR of *CD166/ALCAM*, the main reported CD6 ligand (Zhou et al. 2011). All SNPs were in Hardy-Weinberg equilibrium, except for the rs2241002 in the CD cohort (p=0.028). Description of the IBD cohorts is shown in **Table III.2** from the Materials and Methods section.

No significant association with disease susceptibility was found for the individual SNPs analysed following comparisons of controls with the CD and UC cohorts, either separately (CD *vs.* controls, UC *vs.* controls) or together (IBD *vs.* controls).

Next, the effect of the aforementioned *CD5*, *CD6* and *CD166/ALCAM* gene variants on different clinically relevant parameters of CD (age at diagnosis, behaviour, location, perianal disease, biological therapy requirement, and prognosis) and UC (age at diagnosis, extent, biological therapy requirement, and prognosis) was assessed. Sex and smoking are known disease modifying factors in IBD, so they were included as co-variants in all single SNP analyses. In all cases

inclusion of such factors improved the goodness of fit of the statistical models, measured as a decrease in the AIC. In the case of *CD5*, a significant association was found for the *CD5* rs2241002^{CC} genotype with preferential ileal location in the CD cohort (**Table IV.1**).

Table IV.1. Linear regression analysis of *CD5* rs2241002 SNP association with CD location*, corrected for sex and smoking.

Model	Genotype	n	mean	s. e.	Difference of means (95% CI)	*q* value
Dominant	C/C	738	2.148	0.025		0.005
	C/T-T/T	414	2.005	0.035	-0.142 (-0.224, -0.059)	

(*) Variable "location" is codified as: colonic=1, ileocolonic=2, ileal=3.

It is known that CD location can influence the risk of developing stenosis and fistulae. Given the association of the rs2241002 SNP with CD location, the effect of this SNPs on stenosis-free and fistulae-free survival was tested, with not significant results found as shown in **Figure IV.6**.

Haplotypic analyses showed increased need of biologic therapies in CD patients carrying the *CD5* rs2241002^{C} rs2229177^{T} haplotype compared with those carrying the most common rs2241002^{C} rs2229177^{C} haplotype (**Table IV.2**). Similarly, UC patients carrying the *CD5* rs2241002^{T} rs2229177^{T} haplotype had a worse prognosis than those carrying the most common rs2241002^{C} rs2229177^{C} haplotype (**Table IV.2**).

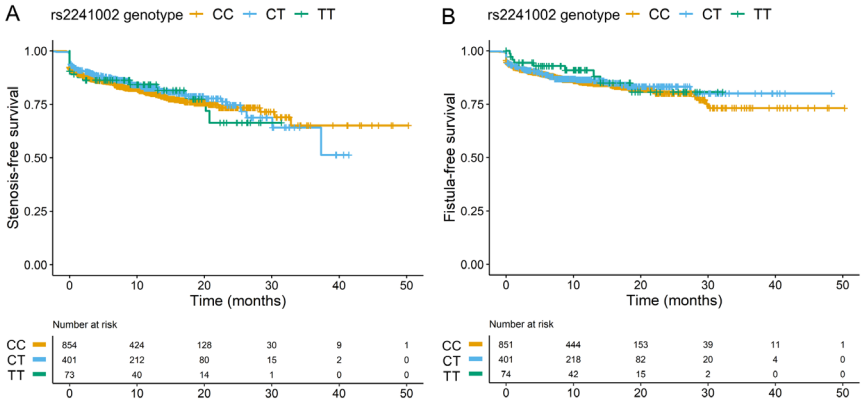


Figure IV.6. Stenosis and fistulae in CD patients according to rs2241002. Stenosis-free survival (A) and fistulae-free survival (B) of CD patients carrying different allelic combinations of *CD5* rs2241002 SNP. Statistical differences were assessed by the Cox proportional hazards model. In the stenosis-free survival analysis (A) HR comparing rs2241002^{TT} with rs2241002^{CC} was 0.93, (95% CI 0.57–1.50), p = 0.753, and HR comparing rs2241002^{CT} with rs2241002^{CC} was 0.88, (95% CI 0.70–1.12), p = 0.316. In the fistula-free survival analysis (A) HR comparing rs2241002^{TT} with rs2241002^{CC} was 0.81, (95% CI 0.45–1.46), p = 0.481, and HR comparing rs2241002^{CT} with rs2241002^{CC} was 0.92, (95% CI 0.70–1.21), p = 0.561.

Table IV.2. Logistic regression analysis of *CD5* haplotype association with biological therapy requirement in CD (top half) and to prognosis in UC (bottom half).

Haplotype		% in CD patients	Biological therapies		*p* val	OR (95% CI)
			% no	% yes		
rs2241002	rs2229177					
C	C	43.4	45.3	42.2		
C	T	35.9	33.4	37.5	**0.048**	1.20 (1.00, 1.44)
T	T	17.0	17.4	16.7	0.811	1.02 (0.83, 1.27)
T	C	3.7	3.8	3.7	0.861	1.05 (0.64, 1.72)
Haplotype		% in UC patients	Prognosis		*p* val	OR (95% CI)
			% good	% poor		
rs2241002	rs2229177					
C	C	43.3	45.2	39.5		
C	T	37.1	37.1	37.2	0.345	1.14 (0.87, 1.49)
T	T	14.9	13.7	17.0	**0.048**	1.42 (1.00, 2.02)
T	C	4.7	3.9	6.3	0.097	1.78 (0.90, 3.51)

CD6 SNPs, were also tested for associations with all the mentioned CD and UC parameters. The rs17824933^{GG} genotype was found associated with preferential ileal location in CD patients (**Table IV.3**). Again, because CD location can influence the risk of developing stenosis and fistulae, association between the rs17824933 SNPs and stenosis-free and fistulae-free survival was tested. As seen in **Figure IV.7** the rs17824933^{GG} genotype was found associated with shorter fistula-free survival (HR = 1.56, 95% CI 1.01–12.42, p = 0.046).

Table IV.3. Linear regression analysis of *CD6* rs17824933 SNP association with CD location*, corrected for sex and smoking.

Model	rs17824933 genotype	n	mean	s. e.	Difference of means (95% CI)	*q* value
Recessive	C/C-C/G	1074	2.081	0.021		0.022
	G/G	77	2.299	0.074	0.218 (0.060, 0.377)	

(*) Variable "location" is codified as: colonic=1, ileocolonic=2, ileal=3.

Moreover, the *CD6* minor rs12360861^{A} allele showed association with better prognosis in CD patients (**Table IV.4**). After testing *CD6* SNPs for association with UC parameters, association of the *CD6* rs17824933^{GG} genotype with higher extent (left or extensive colitis) was revealed (**Table IV.4**).

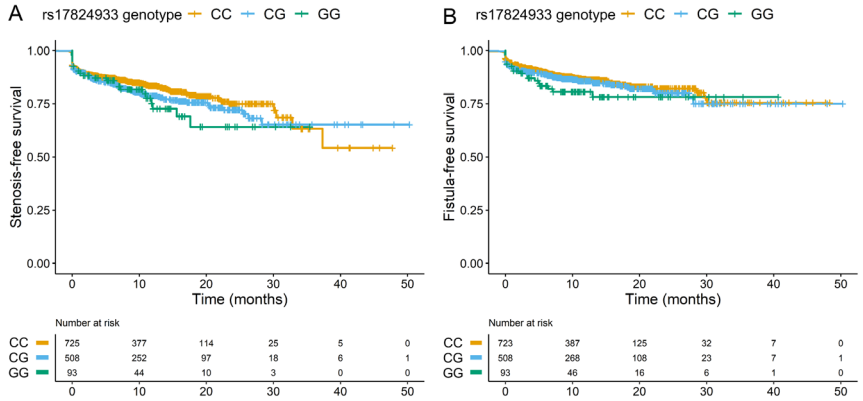


Figure IV.7. Stenosis and fistulae in CD patients according to rs17824933. Stenosis-free survival (A) and fistulae-free survival (B) of CD patients carrying different allelic combinations of *CD5* rs17824933 SNP. Statistical differences were assessed by the Cox proportional hazards model. In the stenosis-free survival analysis (A) HR comparing rs17824933^{GG} with rs17824933^{CC} was 1.28, (95% CI 0.85–1.92), p = 0.230, and HR comparing rs17824933^{CG} with rs17824933^{CC} was 1.05, (95% CI 0.84–1.31), p = 0.671. In the fistula-free survival analysis (B) HR comparing rs17824933^{GG} with rs17824933^{CC} was 1.56, (95% CI 1.01–12.42), p = 0.046, and HR comparing rs17824933^{CG} with rs17824933^{CC} was 1.19, (95% CI 0.92–1.55), p = 0.195.

CD5, *CD6* and *CD166/ALCAM* SNP association with IBD extraintestinal manifestations was also assessed. These included peripheral arthritis/arthralgia, ankylosing spondylitis, sacroiliitis, sclerosing cholangitis, cutaneous manifestations (pyoderma gangrenosum or erythema nodosum), and ocular manifestations (uveitis or iritis). As shown in **Table IV.4**, a significant association of homo- or heterozygous combinations of the *CD6* rs17824933^{G} allele with lower risk of ankylosing spondylitis was found in the whole cohort of IBD patients.

Table IV.4. Logistic regression analysis of *CD6* rs12360861 and rs17824933 SNPs association with CD prognosis (top), UC extent (middle) and ankylosing spondylitis in IBD patients (bottom), corrected for sex and smoking.

Model	rs12360861 genotype	CD good prognosis (%)	CD poor prognosis (%)	OR (95% CI)	*q* value
Log-additive	A alleles (0,1,2)	127 (18.9)	544 (81.1)	0.62 (0.45, 0.86)	0.027
Model	rs17824933 genotype	Ulcerative proctitis (%)	Left/extensive colitis (%)	OR (95% CI)	*q* value
Recessive	C/C-C/G	151 (98.7)	758 (93.0)		0.010
	G/G	2 (1.3)	57 (7.0)	5.68(1.37,23.48)	
Model	rs17824933 genotype	Ankylosing spondylitis (%)	No ankylosing spondylitis (%)	OR (95% CI)	*q* value
Dominant	C/C	456 (54.1)	51 (71.8)		0.016
	C/G-G/G	387 (45.9)	20 (28.2)	0.45 (0.27, 0,78)	

No statistical association was observed with any of the clinical parameters analysed for *CD166/ALCAM* rs6437585 SNP, even though it had been reported to influence *CD166/ALCAM* transcriptional activity and MS risk (Wagner et al. 2013; Zhou et al. 2011).

2.2 Impact of *CD5* and *CD6* gene variation on clinical expression of pSS

A total of 212 pSS patients with mean age of 54 years at diagnosis were included in the study, most of which were females (95.3%) and presented dry mouth (100%) and dry eyes (96.7%). General characteristics of the patient cohort are shown in **Table III.3** from the Materials and Methods section.

The *CD5* and *CD6* SNPs previously studied in the IBD studies were also investigated for association with clinical parameters of pSS. The study also included the analysis of a set SNPs mapping at coding (rs579565, rs1044243) and non-coding (rs6437585) regions of *CD166/ALCAM*, which encodes the best studied CD6 ligand. All the SNPs were tested for association with each of the following clinical

parameters: age at diagnosis, xerostomia, xerophthalmia, Scirmer's test, salivary scintigraphy, minor salivary gland biopsy positivity, ANA positivity, RF positivity, anti-Ro/La antibody positivity, monoclonal gammopathy, C3 and C4 complement levels, presence of cryoglobulins, hematological cytopenias (anemia, leukopenia, thrombocytopenia, neutropenia, lymphopenia), ESSDAI domain activity (constitutional, lymphadenopathy, glandular, articular, cutaneous, pulmonary, renal, muscular, peripheral nervous system, central nervous system, hematological, biological), the total baseline ESSDAI and the total cumulative ESSDAI. Sex is a major risk factor in pSS, so statistical models were generated with or without including sex as a covariant, and their goodness of fit compared with the AIC. The results presented here do not include sex as a covariant, as these models had lower AIC.

The *CD5* rs2241002^{C} allele was found associated with higher frequency of anti-Ro/La antibody positivity (**Table IV.5**). Haplotypic analyses also showed association of the *CD5* rs2241002^{T}-rs2229177^{C} haplotype with increased risk of anemia and thrombocytopenia (**Table IV.6**).

Table IV.5. Logistic regression analysis of *CD5* SNP rs2241002 association with and anti-Ro/anti-La antibodies.

Model	Genotype	Anti-Ro/La positivity		OR (95% CI)	*q* value
		Negative (%)	Positive (%)		
Recessive	C/C-C/T	55 (90.2)	149 (98.7)		0.046
	T/T	6 (9.8)	2 (1.3)	0.12 (0.02, 0.63)	

Table IV.6. Logistic regression analysis of *CD5* haplotype association with anemia (top half) and thrombocytopenia (bottom half).

rs2241002	rs2229177		Anemia			
		% in pool	% no	% yes	*p* val	OR (95% CI)
C	C	41.0	41.8	39.9		
C	T	39.1	38.9	38.0	0.941	1.02 (0.58, 1.78)
T	T	15.2	16.5	12.0	0.399	0.69 (0.29, 1.62)
T	C	4.7	2.8	10.0	**0.032**	4.48 (1.14, 17.60)
			Thrombocytopenia			
		% in pool	% no	% yes	*p* val	OR (95% CI)
C	C	41.0	45.2	35.9		
C	T	39.1	37.1	35.9	0.905	1.07 (0.46, 2.50)
T	T	15.2	13.7	14.1	0.872	0.93 (0.27, 3.19)
T	C	4.7	3.9	14.1	**0.036**	5.83 (1.12, 30.29)

Regarding *CD6* SNPs, association of the rs17824933^{G} allele with decreased risk of neutropenia, and association of the rs11230563^{T} allele with increased leukopenia and neutropenia but decreased ESSDAI peripheral nervous system (PNS) activity was found (**Table IV.7**). Haplotypic analyses also showed association of the *CD6* rs17824933^{G}-rs11230563^{C}-rs12360861^{G} haplotype with increased risk of cutaneous ESSDAI activity (**Table IV.8**).

