Effects of astrocyte-targeted production of either **IL-6 or IL-10** after facial nerve axotomy in the adult mouse

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4. HYPOTHESIS AND OBJECTIVES

Hypothesis:

After peripheral nerve injury, astrocyte-targeted production of either IL-6 or IL-10 alters the pattern of glial reactivity and lymphocyte recruitment. These alterations will result in changes in the neuronal death/survival ratio and will influence the axonal regeneration capability.

General objective:

The general objective of this thesis is to increase our knowledge on the role played by two cytokines such as the regulatory cytokine IL-6 and the counter-regulatory cytokine IL-10 along the neuroinflammatory process in the CNS following peripheral nerve axotomy.

Specific objectives:

1. To characterize the effects of either astrocyte-targeted IL-6 or IL-10 production on the pattern of microglial and astroglial activation along the different degenerative/regenerative phases following FNA.
2. To determine the changes induced by astrocyte-targeted IL-6 and IL-10 production on lymphocyte recruitment after FNA.
3. To analyze the effects of astrocyte-targeted IL-6 and IL-10 production on short and long-term facial motor neuron survival after FNA.
4. To assess the influence of astrocyte-targeted IL-6 and IL-10 production on axonal regeneration after FNA.

5. SUMMARY OF RESULTS AND DISCUSSION

This doctoral thesis is the compendium of the studies we have done to characterize the effects of astrocyte-targeted production of either IL-6 or IL-10 on the pattern of CNS glial activation, leukocyte infiltration, neuronal survival and axonal regeneration after peripheral nerve injury. Specifically, along these studies, two lines of transgenic mice were used: the GFAP-IL6Tg, characterized more than twenty years ago (Campbell et al. 1993), and the GFAP-IL10Tg recently generated in our laboratory and described by our research team (Almolda et al. 2014). These two transgenic mice produce the cytokines IL-6 and IL-10, respectively, under the GFAP promoter, i.e. specifically in astrocytes. It should be noted that when astrocytes become reactive they increase the GFAP expression and consequently the production of those transgenic cytokines. The paradigm we used in our studies is the transection of the facial nerve. The cerebral area in the CNS where we focus our analysis was the facial nucleus placed in the brainstem, location of the FMN soma. Our results revealed that transgenic production of IL-6 and IL-10 induced significant changes in the microglial and leukocytic responses generated after FNA that correlate with important modifications in neuronal survival and nerve regeneration. Thus, in GFAP-IL6Tg mice, there is an increase in neuronal death and an impairment of effective functional axonal regeneration while in GFAP-IL10Tg mice the ratio of neuronal survival is higher, although we have not found significant changes in effective functional axonal regeneration.

As a result of the studies conducted, we have published two articles in the journal GLIA (which will be referred in the text as Article 1 and Article 2), a book chapter in press (Article 3) and an additional item, which is manuscript in preparation (Article 4). These articles are included as Annex I.

5.1 Altered glial reactivity in GFAP-IL6Tg and GFAP-IL10Tg mice

In agreement with other studies (Ha et al. 2006; Jinno and Yamada 2011; Kalla et al. 2001; Schoen et al. 1992; Svensson et al. 1994), our observations showed that FNA induces an important gliosis in WT animals. Reactive microglial cells undergo proliferation and suffer important phenotypical modifications including changes in morphology as well as in the expression of several activation markers. Activated microglia change its shape from ramified to elongated cells that wrap FMNs and subsequently transform into the round and poorly ramified cells (amoeboid forms). These forms of reactive microglia usually are grouped forming the characteristic microglial clusters associated with this kind of lesion. Meanwhile, astrocytes become hypertrophied and start a progressive upregulation of GFAP expression. Finally, at later time-points, the astrocytic processes embrace the FMNs replacing the microglial wrapping.

Both astrocyte-targeted production of either IL-6 or IL-10 induced important changes in the glial response associated to FNA. In general, these changes are more pronounced in GFAP-IL6Tg than in GFAP-IL10Tg animals, pointing towards a more robust effect of IL-6 on the glial response in this specific lesion paradigm. Regarding astrocytes, no differences in the pattern of GFAP expression were observed in GFAP-IL10Tg mice when compared with WT along all survival times analyzed, whereas in GFAP-IL6Tg animals, the astroglial response, evaluated in terms of GFAP immunoreactivity, was less intense than in WT (Article 1 and 2). This result is striking as, attending to previous published data, one might have expected an increase of GFAP in GFAP-IL6Tg mice after FNA. In fact, GFAP-

IL6Tg mice had increased basal expression of GFAP in specific brain areas such as the cerebellum (Campbell et al. 1993; Chiang et al. 1994), and, after FNA, IL-6 deficient mice showed less GFAP than lesioned WT (Klein et al. 1997).