Table IV.7. Logistic regression analysis of *CD6* rs17824933 and rs11230563 SNPs association with neutropenia, leukopenia, and peripheral nervous system (PNS) activity.

Model	rs17824933 genotype	Neutropenia No (%)	Yes (%)	OR (95% CI)	*q* value
Dominant	C/C	75 (50.3)	33 (73.3)		0.022
	C/G-G/G	74 (49.7)	12 (26.7)	0.37 (0.18, 0.77)	
Model	rs11230563 genotype	Leukopenia No (%)	Yes (%)	OR (95% CI)	*q* value
Recessive	C/C-C/T	121 (85.8)	34 (65.4)		0.019
	T/T	20 (14.2)	18 (34.6)	3.20 (1.53, 6.73)	
Model	rs11230563 genotype	Neutropenia No (%)	Yes (%)	OR (95% CI)	*q* value
Recessive	C/C-C/T	127 (85.8)	28 (62.2)		0.008
	T/T	21 (14.2)	17 (37.8)	3.67 (1.72, 7.84)	
Model	rs11230563 genotype	PNS activity No (%)	Yes (%)	OR (95% CI)	*q* value
Dominant	C/C	50 (28.7)	12 (60.0)		0.041
	C/T-T/T	124 (71.3)	8 (40.0)	0.28 (0.10, 0.70)	

Table IV.8. Logistic regression analysis of *CD6* haplotype with ESSDAI cutaneous activity.

rs17824933	rs11230563	rs12360861	% in pool	Cutaneous activity % no	% yes	*p* val	OR (95% CI)
C	C	G	32.6	35.2	20.1		
G	C	G	23.6	22.1	31.4	**0.012**	2.85 (1.26, 6.43)
C	T	A	22.4	22.3	20.8	0.141	1.81 (0.82, 4.00)
C	T	G	20.6	20.0	25.8	0.055	2.26 (0.98, 5.12)

In the case of *CD166/ALCAM*, haplotypic analyses revealed association of the *CD166/ALCAM* rs6437585^{C}-rs579565^{G}-rs1044243^{T} haplotype with increased ANA positivity, ESSDAI PNS activity and hematologic cytopenias, including anemia and lymphopenia (**Table IV.9**).

Table IV.9. Logistic regression analysis of *CD166/ALCAM* haplotype with antinuclear antibodies (ANA), cytopenia, anemia, lymphopenia, and ESSDAI peripheral nervous system (PNS) activity.

rs6437585	rs579565	rs1044243	% in pool	ANA positivity % negative	% positive	*p* val	OR (95% CI)
C	G	C	55.1	58.4	54.3		
C	A	C	27.3	30.5	27.2	0.685	0.87 (0.46, 1.66)
C	G	T	13.0	3.7	14.3	**0.045**	4.64 (1.04, 20.81)
T	G	C	3.0	4.5	3.0	0.494	0.57 (0.11, 2.90)
				Cytopenia			
				% no	% yes		
C	G	C	55.4	58.0	53.1		
C	A	C	27.1	27.8	26.3	0.975	0.97 (0.61, 1.54)
C	G	T	12.8	9.0	16.5	**0.027**	2.14 (1.08, 4.21)
T	G	C	3.0	3.5	3.0	0.657	0.71 (0.16, 3.15)
				Anemia			
				% no	% yes		
C	G	C	55.4	57.1	49.0		
C	A	C	27.1	26.7	27.6	0.632	1.15 (0.65, 2.06)
C	G	T	12.8	11.0	20.7	**0.030**	2.25 (1.08, 4.66)
T	G	C	3.0	3.6	0.0	--	--
				Lymphopenia			
				% no	% yes		
C	G	C	55.4	56.1	56.3		
C	A	C	27.1	27.4	18.8	0.907	0.95 (0.44, 2.08)
C	G	T	12.8	11.3	18.8	**0.030**	2.64 (1.10, 6.35)
T	G	C	3.0	3.2	0.0	--	--
				PNS activity			
				% no	% yes		
C	G	C	55.1	55.6	52.5		
C	A	C	27.3	28.1	20.0	0.404	0.70 (0.30, 1.62)
C	G	T	13.0	11.5	25.0	**0.036**	2.56 (1.06, 6.15)
T	G	C	3.0	3.1	0.0	--	--

Case-control analyses to assess the influence of each *CD5*, *CD6* and *CD166/ALCAM* SNPs on pSS risk were also performed, either on the whole cohorts or only with female patients. The *CD166/ALCAM* rs579565^{A} allele was significantly associated with increased susceptibility to pSS in females (**Table IV.10**).

Table IV.10. Logistic regression analysis of *CD166/ALCAM* SNP rs579565 association with pSS susceptibility in females.

Model	Genotype	Controls (%)	pSS cases (%)	OR (95% CI)	*q* value
Recessive	G/G-G/A	139 (97.9)	169 (91.4)		0.064
	A/A	3 (2.1)	16 (8.6)	4.39 (1.25, 15.36)	

Case-control analyses to test the effect of *CD5*, *CD6* and *CD166/ALCAM* haplotypes on pSS risk were also performed. The results showed that the only significant associations with pSS susceptibility were with the *CD166/ALCAM* rs6437585^{C}-rs579565^{A}-rs1044243^{C} (CAC) and rs6437585^{C}-rs579565^{G} rs1044243^{T} (CGT) haplotypes (**Table IV.11**), which were over-represented in the case cohort, indicating association of the rs579565^{A} and rs1044243^{T} alleles association with pSS susceptibility. The results obtained in the pSS cohort generally highlight the clinical relevance of *CD5* and *CD6* variation.

Table IV.11. Logistic regression analysis of *CD166/ALCAM* haplotype association with pSS susceptibility in females.

rs6437585	rs579565	rs1044243	% in pool	% controls	% pSS cases	*p* val	OR (95% CI)
C	G	C	58.5	63.3	54.8		
C	A	C	24.4	20.6	27.3	**0.044**	1.51 (1.01, 2.24)
C	G	T	11.4	8.8	13.3	**0.046**	1.72 (1.01, 2.95)
T	G	C	4.2	5.8	2.7	0.274	0.62 (0.26, 1.47)

3 *CD5* and *CD6* gene variation in cancer

3.1 Impact of *CD5* and *CD6* gene variation on clinical expression of PCa

After interrogating the role of *CD5* and *CD6* gene variation in disorders characterized by excessive activation of the immune system (IBD and pSS), we proceeded to do the same in PCa, a disorder that manifests when an anti-tumor immune response is ineffective. As before, PCa patients (*n*=376) were genotyped for functionally relevant *CD5* (rs2229177, rs2241002) and *CD6* (rs12360861, rs11230563, rs17824933) SNPs, as well as for *CD166/ALCAM* (rs6437585, rs579565, rs1044243, rs35271455) SNPs. All SNPs were in Hardy-Weinberg equilibrium. Description of the study cohort is shown in **Table III.4** from the Materials and Methods section.

Association of single *CD5*, *CD6* and *CD166/ALCAM* SNPs with ISUP grade was assessed by generalized linear models (logistic regression). None of the analyzed SNPs was significantly associated with ISUP grade. However, analyses of *CD5*, *CD6* and *CD166/ALCAM* haplotypes revealed association between *CD5* haplotypes and ISUP grade (**Table IV.12**). Particularly, the CD5 rs2241002^{C}-rs2229177^{T} haplotype was associated with increased risk of having an ISUP grade group ≥ 2 when compared with the most common haplotype rs2241002^{C}-rs2229177^{C}.

Table IV.12. Logistic regression analysis of *CD5* haplotype association with ISUP grade.

Haplotype		% in	ISUP grade			
rs2241002	rs2229177	pool	=1 (%)	≥2 (%)	*p* val	OR (95% CI)
C	C	43.2	47.3	41.1		
C	T	34.7	28.3	38.0	**0.026**	1.52 (1.05, 2.21)
T	T	16.5	19.3	15.1	0.508	0.86 (0.55, 1.35)
T	C	5.6	5.1	5.9	0.508	1.34 (0.56, 3.17)

The association of *CD5*, *CD6* and *CD166/ALCAM* SNPs with BR was assessed by Cox regression. For each SNP, patients were stratified according to their genotype, and homozygosis for the major allele was taken as the reference genotype. As shown in **Figure IV.8**, association with shorter BCR-free survival was observed for the minor *CD6* rs12360861^{AA} genotype (HR = 2.65, CI 1.39–5.05, p = 0.003) and the minor *CD166/ALCAM* rs579565^{AA} genotype (HR = 1.86, CI 1.02–3.39, p = 0.043).

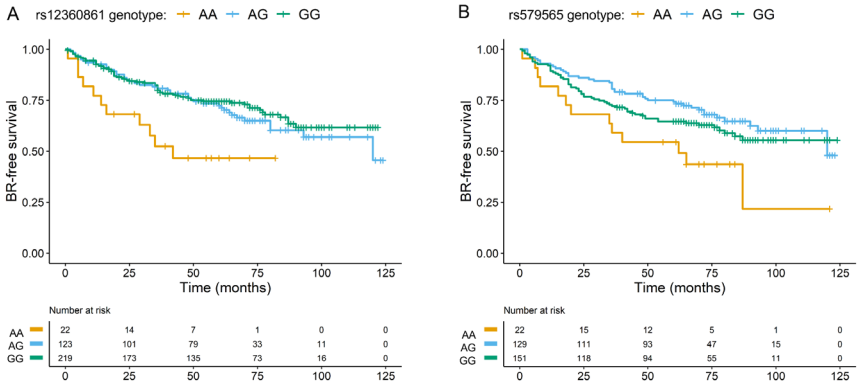


Figure IV.8. BR-free survival curves according to *CD6* rs12360861 and *CD166/ALCAM* rs579565 genotypes. (**A**) BR-free survival curve of PCa patients according to *CD6* SNP rs12360861 genotype. HR comparing homozygous rs12360861^{AA} with homozygous rs12360861^{GG} was 2.65, (95%b CI 1.39–5.05), *p* = 0.003. (**B**) BR-free survival curve of PCa patients according to *CD166/ALCAM* SNP rs579565 genotype. HR comparing homozygous rs579565^{AA} with homozygous rs579565^{GG} was 1.86, (95%b CI 1.02–3.39), *p* = 0.043.

Together with observations from the IBD and pSS cohorts, the results obtained in the PCa cohort generally highlight the clinical relevance of *CD5* and *CD6* variation.

4 Transcriptomic study of *CD5* variation

The results presented so far, together with previous reports, reinforce the clinical relevance of *CD5* and *CD6* gene variation. However, the underlying molecular mechanisms have been less explored. *CD5* variation at the rs2229177 SNP has been reported to cause differential CD5 signaling and TCR inhibition. To broaden the knowledge on the molecular impact of *CD5* variation, we stably transduced the human $CD5^-$ B cell Daudi line with lentiviral vectors encoding the *CD5* Ala471 or Val471 isoforms, in order to study possible differences in their transcriptomes.

Daudi cells expressing CD5 Ala471 or Val471 were left unstimulated or stimulated for 24 h with anti-CD5 or anti-IgM antibodies, for further analysis of cell surface activation marker expression by flow cytometry. As illustrated in **Figure IV.9**, $CD5^+$ Daudi cells showed decreased expression for some of the analyzed activation markers (CD69, CD80, CD83 and CD86) after CD5 crosslinking (but not after IgM crosslinking) compared with $CD5^-$ Daudi controls. However, no differences were seen between cells expressing the different CD5 isoforms.

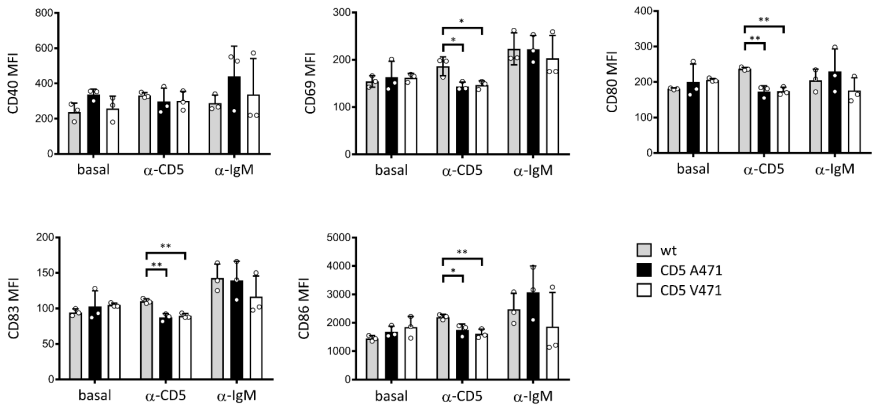


Figure IV.9. Expression of cell surface markers in WT and CD5 variant-expressing Daudi cells subjected to different stimulation conditions. Mean fluorescence intensity (MFI) of cell surface markers after stimulation with anti-CD5 or anti-IgM mAbs. Statistical differences were assessed by one-way ANOVA and Tukey's multiple comparison tests. *, $p<0.05$. **, $p<0.01$.

As a pilot study, RNA was extracted from unstimulated and anti-IgM-stimulated Daudi cells and subjected to mass sequencing (RNAseq). Since no biological replicates were included in this experimental design, proper statistical inference was not possible. An exploratory analysis was performed by sub-sampling single samples to generate pseudo-replicates, which provides a preliminary description but does not allow to draw generalizable conclusions.

A Gene Ontology (GO) pathway enrichment analysis suggested transcriptional differences among the three cell lines (untransduced *vs* CD5 Ala471- and CD5 Val471-transduced Daudi cells). Some of the changes in CD5-expressing Daudi cells (either Ala471or Val471) were reminiscent of those previously reported by Gary-Gouy et al., including processes related with cell adhesion, signal transduction and cell cycle, while others like mRNA processing suggested an inverted trend (**Tables IV.13** and **IV.14**) (Gary-Gouy et al. 2007).

Table IV.13. Biological process GO terms enriched in CD5 Ala471 vs untransduced (WT) Daudi cells under basal or IgM crosslinking conditions.

	Basal	**Anti-IgM stimulation**
Enriched in CD5 Ala471	Establishment of protein localization to endoplasmic reticulum (ER) Cotranslational protein targeting to membrane SRP-dependent cotranslational protein targeting to membrane Protein targeting to ER Protein localization to ER Protein targeting to membrane Cytoplasmic translation Oxoacid metabolic process Cellular amide metabolic process Establishment of protein localization to membrane Organic acid metabolic process Translational initiation Signal transduction Cell adhesion Amide biosynthetic process Biological adhesion Response to acid chemical Peptide metabolic process Nuclear-transcribed mRNA catabolic process, nonsense-mediated decay Translation	Mitotic cell cycle process Cell cycle process Cellular response to jasmonic acid stimulus Response to jasmonic acid Cell division DNA replication Cell cycle Cellular process Mitotic cell cycle phase transition Cell cycle phase transition Prostaglandin metabolic process Prostanoid metabolic process Polyketide metabolic process Aminoglycoside antibiotic metabolic process Doxorubicin metabolic process Daunorubicin metabolic process Cellular response to prostaglandin D stimulus Response to prostaglandin D Chromosome organization Tertiary alcohol metabolic process
Enriched in WT	No significant terms enriched	No significant terms enriched

Table IV.14. Biological process GO terms enriched in CD5 Val471 vs untransduced (WT) Daudi cells under basal or IgM stimulation conditions.

	Basal	**Anti-IgM stimulation**
Enriched in CD5 Val471	Cellular response to jasmonic acid stimulus Response to jasmonic acid Cellular response to prostaglandin D stimulus Response to prostaglandin D	Cellular nitrogen compound metabolic process Nucleobase-containing compound metabolic process Nucleic acid metabolic process Heterocycle metabolic process Cellular aromatic compound metabolic process Organic cyclic compound metabolic process Cellular metabolic process Mitotic cell cycle process Metabolic process Cell cycle process Cellular process Nitrogen compound metabolic process RNA splicing, via transesterification reactions RNA splicing, via transesterification reactions with bulged adenosine as nucleophile mRNA splicing, via spliceosome DNA metabolic process Anaphase-promoting complex-dependent catabolic process Primary metabolic process Macromolecule metabolic process Organic substance metabolic process
Enriched in WT	Protein targeting to membrane Protein targeting to ER SRP-dependent cotranslational protein targeting to membrane Establishment of protein localization to ER Cotranslational protein targeting to membrane Protein localization to ER Establishment of protein localization to membrane	Detection of chemical stimulus involved in sensory perception of taste Regulation of tumor necrosis factor superfamily cytokine production Positive regulation of prostaglandin secretion involved in immune response Regulation of protein secretion Detection of chemical stimulus involved in sensory perception of bitter taste Regulation of tumor necrosis factor production Regulation of peptide secretion Positive regulation of tumor necrosis factor superfamily cytokine production Regulation of neurological system process Regulation of secretion Regulation of secretion by cell Regulation of system process Negative regulation of actin nucleation Positive regulation of tumor necrosis factor production Protein localization to early endosome Suppression by virus of host JAK-STAT cascade Suppression by virus of host STAT1 activity Suppression by virus of host STAT2 activity Suppression by virus of host STAT activity Negative regulation by organism of signal transduction in other organism involved in symbiotic interaction

Differences in relevant pathways concerning cell division, adhesion, and lipid metabolism were also suggested by comparing CD5 Ala471 vs CD5 Val471 (**Table IV.15**). This preliminary result will encourage further transcriptional assays with a more robust experimental design and data analysis.

Table IV.15. Biological process GO terms enriched in CD5 Ala471 vs CD5 Val 471 under basal or IgM stimulation conditions.

	Basal	**Anti-IgM stimulation**
Enriched in CD5 Ala471	Cell cycle process Mitotic cell cycle process Regulation of cell cycle process Cell division DNA metabolic process Regulation of cell cycle Chromosome organization Chromosome segregation Regulation of mitotic cell cycle Regulation of cell cycle phase transition Regulation of mitotic cell cycle phase transition Nucleic acid metabolic process Cell cycle DNA replication Regulation of chromosome segregation Cellular response to DNA damage stimulus Microtubule cytoskeleton organization Microtubule cytoskeleton organization involved in mitosis Mitotic cell cycle Microtubule-based process	Cell adhesion Cell-cell adhesion via plasma-membrane adhesion molecules Biological adhesion Cell-cell adhesion Homophilic cell adhesion via plasma membrane adhesion molecules G protein-coupled receptor signaling pathway Detection of chemical stimulus involved in sensory perception of bitter taste
Enriched in CD5 Val471	Homophilic cell adhesion via plasma membrane adhesion molecules Cell-cell adhesion via plasma-membrane adhesion molecules Cell-cell adhesion	Nucleic acid metabolic process Cellular nitrogen compound metabolic process Electron transport chain Nucleobase-containing compound metabolic process Heterocycle metabolic process DNA metabolic process Cellular aromatic compound metabolic process Mitochondrial electron transport, NADH to ubiquinone Organic cyclic compound metabolic process Respiratory electron transport chain Generation of precursor metabolites and energy Cellular response to stress Antigen processing and presentation of peptide antigen NADH dehydrogenase complex assembly Mitochondrial respiratory chain complex I assembly Antigen processing and presentation of exogenous antigen Antigen processing and presentation of exogenous peptide antigen Chromosome organization RNA splicing, via transesterification reactions Negative regulation of cell cycle

V DISCUSSION

Compelling evidence shows that positively selected immune gene variants conferring increased resistance to infectious agents during human evolution are today associated with increased risk of inflammatory disorders but decreased risk of cancer, the opposite sides of the same coin (Isakov 2016). CD5 and CD6 are closely related immune receptors involved in the recognition and sensing of bacterial, viral and/or parasitic MAMPs (Velasco-de Andrés et al. 2020) and in the fine tuning of lymphocyte activation signals delivered by the TCR and the BCR (Cho and Sprent 2018; Gimferrer et al. 2004; Lankester et al. 1994). A human genome data analysis identified the *CD5* locus, which is contiguous to *CD6*, as one of the most plausible targets of natural selection in recent human evolution (Carnero-Montoro et al. 2012). Therefore, it can be assumed that changes in the expression level or the amino acid sequence of CD5 and CD6 can impact the susceptibility to or the phenotypical characteristics of immune-mediated disorders. On this basis, the present thesis aimed at determining whether surface expression and/or genetic variation of CD5 and CD6 has any role on experimental and clinical models of immune-mediated diseases, including both IMIDs and cancer.

From the functional point of view, CD5 and CD6 are considered relevant signaling co-receptors positioned at the interphase of the innate and adaptive immune responses, due to their main expression on lymphocytes (characteristic of the adaptive immune system) and their MAMP recognition abilities (characteristic of the innate immune system). After binding to their endogenous or exogenous ligands, both receptors transduce intracellular signals modulating lymphocyte activation, which enhance or attenuate ongoing immune responses (anti-infectious, autoimmune or anti-tumoral). Currently available

information clearly supports a negative modulatory (inhibitory) function for CD5 during intracellular signaling mediated by the TCR or the BCR, which would make CD5 a good candidate to be included into the list of inhibitory immune checkpoints (Freitas, Johnson, and Weber 2018; Voisinne, Gonzalez de Peredo, and Roncagalli 2018). On the other hand, the interaction of CD6 cytoplasmic tail with activating and inhibitory mediators provides CD6 with a dual function (either co-stimulatory or co-inhibitory) likely depending on differential inputs present in different physiological and pathological conditions (Mori et al. 2021).

Previous *in vivo* studies with knockout mouse lines, blocking antibodies and soluble decoy receptors have suggested a relevant role for CD5 and CD6 in some experimental models of IMIDs (e.g. EAE, CIA, psoriasis) and cancer (e.g. B16-F0 melanoma) (Axtell et al. 2006; Consuegra-Fernández et al. 2018; Orta-Mascaró et al. 2016; Simões et al. 2017, 2020). Moreover, some preliminary clinical studies have reported on the impact of CD5 and CD6 gene variation in the prognosis or phenotypical characteristics of some autoimmune (SLE, MS, psoriasis and Behçet's disease) and neoplastic (CLL and melanoma) disorders (Cenit et al. 2014; Consuegra-Fernández et al. 2018; Delgado et al. 2017; Potrony et al. 2016; Swaminathan et al. 2010; Zheng et al. 2016).

In the present thesis we have extended the study of the immunomodulatory role of *CD5* and *CD6* expression and variation in immune-mediated disorders, including IMIDs (IBD and pSS) and cancer (PCa). They were selected based on their high prevalence and their immunopathological basis, for which evidence of *CD5* and *CD6* involvement is suspected but not yet reported. Although the exact

etiology of most IMIDs is far from being completely known, it is widely accepted that interaction between certain genetic backgrounds and environmental triggers results in exacerbated immune responses against self or harmless structures. In both IBD and pSS, the genetic background has been only partially described and involves several genes related with pathogen sensing and immune system activation (Ben-Eli et al. 2019; Cruz-Tapias et al. 2012; Lessard et al. 2013; Qin et al. 2013; Ramos-Casals et al. 2009; Soto-Cárdenas et al. 2015; Uniken Venema et al. 2017). Regarding environmental triggers, intestinal dysbiosis and viral infections are frequently claimed, respectively, as initiators of immune-mediated epithelial cell damage. Thus, IBD and pSS represent good clinical models for the study of receptors involved in both pathogen recognition and modulation of lymphocyte activation.

Cancer stands for a situation where the immune response is attenuated or evaded. Unlike highly immunogenic solid cancers such as melanoma, PCa is a good representative of “cold tumors” in which even an immunosuppressive microenvironment can predominate (Stultz and Fong 2021). Again, PCa provides a good alternative clinical model for the study of receptors involved in modulation of lymphocyte interplay with epithelial cancer cells in a poorly immunogenic setting. Immunotherapy of cancer relies on understanding the mechanisms that drive immunoediting—the progression from elimination to immune escape. One of such mechanisms is the ability of the tumor microenvironment to interact with immune checkpoint receptors on TILs. Two of the most studied immune checkpoints are CTLA-4 and PD-1, and cancer immunotherapies based on mAb blocking of these molecules have been developed. However, such treatments are effective only in a

fraction of cancer patients. Therefore, identification of both new targets and factors underlying this heterogeneous effectiveness, including genetic variation, is necessary.

1 Inflammatory bowel diseases

Inflammatory bowel diseases (IBD) are a group of diseases characterized by the chronic inflammation of the gastrointestinal tract. They mainly include Crohn's disease (CD) and ulcerative colitis (UC). Their etiology is uncertain, but it is considered that in genetically predisposed individuals environmental factors can trigger a loss of immune tolerance towards intestinal microbiota, inducing a damaging immune response. Such response is extended in some patients to self-antigens, such as Glycoprotein 2 in CD (Roggenbuck et al. 2009) or tropomyosin in UC (Ebert et al. 2006). Onset of IBD occurs around the second and third decades of life (Xavier and Podolsky 2007), and only a small percentage of cases start at a pediatric age, usually with worse prognosis (Moazzami, Moazzami, and Rezaei 2019). Both CD and UC are characterized by cycles of remission and relapse. During relapse or active disease patients may present abdominal pain, diarrhea, rectal bleeding, fever, and weight loss. A fraction of IBD patients also present extraintestinal manifestations. They include osteoarticular manifestations in axial (e.g.: sacroiliitis, ankylosing spondylitis) or peripheral joints, dermal (e.g.: erythema nodosum, pyoderma gangrenosum), ocular, hepatobiliary, pancreatic, pulmonary, and endocrine manifestations.