As it will be detailed below, in terms of microglial activation, when compared to their corresponding WT, both GFAP-IL6Tg and GFAP-IL10Tg mice showed important modifications in proliferation, FMN wrapping, cluster formation, phagocytosis and the expression of several activation markers.

5.2 Effects of IL-6 and IL-10 on microglial dynamics

Our observations showed that, in basal conditions, both WT and GFAP-IL10Tg mice had similar number of microglial cells in the FN, whereas GFAP-IL6Tg mice showed higher microglial density. After FNA, in agreement with previous works (Conde and Streit 2006; Jones et al. 1997), our observations showed that microglial cells in WT animals increased in number during the early time-points after axotomy and, at later stages, microglial cell population gradually decreased (Article 1 and 2). Our results demonstrated that the increase in microglial cell number was due to proliferation, as the expression of the mitosis marker phosphohistone-3 (PH3) increased along FNA evolution (Suppl Fig.1). Although in GFAP-IL10Tg mice the evolution of microglial cell numbers along the course of FNA was similar to WT, in GFAP-IL6Tg we found a higher increase in the number of microglial cells at 3 dpi. Some studies support the idea that IL-6 controls the proliferative capacity of microglial cells, showing that treatment of microglial-astroglial co-cultures with IL-6 led to a slight stimulatory effect on microglial proliferation (Kloss et al. 1997), whereas the lack of IL-6 in deficient mice induced a reduction of microglial proliferation after FNA (Klein et al. 1997). Despite the proliferative effects described for IL-6 (Klein et al. 1997; Kloss et al. 1997) and the higher number of cells observed in our study after FNA in GFAP-IL6Tg mice, we found equal numbers of PH3+ cells at 3 dpi and less PH3+ dividing cells at 7 dpi than in WT. A possible explanation is the possibility that in GFAP-IL6Tg animals higher rates of proliferation took place before 3 dpi. Regarding GFAP-IL10Tg mice, the numbers of PH3+ proliferative cells at 3 and 7 dpi were similar to WT, indicating that astrocyte-targeted IL-10 production does not have a direct effect on microglial proliferation in this paradigm. This is supported by other *in vitro* studies, which demonstrated no effects of IL-10 in promoting microglial proliferation (Kloss et al. 1997; Sawada et al. 1999).

At later time-points after axotomy, supernumerary microglia was eliminated to achieve similar numbers as in basal conditions (Jones et al. 1997). Remarkably, in our study at 28 dpi, although microglial cell density decreases in comparison to the previous time-points in the different experimental groups, it is notably higher in both GFAP-IL6Tg (Article 4) and GFAP-IL10Tg (Article 2) than in WT mice. These results suggest that production of IL-6 and IL-10 could exert a protective role on microglial cells by regulating programmed cell death, which is the mechanism proposed by some authors to eliminate extra microglial cells (Raivich et al. 1998b). In this regard, studies *in vitro* reported that both IL-6 and IL-10 could promote microglial survival (Coelho-Santos et al. 2012; Strle et al. 2002).

5.3 Astrocyte-targeted production of IL-6 and IL-10 conditions microglial wrapping

In addition to the increase in cell number, we clearly described morphological changes in microglial cells along FNA. These modifications are seen in the different experimental groups with several