IBD treatment aims at reducing inflammation triggering these symptoms by means of anti-inflammatory drugs (corticosteroids and aminosalicylates), immunosuppressors (e.g.: azathioprine, mercaptopurine and methotrexate) and biological treatments

(Nakase et al. 2021). The latter are mAbs against several targets, such as TNFα (infliximab, adalimumab, golimumab and certolizumab), integrin $\alpha_4\beta_7$ (vedolizumab) and the p40 subunit of IL-12 and IL-23 (ustekinumab) (Danese, Vuitton, and Peyrin-Biroulet 2015; Herrlinger and Stange 2021). In IBD patients unresponsive to these therapies, surgical interventions are an option (Larson and Pemberton 2004).

Although IBDs they share the aforementioned characteristics, CD and UC are different diseases presenting distinct clinical courses and pathogenic mechanisms. CD can affect any part of the gastrointestinal tract, from the mouth to the anus, frequently involving the terminal ileum and/or the colon. CD is a transmural granulomatous disease, meaning that lesions extend to deep layers of the gut (from the mucosa to the serosa) and granulomas are found. CD lesions are asymmetric and present a "patchy distribution"—several regions can be affected separated by healthy tissue. According to the Montreal classification (Silverberg et al. 2005), location of CD is classified as ileal (L1) when it only affects the terminal ileum, colonic (L2) when it only affects any part of the colon, ileocolonic (L3) when both the terminal ileum and some part of the colon are involved, and upper gastrointestinal tract (L4) when disease is isolated between the mouth and the anterior ileum (**Figure V.1**). Additionally, L4 can be added as a modifier to L1, L2 or L3 when concomitant upper gastrointestinal disease is present. CD can also be classified according to its behavior. Inflammatory behavior (B1) indicates an initial phase consisting only of inflammation, structuring behavior (B2) is assigned when strictures or stenoses are present, and penetrating behavior (B3) when fistulas are present (**Figure V.1**).

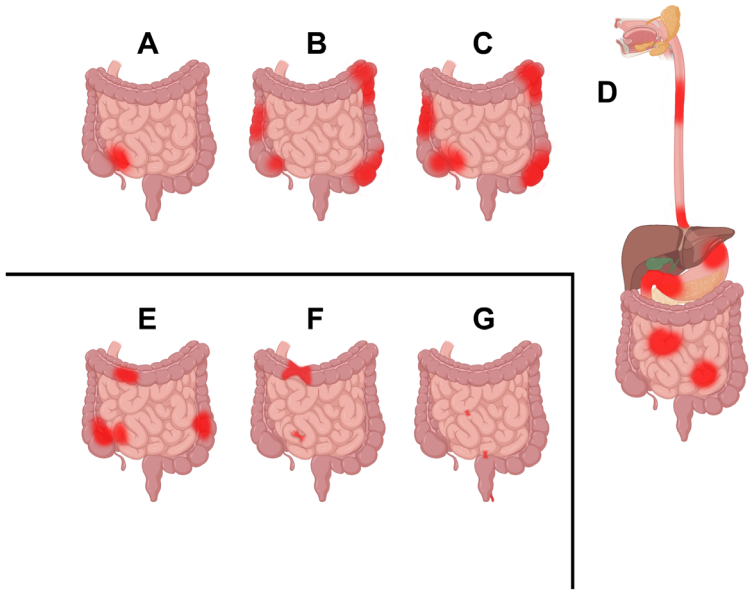


Figure V.1. CD location and behavior according to the Montreal classification (Silverberg et al. 2005). Location can be classified as ileal = L1 (**A**), colonic = L2 (**B**), or ileocolonic = L3 (**C**). Upper gastrointestinal tract = L4 (**D**) may present alone or in combination with L1, L2 or L3. Behavior is classified as inflammatory = B1 meaning absence of stenosis and fistulas (**E**), stenosing (stricturing) = B2 (**F**), or fistulizing (penetrating) = B3 (**G**).

UC is characterized by inflammation of the colonic and rectal mucosa. The rectum is always involved, and its extent is continuous and variable, ranging from proctitis (inflammation only in the rectum) to pancolitis (inflammation of the entire colon). The Montreal classification (Silverberg et al. 2005) defines ulcerative colitis extent as follows: ulcerative proctitis (E1) when involvement is limited to the rectum, left-sided UC (E2) when involvement is limited to a portion of the colorectum distal to the splenic flexure, and extensive UC (E3) when involvement extends proximally to the splenic flexure (**Figure V.2**).

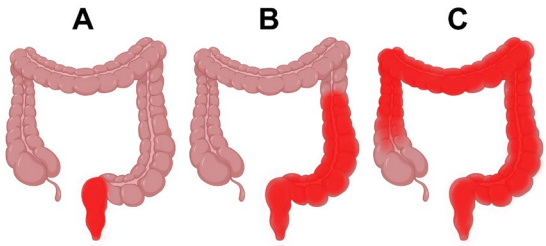


Figure V.2. UC extent according to the Montreal classification (Silverberg et al. 2005): ulcerative proctitis = E1 (**A**), left-sided UC = E2 (**B**), extensive UC = E3 (**C**).

1.1 Immunopathology of IBD

The mucosal immune system contains about 75% of all lymphocytes and produces most immunoglobulins (Murphy and Weaver 2017). In healthy individuals, the mucosal immune system maintains homeostasis by simultaneously protecting against pathogens and preserving tolerance towards commensal microbiota. In IBD patients, this balance is deregulated at several levels. Naïve $CD4^+$ T cells are activated by DCs at the gut-associated lymphoid tissue (GALT) or mLNs, subsequently differentiating into effector, regulatory, and memory T cells. Effector $CD4^+$ T cells can upregulate $\alpha_E\beta_7$ integrin and migrate to the epithelium. There, several $CD4^+$ T cell subsets secrete cytokines, recruit other cell types, and mediate damage. Importance of $CD4^+$ T cells in IBD has been shown by remission after administration of CD4 depleting antibodies (Emmrich et al. 1991; Stronkhorst et al. 1997), CD4 depletion in HIV infection (Greenwald and James 1995; Skamnelos et al. 2015), and current use of biological therapies targeting $CD4^+$ T cell differentiation or their cytokines (Hanauer et al. 2002; Sands et al. 2019).

Roles for different T helper (Th) cell subsets have been reported in IBD. Th1 cells aberrantly accumulate in the intestinal tract of CD patients and are key mediators of the disease (Matsuoka et al. 2004; Parronchi et al. 1997). SNPs linked to increased *IFNG* gene expression are associated with IBD risk (Fisher et al. 2008), and anti-TNF therapies are successful in relieving IBD symptoms (Rutgeerts et al. 2006, 2012). STAT4 and T-bet are transcription factors needed for initiation and maintenance of Th1 polarization. Altered ratios of STAT4α and STAT4β isoforms are detected in active IBD patients (Jabeen et al. 2015), and SNPs in T-bet binding regions are associated with IBD risk (Duerr et al. 2006; Jostins et al. 2012). While a few studies appear to be contradictory, in general Th1 plays more of an inflammatory rather than protective role in human IBD (Imam et al. 2018).

Although some studies have challenged the paradigm of increased Th2/Th1 balance in UC (Granlund et al. 2013), there is strong evidence supporting it, including a system able to distinguish CD and UC patients depending on the Th1/Th2 balance at the lamina propria, with an accuracy of 83.3% (Li et al. 2016). *IL4* mRNA expression is undetectable in IBD patients (Niessner and Volk 1995), but *IL5* and *IL13* mRNA expression is increased in UC patients (Fuss et al. 1996; Heller et al. 2005; Nemeth et al. 2017). GATA3, a transcription factor that defines the Th2 lineage and blocks Th1 polarization, is expressed in a higher proportion in UC patients (Ohtani et al. 2010; Popp et al. 2017).

In a healthy state, Th17 maintain commensal microbiota at barriers such as the gut, but in IBDs they can exacerbate the disease (Weaver et al. 2013). SNPs in the *IL23R* locus, which is important for Th17

polarization, are associated with IBD risk (see section V.1.2). IL-17$^+$ T cells are found elevated in tissues with active IBD (Fujino et al. 2003). However, IL-17 blockade in clinical trials exacerbated the disease (Hueber et al. 2012; Targan et al. 2016). This might be partly to the ability of IL-17 to block other Th subsets (O'Connor Jr et al. 2009) or its role in maintaining integrity of the epithelial barrier (Lee et al. 2015). The latter is shared with IL-22, secreted by Th22 cells, which has a protective effect in IBD, as observed in mouse models and patients (Basu et al. 2012; Kotenko et al. 2001; Sugimoto et al. 2008; Wolk et al. 2007; Zenewicz et al. 2008).

Treg cells (CD4$^+$ FoxP3$^+$) are increased in active IBD (Maul et al. 2005). However, it is hypothesized that these cells are less functional, or that they are in fact part of cell populations sharing Treg and Th17 characteristics (Hovhannisyan et al. 2011; Mitsialis et al. 2020).

Antibodies, produced by B cells, also have a role in IBD. Presence of certain antibodies is detected in IBD patients, as is the case of anti-*Saccharomyces cerevisiae* in CD patients and perinuclear antineutrophil cytoplasmic autoantibodies (pANCA) in UC patients (Main et al. 1988; Quinton et al. 1998; Rump et al. 1990; Saxon et al. 1990). However, it is still unclear whether these antibodies are directly involved in IBD pathogenesis (Chang 2020). It has also been observed that inflamed IBD tissue has increased IgG but decreased IgA compared with normal tissue (Brandtzaeg et al. 1974; Martin et al. 2019). Higher capacity of IgG isotypes to recruit immune cells and activate complement may result in tissue damage.

After the release of cytokines and chemokines, monocytes and neutrophils migrate to the affected intestinal areas (Cader and Kaser 2013; Wéra, Lancellotti, and Oury 2016), where they amplify tissue

damage by several mechanisms. One is the generation of reactive oxygen species like H_2O_2, $O_2^{\cdot-}$, $HO^{\cdot}$ and hypohalous acids (e.g.: HClO) thanks to enzymes like NADPH oxidase (NOX) and myeloperoxidase (MPO) (Chami et al. 2018). Others are the release of matrix metalloproteases, formation of neutrophil extracellular traps, and further cytokine release (Drury et al. 2021; Lin et al. 2020). Innate lymphoid cells (ILC) of the ILC1, ILC2 and ILC3 have also been shown to play a role in IBD, where they amplify production of Th1, Th2 and Th17 cytokines (Geremia and Arancibia-Cárcamo 2017). The role of NK cells in IBD is lesser known, but studies in the DSS-induced colitis mouse model suggests that they are able to downmodulate neutrophil activity, thus exerting a protective role (Hall et al. 2013).

1.2 Immunogenetics of IBD

More than three decades ago, twin studies highlighted the importance of genetic influence in IBD (Tysk et al. 1988). Both CD and UC were found to be significantly inheritable, with CD showing more heritability than UC. Although very rarely (in 15-20% of IBD patients younger than 6) IBD is caused by monogenic variants (Zheng, de la Morena, and Suskind 2021), the genetic basis underlying most IBD cases is polygenic. Identification of susceptibility alleles is complex, because many genes are involved—by 2015, 200 loci had been identified (Liu et al. 2015)—and often risk alleles require other genetic and environmental triggers to manifest the disease (Cadwell et al. 2010; Khor, Gardet, and Xavier 2011). In 2001, hypothesis-driven studies identified *NOD2* as the first susceptibility gene (Hugot et al. 2001; Ogura et al. 2001). Since then, genome-wide association studies (GWAS), resequencing of candidate genomic regions, *in silico* fine-mapping analyses and whole exome/genome sequencing of large case and control cohorts have been used to identify genomic IBD risk

loci (Uniken Venema et al. 2017). Even though CD and UC are clinically different entities, approximately 30% of the identified IBD genetic loci are shared between these diseases (Khor et al. 2011). Risk loci include genes involved in the epithelial and immune functions, autophagy, apoptosis and oxidative stress, among others.

NOD2 variants were the first ones to be associated to IBD (Hugot et al. 2001; Ogura et al. 2001), and later resequencing and fine-mapping studies confirmed them and identified further variants in this gene (Huang et al. 2017; Rivas et al. 2011). *NOD2* encodes an intracellular receptor that binds to muramyl-dipeptide, a ubiquitous component of Gram-positive and -negative bacterial cell walls, thus acting as a cytosolic bacterial sensor important for the innate immunity. NOD2 is mainly expressed in immune and epithelial cells, and upon ligand recognition, it activates the NF-κB pathway leading to cytokine release, and activation of autophagy, among other processes (Shaw et al. 2011). NOD2 variants conferring CD risk (e.g.: fs1007insC, R702W, G908R) interfere with normal NOD2 function. Some hypothesized mechanisms for such increased CD risk include defective α-defensin production in Paneth cells, altered TLR expression, and defective autophagy, which in turn would alter the host-microbiome balance and promote inflammation (Khor et al. 2011; Uniken Venema et al. 2017). Examples of other genetic variants involved in IBD include those in the *CARD9* (Rivas et al. 2011; Zhernakova et al. 2008), *ATG16L1* (Hampe et al. 2007), and *IL23R* (Duerr et al. 2006; Momozawa et al. 2011; Rivas et al. 2011) genes. *CARD9* encodes an adaptor protein that participates in transduction of signals originating in PRRs such as NOD2, Dectin-1, and RIG1 (Underhill and Shimada 2007). ATGL16L1 is essential for autophagy and microbial clearance (He and Klionsky 2009; Mizushima et al. 2003). *IL23R*

encodes one subunit of the IL-23 receptor complex (the other being IL12Rβ1). IL-23 is expressed by macrophages, DCs and endothelial cells, among others, and upon binding to the IL-23 receptor complex in hematopoietic (i.e., T cells, NKT cells and DCs) and non-hematopoietic cells (i.e., keratinocytes) the JAK-STAT pathway is activated, enhancing Th17 function (Abraham and Cho 2009). Loss of function *IL23R* variants, such as R318Q, lead to decreased production of pro-inflammatory cytokines and protection against IBD (Di Meglio et al. 2011; Pidasheva et al. 2011; Sarin, Wu, and Abraham 2011; Sivanesan et al. 2016). In summary, genetic variants impacting immune and autophagic functions, therefore in the host-microbiome interactions, are relevant in IBD.

Despite the number of genetic variants reported to influence IBD, these explain only a small fraction of its genetic variance; around 13–13.6% in CD and around 7.5–9% in UC (Chen et al. 2014; Jostins et al. 2012). Therefore, the number of IBD risk variants is likely to increase. Also, it has been reported that genetic variants not known to influence IBD risk can still be associated with IBD prognosis (Lee et al. 2017). This supports further research in the genetic basis of IBD.

1.3 *CD5* and *CD6* expression and variation in IBD

This thesis provides experimental and clinical evidence for the involvement of *CD5* and *CD6* expression and variation in IBD. Previous GWAS and meta-analysis studies have identified the *CD6* locus (SNP rs11230563) as a susceptibility marker in CD and UC, thus supporting its contribution to IBD etiopathogenesis (Ellinghaus et al. 2016; Jostins et al. 2012). Here, involvement of CD5 and CD6 in IBD was assessed by using genetically modified mice and candidate gene-

driven association analyses with functionally relevant SNPs from *CD5* and *CD6*, as well as from *CD166/ALCAM*.

Etiopathogenic factors for IBD include host genetic susceptibility, dysregulated immune response, intestinal dysbiosis, and impairment of intestinal epithelial barrier function. Under normal circumstances, there is continuous crosstalk between gut microbiota and the immune system, where gut microbiota modulates the host's innate and adaptive immunity and vice versa (Cianci et al. 2018). Gut microbiota is in close contact with the intestinal barrier, consisting of an epithelial cell layer and a variety of immune cells of hematopoietic origin. Epithelial and immune cells from the intestinal barrier (both epithelial and hematopoietic) sense and signal the presence of microbial components via PRRs, which belong to different structural families such as lectin C-type, LRR, Ig, or SRCR domains (Gordon 2002). SRCR domains are constitutive of the CD5 and CD6 receptors, which are expressed on the surface of different lymphocyte subsets present in the intestinal mucosa, such as Tαβ, Tγδ, B1a, NK cells and ILCs (Alonso et al. 2010; Azzam et al. 2001; Berland and Wortis 2002; Braun et al. 2011; Kamoun et al. 1981; Roan and Ziegler 2017). Epithelial cells from the gastrointestinal tract also express the cell adhesion molecule CD166/ALCAM, the best characterised CD6 ligand (Levin et al. 2010). CD166/ALCAM mediates both homotypic (epithelial-epithelial) and heterotypic (epithelial-immune) cell adhesive contacts. Increased expression of both CD6 and CD166/ALCAM has been reported in inflamed mucosa from IBD patients (Ma et al. 2019). This may relate to quantitative trait loci studies in which the rs11230584 SNP in the intergenic region between *CD5* and *CD6* modulates expression of both genes in IBD patients but not in healthy controls (Peters et al. 2016). Taken

together, their tissue and cell expression pattern, microbial recognition properties and ability to modulate lymphocyte activation and function provide the basis for considering both CD5 and CD6 as contributors to IBD pathogenesis.

1.3.1 *CD5* and *CD6* expression in experimental colitis

The observation that both CD5- and CD6-deficient mice differ from WT controls in their response to DSS-induced colitis further supports their involvement in IBD. In *Cd5*$^{-/-}$ mice, attenuated DSS-induced colitis agreed with a previous report (Dasu et al. 2008). The mechanism underlying such attenuated colitis was already explored and attributed to increased suppressive function of Treg cells from *Cd5*$^{-/-}$ mice (Dasu et al. 2008). This is a conflicting point, since another group reported increased nTreg cell numbers with normal suppressive function in the same *Cd5*$^{-/-}$ mice (Ordoñez-Rueda et al. 2009). An alternative mechanism behind attenuated colitis in *Cd5*$^{-/-}$ mice could be increased AICD of effector T cells resulting from the absent inhibitory role assigned to the CD5 receptor (Axtell et al. 2004; Mori et al. 2021).

Regarding *Cd6*$^{-/-}$ mice, no analysis of DSS-induced colitis has been brought forward, in spite of reports of *Cd6*$^{-/-}$ mice behaviour in several other immune-related inflammatory disease models (i.e., intestinal ischemia-reperfusion, bovine or avian type II collagen-induced arthritis, chronic GvHD-induced lupus-like, imiquimod-induced psoriasis-like skin inflammation, EAE, and autoimmune uveitis) (Consuegra-Fernández et al. 2017, 2018; Enyindah-Asonye, Li, Ruth, et al. 2017; Enyindah-Asonye, Li, Xin, et al. 2017; Li et al. 2020; Orta-Mascaró et al. 2016; Zhang et al. 2018). *CD6* deficiency results in attenuated or exacerbated phenotypes according to mouse

background and experimental models responsive to different underlying mechanisms (e.g., increased AICD or defective Treg function). This puzzling situation has been unveiled by CD6 receptor's multitask signalosome, which may sustain either negative or positive regulatory functions in T cell activation (Mori et al. 2021). Such a dual role accounts for past difficulties in classifying it as a co-inhibitor or -stimulatory receptor.

Here we observed that *Cd6*$^{-/-}$ mice exhibit an exacerbated DSS-induced colitis phenotype. The multifaceted nature of CD6 makes hard to pinpoint a single mechanism mediating such effect. However, a series of experiments were performed to evaluate the role of different CD6^{+} cells in experimental colitis: T cells, B1a cells and NK cells.

The innate immune response is the main responsible behind DSS-induced colitis, which can actually be induced in absence of T cells (Dieleman et al. 1994). However, adaptive immune responses also occur during the DSS model, and oral antigen-specific T cells are developed (van Dop et al. 2010; Morgan et al. 2013). To assess the role of CD6 on T cells and adaptive responses during colitis, an adoptive cell transfer model was carried out. Naïve T cells (CD4^{+}CD45RB^{high}) from either WT or *Cd6*$^{-/-}$ mice were injected into *Rag2*$^{-/-}$ mice to induce colitis. The lack of differences in terms of body weight loss and DAI suggested that CD6 expression on T cells plays little to no role in such experimental colitis mocel. Interestingly, lower percentages of CD4^{+} cells were detected in the lamina propria immune infiltrate of mice receiving *Cd6*$^{-/-}$ T cells. This would suggest decreased T cell migration in lack of CD6-ALCAM interactions, although it did not have a noticeable clinical impact. Another immune

alteration described in *Cd6*$^{-/-}$ mice, which might impact DSS phenotype, is defective Treg function (Consuegra-Fernández et al. 2017). The impact of such defective Treg function in the DSS phenotype remains to be explored.

Apart from T cells, CD6 is expressed on B1a cells, which are responsible for the production of natural antibodies and well represented in the GALT. It has been described that *Cd6*$^{-/-}$ mice have reduced serum concentration of natural polyreactive antibodies (Enyindah-Asonye, Li, Xin, et al. 2017). DSS-induced colitis relies on the damaging effect of DSS on the epithelial barrier of the gut, thus allowing bacterial translocation into the inner layers of the intestinal mucosa (Johansson et al. 2010). Therefore, we hypothesized that the decreased concentration of circulating natural antibodies in *Cd6*$^{-/-}$ mice might result in increased bacterial translocation. To test this hypothesis, organs directly draining the gut (i.e., mLNs and the liver) were disaggregated and seeded on blood agar plates. No differences in CFU counts were observed between *Cd6*$^{-/-}$ and WT control mice, indicating a lack of impact of CD6 expression on bacteria translocation during DSS-induced colitis. However, differences in local epithelial penetration of bacteria and/or dissemination of microbial components cannot be discarded.

CD6 is also expressed by the major circulating NK cell subset (CD56^{dim} CD16^{+}), characterised by high IFN-γ production (Braun et al. 2011). Recent studies have shown that blocking anti-CD6 mAbs modify NK cell phenotype, altering the expression of several NK cell markers (Ruth et al. 2021). NK cells are able to attenuate DSS colitis thanks to their cross-talk with neutrophils, which mediate inflammation and tissue injury (Hall et al. 2013), so it was hypothesised that NK cells

might mediate the exacerbated DSS colitis phenotype of *Cd6*$^{-/-}$ mice. Indeed, reduced expression of *Ncr1* mRNA, one of the NK triggering receptors, was observed in the colon from *Cd6*$^{-/-}$ mice undergoing DSS colitis. This was concomitant with reduced *Ifng* mRNA expression, one of the several mediators by which NK cells block neutrophil migration (Feng et al. 2006; Figueiredo et al. 2007). This would be coherent with the observed increase in mRNA expression of *Lcn2*, which codes for lipocalin 2—a protein present in neutrophil secondary granules and relevant in experimental IBD (Singh et al. 2016). *Cd6*$^{-/-}$ mice also presented increased *Cxcl1* mRNA expression, which can promote further neutrophil migration and infiltration.

While this is a feasible explanation of the mechanistic effects of CD6 deficiency in experimental colitis, other effects cannot be excluded. Noteworthily, we observed decreased expression of IFN-γ (the prototypical Th1 cytokine) and of GATA3 (the master regulator of Th2 differentiation), no differences in IL-17A and IL-10 expression, and increased expression of IL-6 and CXCL1, a cytokine and a chemokine involved in promotion of Th17 cell differentiation and function. This points to a scenario of preserved Th17 response with decreased Th1 and Th2 responses, which can favor disbalanced Th1/Th2/Th17 ratio, which can favor the severity of colitis (Mikami et al. 2010).

As stated above, genetic susceptibility is only one of the known factors in IBD etiopathogenesis. The importance played by other environmental factors is illustrated by seasonal-dependent onset and exacerbation patterns in IBD patients (Araki et al. 2017; Dharmaraj et al. 2015; Peng et al. 2015). Interestingly, seasonal variations regarding susceptibility to DSS-induced colitis were also observed in

Cd6$^{-/-}$ mice. More precisely, the exacerbated DSS-induced colitis phenotype of *Cd6*$^{-/-}$ mice was evidenced during the spring/summer but not the autumn/winter season. This seasonal dependance is reminiscent of that reported for other IMID mouse models of (*i.e.*, EAE) (Teuscher et al. 2004).

1.3.2 *CD5*, *CD6* and *CD166/ALCAM* variation in IBD

In humans, no *CD5* or *CD6* deficiencies have been reported. Nevertheless, genetic analyses involving functionally relevant *CD5* or *CD6* SNPs show that they might act as susceptibility or disease modifier markers for immune-related disorders, as described in section I.3. On this basis, we investigated the role of the *CD5* rs2241002 and rs2229177, the *CD6* rs17824933, rs11230563 and rs12360861 SNPs, and the *CD166/ALCAM* rs6437585 SNP.

The nonsynonymous *CD5* rs2241002 SNP (Pro224>Leu at the SRCR2 domain) was associated with CD location. Further analyses showed association of *CD5* haplotypes containing the cytoplasmic rs2229177^{T} variant with severity parameters in CD (requirement of biological treatments) and UC (poor prognosis) patients. The rs2229177^{T} allele involves the substitution of ancestral Ala471 for Val, which results in increased CD5 inhibitory capacity and has a clinical impact in IMIDs as is the case of SLE (Carnero-Montoro et al. 2012; Cenit et al. 2014). The increased inhibitory capacity of the Val471 variant can turn activated lymphocytes less sensitive to AICD and more damaging, which would explain the increased requirement of more intensive therapies observed in CD and UC patients. Interestingly, reports show that the clinical effect of variation at the rs2229177 SNP is more apparent when the rs2241002 SNP is fixed at a C-C genotype (Delgado et al. 2017; Potrony et al. 2016), which is reminiscent of the

observation of significant associations in CD5 haplotypes but not in single SNPs in the CD and UC cohorts.

CD6 SNP analyses showed association of the rs17824933^{G} allele with preferred ileal CD location and increased UC extent. These results consolidate the damaging effect of the rs17824933^{G} allele in inflammatory diseases, as suggested from its reported association with more aggressive forms of psoriasis and with increased MS susceptibility (Consuegra-Fernández et al. 2018; Wagner et al. 2014). Patients with left-sided or extensive UC also tend to need more aggressive therapies and are at higher risk of developing colorectal cancer (Fumery et al. 2018). A relatively short follow-up (median 12.37 years; Q1 7.43 years; Q3 19.21 years) combined with the low frequency of the rs17824933^{GG} genotype may underlie the lack of significant differences observed for this SNP regarding prognosis.