differences among them that we will discuss in the following paragraphs. In accordance with the bibliography, our results showed that at early stages, mostly at 7 dpi, microglia approach to the axotomized FMN and wrap them. Wrapping microglia has been described to interpose between the pre-synaptic and post-synaptic elements, a process known as "synaptic stripping", in order to disconnect excitatory inputs to motor neurons and allow axonal regeneration and functional recovery (Blinzinger and Kreutzberg 1968; Graeber et al. 1993; Kreutzberg 1996a; Perry and O'Connor 2010) (For a detailed review, see Article 3). In our study, no appreciable differences in microglial wrapping were observed between WT and GFAP-IL10Tg mice at any time-point after FNA (Article 2). In turn, GFAP-IL6Tg mice presented lower attachment of microglial cell processes to the axotomized FMN surface at 3 dpi (Article 1) that correlated with the less neuronal survival seen at 21 dpi. In addition, it should be noted that, in comparison with WT, GFAP-IL6Tg animals have a persistence of microglial wrapping at later time-points that could also be an indicative of dysfunctional cross-talk between microglia and FMN. In fact, other authors have already linked defects in the microglial wrapping to FMN with increasing rates of neuronal death (Hao et al. 2007; Makwana et al. 2007). The importance of cytokines in modulating microglial wrapping has already been described in previous works. Thus in IL-6KO mice, microglia presented abnormal morphology of the branches wrapping enwrap FMN (Galiano et al. 2001) and in MCSF deficient mice, microglia approached to FMN but failed to enwrap them (Raivich et al. 1994). Together with these observations, our findings in GFAP-IL6Tg mice support the idea postulated by some authors that microglial wrapping is playing a neuroprotective role in this paradigm (Hao et al. 2007; Makwana et al. 2007). Our results in GFAP-IL10Tg mice showed increased neuronal survival but not qualitative changes in the amounts of microglial wrapping. Despite there was not a significant increase in microglial wrapping in axotomized GFAP-IL10Tg animals, it is possible that there is a more efficient molecular communication with the wrapped FMN that could facilitate the neuroprotection observed in these animals.

In the search for molecules regulating microglial wrapping, we found important changes in the expression of some integrins in both GFAP-IL10Tg and GFAP-IL6Tg mice. Integrins are linked to the ability of microglia to attach FMN and, thus, to microglial wrapping (Graeber et al. 1988a; Kloss et al. 1999; Moneta et al. 1993; Petitto et al. 2003). In this regard, we have observed constitutive expression of CD11b and CD18, two subunits of the heterodimeric integrin MAC-1, also known as complement receptor-3 (CR3), in WT animals that is strongly upregulated after FNA. When compared to the WT, GFAP-IL10Tg mice have increased expression of CD18 at 3 and 14 dpi and increased expression of CD11b at 28 dpi (Suppl. Fig. 2). These modifications in integrin expression might play a role by improving the communication between microglia and FMN and therefore contribute to the neuroprotective effect seen in GFAP-IL10Tg mice. In agreement, other authors suggested that CD18 plays a role in maintaining neuronal survival after FNA (Makwana et al. 2007). In the case of GFAP-IL6Tg, we observed increased CD11b and CD18 at 3 dpi but then, strikingly, the levels of integrin expression drop drastically, specifically in the case of CD11b (Article 1). This reduction could explain the failure of complete microglial wrapping observed in GFAP-IL6Tg mice at 3 dpi and hence could be related to the lack of neuroprotection in this transgenic mice. Remarkably, integrin expression is also important for the migration and aggregation of microglia and the posterior formation of clusters which are described around 14 dpi (Kloss et al. 1999).

5.4 Important changes in microglial cluster formation in both GFAP-IL6Tg and GFAP-IL10Tg mice

One interesting observation of our study is the low number of microglial clusters observed in GFAP-IL6Tg mice and the high number found in GFAP-IL10Tg mice when compared to WT (Article 1 and 2). Microglial clusters are usually defined as accumulations of activated microglial cells. Also lymphocytes have been described in close relationship with microglial clusters (Raivich et al. 1998b). Microglial clusters are found around axotomized FMN, and have been commonly linked with phagocytosis of dead neurons after FNA (Raivich et al. 1998b). Some authors have even used the number of microglial clusters as an indirect way to measure motor neuronal death in this paradigm (Petitto et al. 2003). Following this reasoning and according to the modifications in neuronal death observed in our study, we expected an increase in the number of clusters in GFAP-IL6Tg mice and a decrease in GFAP-IL10Tg mice. However, as already mentioned, we observed that the number of clusters was inversely proportional to the number of death FMN, suggesting that microglial clustering may have another functions rather than simple the phagocytosis of the degenerating neurons. In connexion with this, we should mention that microglial cell clusters have also been related with microglial proliferation (Dissing-Olesen et al. 2007) and with interaction with myelin specific T-cells (Grebing et al. 2016) after entorhinal cortex lesion. In addition, the fact that, in multiple sclerosis, microglial clusters express MHC-II, CD40 and CD86; (Peferoen et al. 2015), and high levels of IL-10, (van Horssen et al. 2012); suggests that they may constitute the locations where interaction with infiltrated lymphocytes take place and therefore can act as major regulators of inflammation. The defect in cluster formation observed in GFAP-IL6Tg mice could be related to the drop in CD11b expression observed in these animals at 14 dpi, reflecting impairment in the migration and accumulation of microglia.