The *CD6* rs17824933^{G} allele was further associated with lower risk of ankylosing spondylitis in the whole IBD cohort. This result appears to contradict the above-mentioned deleterious contribution of this variant in UC, as well as in psoriasis and MS. However, this variant also showed association with a more ileal location of CD. Joint extraintestinal manifestations of IBD are more common in patients with colonic disease than in those with small-bowel disease (Levine and Burakoff 2011). Thus, preferential ileal location in CD patients may account for the association of rs17824933^{G} with lower ankylosing spondylitis risk.

The study also showed association of the *CD6* rs12360861 SNP with prognosis in CD patients but not susceptibility, in agreement with a major genetic contribution to prognosis from loci distinct from those driving disease susceptibility, applicable in this case (Lee et al. 2017).

No statistical association with any of the clinical IBD parameters analysed was observed for the only *CD166/ALCAM* SNP (rs6437585) studied, which has been previously reported to influence *CD166/ALCAM* transcriptional activity and MS risk (Wagner et al. 2013; Zhou et al. 2011).

2 Primary Sjögren's syndrome

Sjögren's syndrome is a systemic autoimmune disease, with the main target being exocrine glands such as salivary and lacrimal glands. Its prevalence increases with age, and it has a gender bias, with a female/male ratio of approximately 10/1 (Haugen et al. 2008; Ramos-Casals et al. 2015). Patients are usually classified in two subgroups: primary Sjögren's syndrome (pSS) when it is presented alone, and secondary Sjögren's syndrome when it is concomitant with other systemic autoimmune diseases such as RA or SLE. However, patient management in both subgroups is the same (Brito-Zerón et al. 2016).

While inflammation of exocrine glands is the predominant symptom, pSS is a systemic disease, presenting with both glandular and systemic, extra-glandular manifestations. Thus, the main symptom is dryness (*sicca*) in the affected mucosae, mainly the eyes and the mouth but also in the respiratory and vaginal mucosae. Extraglandular symptoms can be the result of infiltration of nearby tissue, deposition of immunocomplexes, or non-specific. These include fatigue and musculoskeletal, respiratory, hepatic, renal and nervous system symptoms, among others. pSS patients are at higher risk of death, mainly due to problems derived of immunocomplexes and increased risk of lymphoma (Mavragani and Moutsopoulos 2014).

2.1 Immunopathology of pSS

pSS is characterized by B-cell hyperreactivity, and production of autoantibodies. Circulating autoantibodies against Ro (SSA) and La (SSB) ribonucleoprotein complexes are considered a hallmark of pSS (Routsias and Tzioufas 2010), although other autoantibodies can also be detected (e.g.: RF) (Manuel Ramos-Casals, Brito-Zerón, and Sisó-Almirall 2004). In pSS, glandular tissue is infiltrated by T and B-cells which abnormally respond against autoantigens. While mild lesions are richer in T infiltrates, severe lesions have abundant B cell infiltrates (Voulgarelis and Tzioufas 2010). Epithelial cells have a role in the initiation and perpetuation of the immune response in pSS, through expression of CD40 (Dimitriou et al. 2002), adhesion molecules (e.g.: ICAM-1, VCAM and CD166/ALCAM) (Abidi et al. 2006; Alonso et al. 2010; Tsunawaki et al. 2002) and several chemokines and cytokines (Xanthou et al. 2001). In turn, recruited immune cells, such as DCs, secrete type I IFN, which further activate the immune response (Båve et al. 2005). During early phases of glandular inflammation $CD4^+$ T cells have a predominant Th2 pattern, while in more advanced lesions they mainly secrete Th1 cytokines, with Th17cells also being associated with the histological score (Katsifis et al. 2009; Mitsias et al. 2002). Infiltrating T cells activate B cells and promote their survival thanks to secretion of factors such as BAFF (for B-cell activating factor) and APRIL (for a proliferation-inducing ligand) (Lavie et al. 2004). Activation of B cells may result in the formation of ectopic germinal centers (Salomonsson et al. 2003), and secretion of antibodies against autoantigens expressed by activated and apoptotic epithelial cells, such as the anti-Ro and anti-La antibodies that characterize pSS.

2.2 Immunogenetics of pSS

pSS results from a combination of environmental and genetic factors. Among environmental factors, viral infections play a major role, likely through aberrant activation of type-I and -II IFN signaling. Possible viral triggers of pSS include Epstein-Barr, human T-lymphotropic, and hepatitis C viruses (Lucchesi, Pitzalis, and Bombardieri 2014). Such infections—some of which have a high prevalence in the general population—only trigger autoimmunity in genetically susceptible individuals. One of the major contributors to the genetic basis of pSS is variation in the HLA system, particularly in *HLA-DR* and *HLA-DQ* (Cruz-Tapias et al. 2012; Lessard et al. 2013). A long but incomplete list of other genes associated with pSS pathogenesis includes genes of the type-I interferon pathways (*IRF5*, *IL12A*, *STAT4*), several other cytokines (*TNF*, *IL4*, *IL10*), genes involved in the lymphocyte function (*BLK*, *CXCR5*) and pattern recognition receptors (*SFTPD*, *MBL2*) (Ben-Eli et al. 2019; Hulkkonen et al. 2001; Lessard et al. 2013; Qin et al. 2013; M Ramos-Casals et al. 2004; Ramos-Casals et al. 2009; Soto-Cárdenas et al. 2015).

2.3 *CD5*, *CD6* and *CD166/ALCAM* variation in pSS

The complex and multifactorial pathophysiology of pSS includes still incompletely understood dysregulation of innate and adaptive immune responses involving both cell- and humoral-mediated processes (Lessard et al. 2013). Identifying genetic factors associated with pSS will allow a more precise definition of pathogenic mechanisms leading to the overall pSS phenotype and clinically heterogeneous subsets of patients (Cobb et al. 2008). By using a candidate gene-driven strategy the present work shows evidence on the impact of *CD5*, *CD6* and *CD166/ALCAM* gene variants in

susceptibility and clinical expression of pSS, thus supporting their involvement in pSS pathophysiology.

The rationale behind the assessment of *CD5*, *CD6* and *CD166/ALCAM* variation in pSS is multiple. First, the three genes encode functionally relevant and functionally related cell surface receptors. Both CD5 and CD6 are expressed by all T cell types and the B1a cell subset, with lower levels of expression in other cell types (e.g., macrophages, DCs or NK cells) (Burgueño-Bucio et al. 2019; Martínez et al. 2011), all found in pSS periductal immune cell infiltrates. While the nature of the CD5 ligand is yet uncertain, one of the most-well studied CD6 ligands is CD166/ALCAM, a cell adhesion molecule overexpressed in pSS salivary gland epithelial cells (Abidi et al. 2006; Alonso et al. 2010; Le Dantec et al. 2013), but also RA synovium (Levesque et al. 1998) and MS blood–brain barrier endothelium (Cayrol et al. 2008), thus contributing to T and B cell migration and infiltration at inflamed tissues. Second, several *CD5*, *CD6* and/or *CD166/ALCAM* gene variants have been associated with different IMIDs (see section I.3).

Individual SNP and haplotypic analyses showed association of *CD5*, *CD6* and *CD166/ALCAM* SNPs with different pSS clinical parameters. Thus, the *CD5* rs2241002^{C} allele and the *CD5* rs2241002^{T}-rs2229177^{C} haplotype, previously associated with lupus nephritis—a more aggressive form of SLE—(Cenit et al. 2014), showed association with anti-Ro/anti-La antibody positivity, and with anemia and thrombocytopenia, respectively. This could be interpreted as result of hyperactive autoantibody-producing B cells (most likely CD5^{+} B1a cells) in pSS carriers of such *CD5* variants.

The individual *CD6* rs11230563^{C} allele was associated with higher risk of PNS ESSDAI activity, and the minor *CD6* rs17824933^{G}-

rs11230563^{C}-rs12360861^{G} haplotype with cutaneous ESSDAI activity. This is reminiscent of the increased MS risk and psoriasis severity previously reported for the rs11230563^{C} allele (Consuegra-Fernández et al. 2018; De Jager et al. 2009; Johnson et al. 2010; Leppä et al. 2011; Swaminathan et al. 2010). Noteworthy, both rs17824933^{G} and rs11230563^{C} alleles were also associated with reduced risk of neutropenia. Since both alleles impact the extracellular region of CD6 (increased expression of the CD6Δd3 isoform and Arg225 to Trp substitution at SRCR2, respectively) it remains to be analyzed whether this relates to the reported surface CD6 (and CD166/ALCAM) expression by hematopoietic cell progenitors present in the bone marrow and in mobilized blood (Cortés et al. 1999; Ohneda et al. 2001).

The *CD166/ALCAM* rs6437585^{C}-rs579565^{G}-rs1044243^{T} haplotype was found associated with increased incidence of ANAs, neurological affectation and hematologic cytopenias. These results further support the damaging role of the *CD6* rs17824933^{G} and rs11230563^{C} alleles and of *CD166/ALCAM* rs1044243^{T} allele by worsening some analytical and clinical parameters of pSS. Interestingly, haplotypic analyses also showed association of the *CD166/ALCAM* rs6437585^{C}-rs579565^{A}-rs1044243^{C} and rs6437585^{C}-rs579565^{G}-rs1044243^{T} haplotypes with increased pSS susceptibility. This supports a role for minor rs579565^{A} and rs1044243^{T} alleles pSS susceptibility, which is reminiscent of the earlier age of MS diagnosis reported for the rs579565^{A} allele (Wagner et al. 2014).

In summary, we identified the *CD166/ALCAM* rs579565 and rs1044243 SNPs as pSS risk markers, and the *CD5* rs2241002, *CD6* rs17824933 and rs11230563 and *CD166/ALCAM* rs1044243 SNPs as

disease modifiers markers. Though further studies in independent cohorts will be required to validate these results, our observations are the first to support a role for *CD5*, *CD6* and *CD166/ALCAM* variation in pSS and highlight the shared immunogenetic basis of different IMIDs (Yamamoto and Okada 2019). This result along with the identification of other genetic factors involved in pSS etiopathogenesis may also help to classify patients and allow better identification, management and treatment of the disease.

3 Prostate cancer

PCa is the second most frequent cancer and the fifth most common cause of cancer-related death in males (Sung et al. 2021). It originates in the prostate, where normal glandular cells undergo cell transformation and become cancerous. Therefore, most PCas are classified as adenocarcinomas (cancers of glandular cells). Prostate-specific antigen (PSA) is a protein secreted by glandular epithelial cells of the prostate. While it is normally present in serum in small amounts, PSA concentration increases in presence of PCa and other prostatic diseases, like benign prostate adenoma and prostatitis. This makes PSA a useful biomarker in PCa screening, staging and in post-treatment screening (Cox et al. 1999; Moyer 2012). The most common form of the disease is localized PCa, and in the early stages it is generally slow growing and may not give any symptoms (Moyer 2012; Sung et al. 2021). However, it is a malignant tumor, so it can invade locally (e.g.: the rectum or the bladder) or metastasize to distant sites (mainly to lymph nodes and bones) (Gandaglia et al. 2015), which has a detrimental effect in patient survival (Scosyrev et al. 2012).

PCa risk stratification is based on tumor size, PSA level and histological grading. Traditionally, histological grading of prostate adenocarcinomas was done by the Gleason grading system (Humphrey et al. 2016), where a score ranging from 1 to 5 was assigned to the tissue, with 1 resembling more normal glandular tissue and 5 having the more transformed, less differentiated appearance. The total score of a sample was calculated as the score of the most predominant pattern of the sample plus the score of the next more predominant pattern. Therefore, the total Gleason score of a sample can range from 2=1+1 to 10=5+5. In 2014, the International Society of Urological Pathology (ISUP) developed a new grading classification ranging from 1 to 5 based on the Gleason score (**Table V.1**). The ISUP grading has a good correlation with prognosis and allows better communication of the significance of Gleason scores to the patients (Egevad et al. 2016; Epstein et al. 2016).

Table V.1. Definition of ISUP grade groups and correspondence with Gleason scores. Adapted from Epstein et al. 2016.

ISUP grade	Gleason score	Histological appearance
Group 1	≤6	Only individual discrete well-formed glands.
Group 2	3+4=7	Predominantly well-formed glands with lesser component of poorly formed/fused/cribriform glands.
Group 3	4+3=7	Predominantly of poorly formed/fused/cribriform glands with lesser component well-formed glands.
Group 4	8	Only poorly formed/fused/cribriform glands, or predominantly well-formed glands and lesser component lacking glands, or predominantly lacking glands and lesser component of well-formed glands.
Group 5	9 and 10	Lacks gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands.

In patients without symptoms or concomitant diseases watchful waiting or active surveillance are the most common therapeutic approaches. However, if PCa becomes more aggressive, other treatments are used, including radical prostatectomy, radiotherapy, hormone therapy, chemotherapy, immunotherapy and others (Teo, Rathkopf, and Kantoff 2019). Following therapy PSA can be monitored, with an increase of serum PSA concentrations indicating proliferation of remaining cancer cells even before it becomes macroscopically apparent. PSA increase after curative treatment is referred to as biochemical recurrence (BR) (Cox et al. 1999).

3.1 Immunopathology of PCa

PCa slow growth provides time to generate an antitumor immune response (Bilusic, Madan, and Gulley 2017). Accordingly, to date two immunotherapies have been approved by the FDA to treat PCa: sipuleucel-T (a vaccine based on infusion of stimulated, autologous PBMCs specific for a prostate cancer antigen) and the anti-PD-1 antibody pembrolizumab. Response to these therapies, however, is limited. For sipuleucel-T, median overall survival was improved in 4.1 months and no difference was observed in median time to objective disease progression (Kantoff et al. 2010). In the case of pembrolizumab, 39.6% of eligible patients responded, with 78% of responses lasting six months or more (Marcus et al. 2019). This might be because in most cases PCas are “cold” tumors, with minimal immune infiltrate or with immunosuppressive properties. Unlike the majority of tumors, $CD8^+$ infiltrate in PCa has been associated to poorer outcome due to its tolerogenic phenotype, and $CD4^+$ cells are skewed towards a Treg and Th17 phenotypes (Kaur et al. 2018; Leclerc et al. 2016; Ness et al. 2014; Petitprez et al. 2019; Sfanos et al. 2008). Besides, tumor mutational burden of PCa is low, which has

been associated with lower immune responses (Yarchoan et al. 2019). However, TMB does not always correlate with immune response (Chan et al. 2019) and PCa microenvironment has proven to be heterogeneous. A recent study classified PCa patients according to transcriptomic signatures reflecting their immunophenotype (Meng et al. 2020) with 14.9–24.3% patients presenting the immune-activated subtype, in which immunotherapy is more suitable. This could explain the partial success of immunotherapies in PCa. Therefore, further study of PCa subtypes will help understand the mechanisms of immune exclusion in colder tumors and develop better stratifications and targets (Kwon, Bryant, and Parkes 2021).

3.2 Immunogenetics of PCa

The immune system plays a role in both the initiation and the prognosis of PCa, and immune-related SNPs have a potential role in this malignancy. Recently, the study of PCa immunogenetics has been gaining attention, and several immune response-related loci have been reported as significant PCa biomarkers (Dreussi et al. 2018). One of the most relevant ones is the *RNASEL* locus (Alvarez-Cubero et al. 2011, 2015; Meyer et al. 2010). It is located in the hereditary PCa 1 locus in the chromosome 1 (1q25) and encodes the Ribonuclease L, which is part of the type I IFN response pathway. Other interesting immune-related loci in PCa are *IL6*, *IL10*, *IL1B* and *MMP7* (Dreussi et al. 2018). This evidence supports the study of PCa immunogenetics. However, this field is still in its beginnings and further research is needed to obtain robust results and translate them into the clinical practice.

3.3 *CD5*, *CD6* and *CD166/ALCAM* variation in PCa

Currently PCa risk stratification is based on tumor size, PSA level and ISUP grade, but these factors are not accurate enough to determine the clinical outcome of patients. Clinical and biological markers have a limited capacity to identify, at the time of the treatment (radical prostatectomy, cryotherapy or radiotherapy) which localized PCa patients are at higher risk of progression. On this basis, the use of individualized genetic and molecular prognostic factors could be useful to select high-risk patients who may benefit from adjuvant therapy or closer surveillance. On the other hand, such personalized prognostic factors could help in the selection and low-risk patients who may benefit from active surveillance.

In the present thesis, we assessed the role of *CD5*, *CD6* and *CD166/ALCAM* polymorphisms in PCa aggressiveness and recurrence after radical prostatectomy. We found association of the minor *CD6* rs11230563^{T} and rs12360861^{A} alleles with BR. Clinical relevance of these SNPs is illustrated by their reported role in immune-mediated diseases such as MS and psoriasis. In the case of *CD5*, we found association of the rs2241002^{C}-2229177^{T} haplotype with a higher ISUP grade, when compared with the most common rs2241002^{C}-2229177^{C} haplotype. This is reminiscent of the higher aggressiveness of melanoma reported for rs2241002^{C}-2229177^{T} patients (Potrony et al. 2016) and suggests a role for this haplotype in anti-tumor immune responses and therefore in tumor aggressiveness. In turn, this finding positions *CD5* variation as a putative marker for PCa risk stratification.

The functional impact of *CD5* variation on T cell activation has been previously reported. The *CD5* rs2229177^{T} allele (Val471) is

associated with stronger signaling via CD5 (Carnero-Montoro et al. 2012), which in turn results in stronger inhibition of TCR-mediated signals compared with the rs2229177^{C} allele (Ala471) (Cenit et al. 2014). Thus, we hypothesize that attenuation of TCR signaling could stand for the higher ISUP grade observed in carriers of the rs2241002^{C}-2229177^{T} haplotype. Also, the observation of associations of the rs2229177 SNP only in presence of the rs2241002^{C} allele is in line with the results reported here for IBD (see section V.1.3.2) and previously for melanoma, CLL and SLE (Cenit et al. 2014; Delgado et al. 2017; Potrony et al. 2016). Future research will be needed to uncover the mechanisms behind the rs2241002-rs2229177 SNP interaction.

We also found association of the *CD6* rs12360861 SNP with BR. As shown in **Figure IV.8**, association with shorter BCR-free survival was observed for the minor *CD6* rs12360861^{AA} genotype. The *CD6* rs12360861$^{G>A}$ SNP causes an amino acid substitution (Ala271>Thr) at the CD6 extracellular domain. However, molecular differences between rs12360861 alleles that might explain its effect on PCa have not been described so far. Other non-synonymous extracellular *CD6* SNPs, like rs11230563, have associated with lower expression of the molecule (Swaminathan et al. 2013), likely decreasing epithelial-immune cell interplay.

The *CD166/ALCAM* gene encodes the best characterized CD6 ligand (Bowen et al. 1995; Chappell et al. 2015) and provides heterotypic interactions (CD6-ALCAM) between immune and epithelial/endothelial cells, but also homotypic interactions (ALCAM-ALCAM) involved in cell adhesion and migration, and in progression of several malignancies such as melanoma, breast, colorectal and

bladder cancers (Ofori-Acquah and King 2008). CD166/ALCAM is also necessary for engrafting hematopoietic stem cells into the hematopoietic niche (Chitteti et al. 2014). CD166/ALCAM expression has an impact on tumor progression in PCa patients (Kristiansen et al. 2003, 2005) and is necessary for the development of bone metastases in mouse models of PCa (Hansen et al. 2014). Moreover, PCa metastases occur mainly in the bone (Gandaglia et al. 2015), and have a detrimental effect in patient survival (Scosyrev et al. 2012).

Here we observed association of the *CD166/ALCAM* rs579565^{A} allele with BR-free survival. This is a clinically relevant SNP, as shown by its reported association with MS risk (Wagner et al. 2014). As far as we know, there is no information on the putative functional consequences of the synonymous *CD166/ALCAM* rs579565 SNP (e.g., introduction of cryptic splicing sites, changes in transcription efficiency, or linkage disequilibrium with other gene variants) accounting for its clinical significance. It is worth mentioning that other *CD166/ALCAM* SNPs such as rs6437585 and rs1044243 have reported associations to breast and bladder cancer, supporting the role of genetic variation of *CD166/ALCAM* in cancer (Varadi et al. 2012; Verma et al. 2017; Zhou et al. 2011).

The PCa tumor microenvironment is heterogeneous, which leads to different responses to available immunotherapies such as immune checkpoint inhibitors. Recent immunogenomic work proposes classification of PCa patients in three gene enrichment signatures: non immune, immune-activated and immune-suppressed (Meng et al. 2020). The last two subtypes were dichotomized based on a stromal signature involving Wnt/TGF-β, and C-ECM (for cancer associated extracellular matrix) genes. The work states that PCa patients with immune-activated could benefit from single immune checkpoint

inhibitors, while immune-suppressed patients could benefit from TGF-β inhibitors (Meng et al. 2020). It would be interesting to know how *CD5*, *CD6*, and *CD166/ALCAM* expression or variation fit in those PCa immunophenotypes, since CD166/ALCAM is a TGF-β-responsive marker and functional regulator of PCa metastasis (Hansen et al. 2014), and gene expression studies in patients with resectable NSCLC show that higher *CD5* and *CD6* intra-tumor expression associates to better overall survival and relapse-free survival (Moreno-Manuel et al. 2020).

The strengths of this study include the large cohort of PCa patients, expert pathological review of cases and long-term follow-up of patients diagnosed with clinically localized diseases. Furthermore, the researchers participating in this study were blinded to all clinical information, and genomic information was matched to clinical data only after all patient cases had been processed.

We also acknowledge some study limitations. First, the use of BCR as a significant endpoint has been questioned since only a proportion of patients with BCR will end up developing clinical progression (Pound et al. 1999). However, the detection of BCR after radical prostatectomy is usually the indicator for the application of adjuvant therapies. Eventually, an independent validation will be necessary to definitely ascertain the role of *CD5*, *CD6*, and *CD166/ALCAM* gene variants as PCa prognostic and treatment response indicators.

Results of the present thesis show impact of new genetic variants in PCa aggressiveness and recurrence. These associations position *CD5, CD6* and *CD166/ALCAM* as putative prognosis markers and/or therapeutical targets, and grant future studies to unveil the biological mechanisms underlying them.

4 *CD5* variation and transcription regulation

Accumulating evidence shows clinical relevance of *CD5* and *CD6* gene variation. However, the molecular mechanisms driving such variation are poorly understood. In the case of the CD5 $2229177^{C>T}$ SNP (Ala471>Val), two studies have provided insight into its implications in early signaling events. In COS7 cell transfectants expressing the Ala471 variant, CD5 stimulation with anti-CD5 mAbs resulted in lower MAPK phosphorylation compared with Val471 transfectants (Carnero-Montoro et al. 2012). This phenomenon was also observed in PBMCs isolated from homozygous donors for each of the variants. Also, in HEK293 cell transfectants expressing the Ala471 variant, stimulation with the β-glucan-rich fungal extract Zymosan resulted in lower IL-8 secretion (Carnero-Montoro et al. 2012). In another study, PBMCs isolated from 2229177^{CC} (Ala471) homozygous donors showed increased proliferation after TCR/CD3 stimulation than PBMCs from 2229177^{TT} (Val471) homozygous donors (Cenit et al. 2014). An interpretation for these observations is that the derived *CD5* 2229177^{T} allele (Val471) has increased signaling capacity, resulting in increased ability to downmodulate TCR-mediated signaling. Such models provide insights into the role of *CD5* variation in IMIDs and cancer but have some limitations. Use of cell lines like COS7 and HEK293 provides a uniform background, but it does not match that of T and B cells *in vivo*. On the other side, use of primary cells from donors provides a more representative cellular background, but great genomic variability. Also, these studies focused on very specific early (MAPK phosphorylation) and late (IL-8 secretion, cell proliferation) events of cell signaling.

In the present thesis, we used a transcriptomic-based approach to study the molecular mechanisms underlying *CD5* variation. The use of the Daudi B-like cell line prevents excessive genomic variability found in patient-derived primary cells, while providing a cellular physiology closer to that of B cells than COS9 and HEK293T cell lines. Also, this top-down data reduction provides a wider coverage of biological processes (Pinu et al. 2019). In this preliminary assay, we observed differential expression of relevant pathways depending on the *CD5* variant, including cell-cell adhesion, cell cycle and antigen presentation. However, since no biological replicates were included in this experimental design, proper statistical inference was not possible and generalizable conclusions cannot be drawn from these results. Anyway, they serve as a proof-of-concept for a transcriptomic approach and encourage its use in future studies of the molecular mechanisms underlying *CD5*, *CD6* and *CD166/ALCAM* gene variation. As shown by the reported study of CD5 expression impact on Daudi cell transcriptome, this approach can also be useful in providing insights into the effect of *CD5* gene variation in CLL (Gary-Gouy et al. 2007).

5 Concluding remarks

In summary, the results obtained in this thesis support a role for the CD5 and CD6 lymphocyte receptors, as well as the CD6 ligand CD166/ALCAM, in the pathogenesis of IBD, pSS and PCa. Involvement of CD5 and CD6 in IBD was supported by performing mouse models in CD5- and CD6-deficient mouse lines. Due to the multifaceted nature of the CD6 receptor, multiple putative mechanisms were interrogated, and the results pointed to the involvement of CD6 modulation of NK cell activity.

Candidate gene-driven association studies, based on the well-known functional and clinical relevance of several *CD5*, *CD6* and *CD166/ALCAM* SNPs, led to the discovery of new associations of such SNPs with IBD, pSS and PCa, summarized in **Tables V.2, V3 and V4**. These results were in line with previous reports. For instance, the reported stronger TCR inhibition reported for the rs2241002^{C}-rs2229177^{T} haplotype was apparent as an increased requirement of biological therapies in CD patients and increased ISUP grade group in PCa patients, also reflecting the interaction between the rs2241002 and rs2229177 SNPs.

Table V.2. Summary of association of *CD5* SNPs with clinical parameters of IBD, pSS and PCa.

SNP	IBD	pSS	PCa
rs2241002	T allele associated with preferred colonic CD location. Allelic combinations with rs2229177 associated with biological therapy requirement in CD, prognosis in UC.	C allele associated with increased presence of anti-Ro/La antibodies. Allelic combinations with rs2229177 associated with anemia and thrombocytopenia.	Allelic combinations with rs2229177 associated with ISUP grade group.
rs2229177	Allelic combinations with rs2241002 associated with biological therapy requirement in CD, prognosis in UC.	Allelic combinations with rs2241002 associated with anemia and thrombocytopenia.	Allelic combinations with rs2241002 associated with ISUP grade group.