Another potential candidate molecule involved in microglial cluster formation is CD39, also known as NTPDase1, an ectonucleotidase that regulates purine concentrations in the extracellular space and mediates purinergic-mediated microglial migration (Farber et al. 2008). As described by other authors (Braun et al. 2000; Castellano et al. 1990), we detected constitutive expression of CD39 in both microglial cells and blood vessels in the non-lesioned FN of all experimental groups. While in WT and GFAP-IL10Tg mice the levels of CD39 increased similarly after FNA (Article 2), in GFAP-IL6Tg mice, the expression of this molecule was very restricted and mostly found at 14 dpi (Suppl. Fig. 3), which could also explain why microglial cells are not capable of forming clusters as efficiently as in WT. We can speculate that this reduction in microglial CD39 expression in GFAP-IL6Tg mice after FNA may be responsible of an inappropriate activation of microglial cells towards a more detrimental phenotype. In support of this view, some works reported that macrophages lacking CD39 are unable to shift to a regulatory state and consequently continue to produce inflammatory cytokines (Cohen et al. 2013). CD39 expression on alternative activated macrophages has been associated with an increase in their anti-inflammatory and tissue remodeling activities (Csoka et al. 2012). Furthermore, CD39 expression appears to regulate nucleotide and nucleoside-mediated signaling of lymphocyte migration and differentiation (Dwyer et al. 2007), which could be related to the differences observed in our study in terms of lymphocyte infiltration and their interaction with microglial clusters.

Interestingly, and in agreement with previous works reporting MHC-II expression strictly in microglial clusters (Jones et al. 2005; Kiefer and Kreutzberg 1991; Petitto et al. 2003), our results

showed that MHC-II staining was only found in microglial clusters in WT, GFAP-IL6Tg (Suppl. Fig. 4) and GFAP-IL10Tg (Article 2) mice. Moreover, expression of this molecule in both transgenic animals was significantly higher than in WT. The fact that GFAP-IL10Tg animals have an increase in MHC-II staining is surprising, as a down-regulatory effect of IL-10 on MHC-II expression has been reported (Howard and O'Garra 1992; Moore et al. 2001). In the case of GFAP-IL6Tg mice, the increase in MHC-II we found is in agreement with the literature showing the ability of IL-6 to increase the expression of this molecule both in peripheral macrophages (Wang et al. 2000) and in the microglial cell line BV2 (Shafer et al. 2002). Microglial MHC-II expression seems to play a function by interacting with infiltrating lymphocytes that accumulate nearby the microglial clusters (Byram et al. 2004; Olsson et al. 1992). As we will discuss below, the higher expression of this molecule in GFAP-IL6Tg and GFAP-IL10Tg mice, could be linked to changes in the microglial-lymphocyte cross-talk and therefore in their implication in supporting neuronal survival.

5.5 Astrocyte-targeted production of IL-6 and IL-10 modifies the expression of microglial phagocytic markers

Phagocytosis is one of the main functions assigned to microglial cells after FNA (Petitto et al. 2003; Raivich et al. 1999; Rinaman et al. 1991). In addition to changes in proliferation, wrapping and microglial cluster formation, our study also revealed that the transgenic production of IL-6 and IL-10 induced important modifications in the phagocytic phenotype of microglia. Thus, in both GFAP-IL6Tg (Article 4) and GFAP-IL10Tg mice (Article 2) we have observed important changes in the expression of the Fc gamma Receptor III and the Fc gamma Receptor II (CD16/32), markers commonly associated with phagocytosis (Goodridge et al. 2012; Okun et al. 2010; Ulvestad et al. 1994). While GFAP-IL10Tg mice showed more CD16/32 from 3 to 7 dpi; GFAP-IL6Tg mice experienced a peak in CD16/32 at 14 dpi, preceding the time with higher neuronal death; followed by a drop at 21 dpi. In both animals, an upturn in the expression of CD16/32 occurred at 28 dpi, when the resolution of the lesion is expected and a down-regulation of the general microglial activation markers occurs in WT animals (Almolda et al. 2014). These results make it difficult to assign an absolute or harmful role to the expression of CD16/32 after FNA. Thus, to a better description and understanding of the phagocytic phenotype of microglia, we analyzed the expression of CD68, a lysosomal marker related with the phagocytic activity (Holness and Simmons 1993; Travaglione et al. 2002). In GFAP-IL6Tg, we found alterations at 7 dpi and later time-points after axotomy suggesting that increased functional phagocytosis is taking place and is sustained by IL-6 over time. In contrast, the effect of transgenic production of IL-10 was more evident at early time-points, inducing lower levels of CD68 expression (Article 4). A decrease in CD68 expression may be related with less presence of cellular debris expected in GFAP-IL10Tg mice since neuronal survival is promoted.