Table V.3. Summary of association of *CD6* SNPs with clinical parameters of IBD, pSS and PCa.

SNP	IBD	pSS	PCa
rs17824933	G allele associated with preferred ileal CD location, extensive UC and decreased risk of ankylosing spondylitis.	G allele associated with reduced risk of neutropenia. Allelic combinations with rs1123563 and rs1236861 associated with cutaneous activity.	
rs1123563		T allele associated with increased risk of leukopenia and neutropenia, reduced PNS activity.	
rs1236861	A allele associated with better CD prognosis.		A allele associated with shorter BR-free survival.

Table V.4. Summary of association of *CD166/ALCAM* SNPs with clinical parameters of IBD, pSS and PCa.

SNP	IBD	pSS	PCa
rs579565	--	A allele associated with increased pSS susceptibility. Allelic combinations with rs6437585 and rs144243 associated with susceptibility.	A allele associated with shorter BR-free survival.
rs144243	--	Allelic combinations with rs6437585 and rs579565 associated with ANAs, cytopenia, anemia, lymphopenia, PNS activity and susceptibility.	

Moreover, the damaging role of the CD6 rs17824933^{G} allele in IMIDs was extended from increased MS risk and psoriasis severity to increased UC extension and risk of death in pSS.

While these results highlight common mechanisms underlying different diseases, it is important to note that specific pathological processes can drive diverging effects of certain SNPs. For instance, the *CD5* rs2229177^{T} allele is associated with stronger TCR inhibition. While this could attenuate autoimmune responses in some instances, it might also increase the threshold for AICD and perpetuate autoimmune responses in others. In fact, while this allele is associated with lower risk of lupus nephritis, a severe presentation of SLE, here it was shown to be associated with increased risk of more aggressive therapies in CD patients.

Our observations have also allowed to extend the relevance of genetic variation at certain immune system-related loci from IMIDs to also cancer. This is the case of the *CD6* rs11230563 and rs12360861 SNPs. Previous reports had implicated them in MS, psoriasis, Behçet's syndrome and IBD, and here we also observed association with PCa, being the first time that genetic variation at the *CD6* locus is shown to be associated with cancer.

The approach used in the genetic studies of the present thesis has been that of candidate gene association studies. Because such studies are focused on a genomic region of interest, driven by an *a priori* hypothesis, they present enhanced power and are more suitable than GWAS in small hospital-based cohorts and for lower-frequency SNPs (Jorgensen et al. 2009). This allowed the identification of new IBD associations not observed in GWAS, including those of the *CD5* rs2241002 and rs2229177 SNPs, and the *CD6* rs17824933 and

rs12360861 SNPs. Also, clinically relevant associations of the *CD166/ALCAM* rs579565 SNP were reported for the first time, for pSS and PCa. This case is puzzling, as the alleles of rs579565 are synonymous. Linkage disequilibrium with other SNPs, generation of cryptic splice sites and changes in translation efficiency might account for this effect, but it remains to be explored.

The functional implications at a molecular level are partially known for of some of the studied SNPs: rs2241002 and rs2229177 impact CD5 signaling, rs17824933 impacts CD6Δd3 expression, and rs6437585 impacts *CD166/ALCAM* translation. However, this is not the case for the rest. While the amino acid substitutions caused by rs11230563 and rs12360861 do not directly involve the regions for CD166/ALCAM or bacterial PAMP binding (Chappell et al. 2015; Martínez-Florensa et al. 2018), direct or indirect effects on binding with these or other ligands has not been tested. The transcriptomic analysis of CD5 ala471- vs CD5 Val471-expressing Daudi cells opened a door to further study the molecular impact of genetic variation. This experimental approach allows to attribute observed differences solely to the genetic variant in study, compared with human samples studies in which genomic heterogeneity is present. Transcriptomic analyses are therefore a useful tool to further study the functional effects of the SNPs at the molecular level and gain insights on the mechanism behind their clinical effects.

In summary, the results presented in this thesis support the notion of considering the CD5 and CD6 immunomodulatory receptors as newcomers in the relevant and selected group of immune checkpoint receptors (**Figure V.3**). They also highlight the common genetic basis behind multiple IMIDs and cancers, and grant CD5, CD6 and

CD166/ALCAM potential as stratification markers and therapeutic targets. Indeed, interventions involving CD5 and CD6 targeting are currently in progress at both preclinical and clinical trials (Velasco-de Andrés et al. 2020). On this regard, Itolizumab (a humanized anti-CD6 mAb) is being developed as a therapeutic option in several IMIDs and hematological maligancies (Hernández et al. 2016).

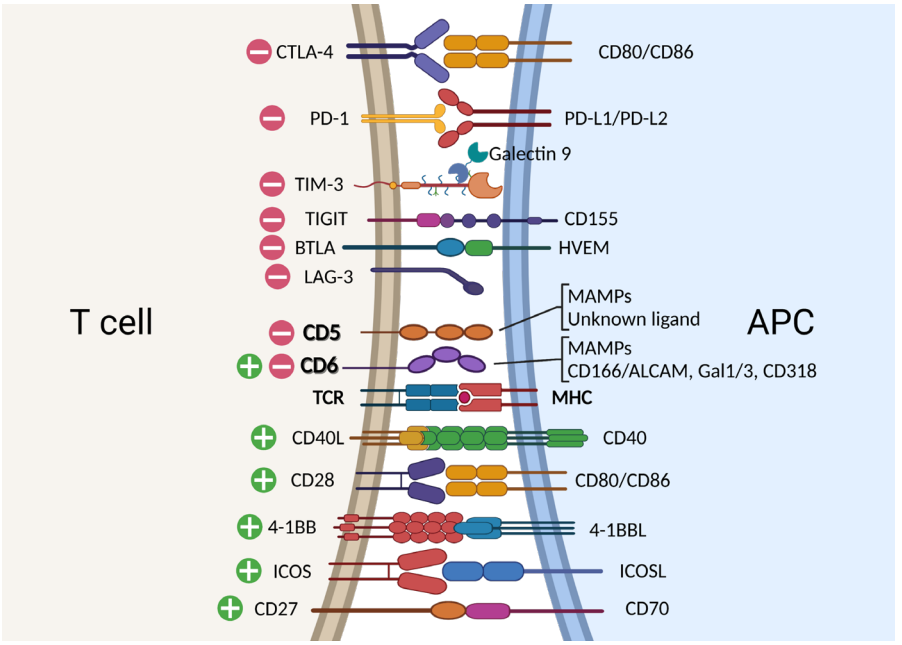


Figure V.3. Immune checkpoints and their ligands. Minus and plus signs indicate inhibitory and activating functions, respectively. Accumulated evidence indicates that CD5 and CD6 can also be considered immune checkpoints. Adapted from Mellman et al. 2011 and Wykes et al. 2017.

VI CONCLUSIONS

1. CD5 and CD6 expression impacts the outcome of experimental models of autoimmune disorders (i.e., IBD).
2. Genetic variation at the *CD5* and *CD6* loci, as well as *CD166/ALCAM* is associated with clinical features of immune-mediated disorders (i.e., IBD and pSS) and cancer (i.e., PCa).
3. The results of the present thesis support the role of CD5 and CD6 in IMIDs and cancer, further positioning them as immune checkpoint receptors and potential therapeutic targets.

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VIII ANNEX

1 Publications in peer-reviewed journals related to the present thesis

Casadó-Llombart S, Velasco-de Andrés M, Català C, Leyton-Pereira A, Lozano F, Bosch E. Contribution of Evolutionary Selected Immune Gene Polymorphism to Immune-Related Disorders: The Case of Lymphocyte Scavenger Receptors *CD5* and *CD6*. International Journal of Molecular Sciences. 2021. 18;22(10):5315. DOI: 10.3390/ijms22105315

Casadó-Llombart S, Velasco-de Andrés M, Català C, Leyton-Pereira A, Suárez B, Armiger N, Carreras E, Esteller M, Ricart E, Ordás I, Gisbert JP, Chaparro M, Esteve M, Márquez L, Busquets D, Iglesias E, García-Planella E, Martín-Arranz MD, Lohmann J, Ayata K, Niess JH, Panés J, Salas A, Domènech E, Lozano F. CD5 and CD6 lymphocyte co-receptor exression and variation impact experimental and clinical inflammatory bowel disease. Under review at Cellular and Molecular Gastroenterology and Hepatology.

Casadó-Llombart S, Gheytasi H, Ariño S, Consuegra-Fernández M, Armiger N, Kostov B, Ramos-Casals M, Lozano F, Brito-Zerón P. Gene variation at loci involved in modulation of lymphocyte activation and cell-adhesion in primary Sjögren's syndrome. Submitted.

Casadó-Llombart S, Ajami T, Galesloot TE, Consuegra-Fernández M, Carreras E, Aranda F, Armiger N, Kiemeney LALM, Alcaraz A, Mengual L, Lozano F. Gene variants in modulators of lymphocyte activation and immune-epithelial cell adhesion: impact on prostate cancer prognosis. Submitted.

2 Communications to congresses related to the present thesis

Casadó-Llombart S, Velasco-de Andrés M, Català C, Leyton-Pereira A, Suarez B, Armiger N, Carreras E, Esteller M, Gisbert JP, Márquez L, Esteve M, Panés J, Ordàs I, Ricard E, Salas A, Domènech E, Lozano F. A role for the scavenger receptor CD6 in inflammatory bowel diseases. Oral communication to the 42 Congreso de la Sociedad Española de Inmunología (SEI)/I Congreso Virtual SEI (Virtual, March 24th–26th, 2021)

Casadó-Llombart S, Velasco-de Andrés M, Català C, Leyton-Pereira A, Suarez B, Armiger N, Carreras E, Esteller M, Gisbert JP, Márquez L, Esteve M, Panés J, Ordàs I, Ricard E, Salas A, Domènech E, Lozano F. Experimental and genetic evidence for the involvement of CD6 in inflammatory bowel diseases. Oral communication to the XIV Congrés de la Societat Catalana d'Immunologia (Barcelona, Spain, November 19th–20th, 2020)

Casadó-Llombart S, Armiger N, Suarez B, Carreras E, Gisbert JP, Márquez L, Esteve M, Panés J, Ordàs I, Ricard E, Salas A, Domènech E, Lozano F. Influence of cd5 and cd6 variants in Crohn's disease. Oral communication to the 41 Congreso de la Sociedad Española de Inmunología (Sevilla, Spain, May 30th–June 1st, 2019)

Casadó-Llombart S, Simões IT, Velasco-de Andrés M, Consuegra-Fernández M, Aranda F, Carreras E, Lozano F. Immunomodulatory effects of a soluble formo f human CD6 in experimental cancer. Poster presented at the 5th European Congress of Immunology (Amsterdam, Netherlands, September 2nd–5th, 2018)

Casadó-Llombart S, Aranda F, Moreno Manuel A, Calabuig Fariñas S, Herreros Pomares A, Gallach-Garcia S, Simoes I, Consuegra-Fernández M, Blasco A, Cunquero Tomas A, Martorell M, Janus-Lewintre E, Camps Herrero C, Lozano F, Sirera R. CD5 and CD6 expression levels as prognostic biomarkers for early-stage non-small cell lung cancer. Poster presented at the 5th European Congress of Immunology (Amsterdam, Netherlands, September 2nd–5th, 2018)

3 Collaborations in other publications in peer-reviewed journals not related to the present thesis

Velasco-de Andrés M, **Casadó-Llombart S**, Català C, Leyton-Pereira A, Lozano F, Aranda F. Soluble CD5 and CD6: Lymphocytic Class I Scavenger Receptors as Immunotherapeutic Agents. Cells. 2020. DOI: 10.3390/cells912289

Velasco-de Andrés M, Català C, **Casadó-Llombart S**, Martínez-Florensa M, Simões I, García-Luna J, Mourglia-Ettlin G, Zaragoza O, Carreras E, Lozano F. The lymphocytic scavenger receptor CD5 shows therapeutic potential in mouse models of fungal infection. Antimicrobial Agents and Chemotherapy. 2020. DOI: 10.1128/AAC.01103-20

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Simões IT, Aranda F, **Casadó-Llombart S**, Velasco-de Andrés M, Català C, Álvarez P, Consuegra-Fernández M, Orta-Mascaró M, Merino R, Merino J, Alberola-Ila J, González-Aseguinolaza G, Carreras E, Martínez V, Lozano F. Multifaceted effects of soluble human CD6 in

experimental cancer models. Journal for Immunotherapy of Cancer. 2020;8:e000172. DOI:10.1136/jitc-2019-000172

Martínez-Florensa M, Català C, Velasco-de Andrés M, Cañadas O, Fraile-Ágreda V, **Casadó-Llombart S**, Armiger-Borràs N, Consuegra-Fernández M, Casals C, Lozano F. Conserved bacterial-binding peptides of the scavenger-like human lymphocyte receptor CD6 protect from mouse experimental sepsis. Front. Immunol. 2018 Apr. DOI: 10.3389/fimmu.2018.00627

Simões IT, Aranda F, Carreras E, Velasco-de Andrés M, **Casadó-Llombart S**, Martinez VG, Lozano F. Immunomodulatory effects of soluble CD5 on experimental tumor models. Oncotarget. 2017 Nov 20;8(64):108156-108169. DOI: 10.18632/oncotarget.22564