We also assessed the expression of a newly identified receptor that may be involved in microglial phagocytosis: TREM2 (Schmid et al. 2002; Takahashi et al. 2005) and its coreceptor "DNAX activation protein of 12kDa" (DAP12)(Bouchon et al. 2001). In CNS homeostatic conditions, TREM2 participate in the constant phagocytic clearance of cell debris by microglia, without triggering inflammatory responses (Neumann et al. 2009). Dysfunction of the pair TREM2/DAP12 leads to chronic neurodegenerative Nasu-Hakola disease (NHD) (Kiialainen et al. 2005; Paloneva et

al. 2001) and some missense TREM2 mutations increase risk of developing Alzheimer's disease (Guerreiro et al. 2013; Jonsson et al. 2013). Considering the importance of TREM2 for the correct CNS function, it has been commonly linked with a neuroprotective role. Nonetheless, studies assessing the role of TREM2 after a variety of CNS challenges brought to light some controversy. For example, silencing microglial TREM2 exacerbated spatial cognitive deficits and tau pathology (Jiang et al. 2015). Moreover, overexpression of TREM2 rescued the symptoms in P301S tau transgenic mice (Jiang et al. 2016b). However, the same research group revealed no improvement after TREM2 overexpression in a mouse model of Alzheimer's disease (Jiang et al. 2016a). Likewise, although a role in dampening inflammation is mainly assigned to TREM2 (Lue et al. 2015; Painter et al. 2015; Turnbull et al. 2006), TREM2-KO mice had attenuated inflammatory response following stroke (Sieber et al. 2013) and reduced recruited macrophages, concomitant with decreased production of inflammatory cytokines after TBI (Saber et al. 2016). In our paradigm, we observed that, in the non-lesioned FN, TREM2 staining was similarly detected around the nucleus of microglial cells of WT, GFAP-IL6Tg and GFAP-IL10Tg. FNA induced a substantial upregulation of microglial TREM2 and DAP12 expression in all groups. In the case of GFAP-IL6Tg mice, TREM2 was increased respect to the WT only at 28 dpi. Although the meaning of such increase is unclear, it could be directly related to the increase in neuronal death in the GFAP-IL6Tg providing a signaling mechanism that favors the removal of damaged cells (Article 4). In front to WT, GFAP-IL10Tg mice haddecreased levels of TREM2 at the early time-points, in parallel with lower levels of CD68 (Article 4). It seems plausible that if there are less FMNs degenerating in these transgenic mice, also there is less need to express signals that promote phagocytosis as well as markers involved in the removal of cellular debris.

In addition to its involvement in signaling mechanisms of phagocytosis, some authors have suggested that TREM2 can perform other functions proposing TREM2 as a general molecule of microglial activation (Schmid et al. 2002). Thus, TREM2 expression has been propossed to control microglial migration (Melchior et al. 2010; Takahashi et al. 2005), to induce the switch from M1 to M2-like phenotype (Jiang et al. 2016b) and to synergize with activation of the CSF1R promoting microglial survival (Wang et al. 2015b). Indeed, we found increased TREM2 expression correlating with a higher microglial density in GFAP-IL6Tg at 28 dpi, supporting a role for TREM2 in the maintenance of microglial survival. Altogether, our observations indicate that TREM2 is clearly altered in activated microglial cells in both transgenic mice after FNA, leading us to postulate that pro- and anti-inflammatory microenvironments may influence the expression of this "eat me" signal after a peripheral nerve injury.

5.6 Alternative markers of microglial activation are barely induced after FNA but not modified in GFAP-IL6Tg and GFAP-IL10Tg mice

Although microglial activation is an unquestionable feature after FNA (Kreutzberg et al. 1989; Moran and Graeber 2004), little is known about whether microglia adopt an alternatively activated phenotype in this paradigm. Considering that *in vitro*, IL-10 is one of the main inducers of M2-like microglia, (Franco and Fernandez-Suarez 2015; Orihuela et al. 2016) and that *in vivo*, blockade of IL-6 inhibits M1-classical activation (Guerrero et al. 2012), we have checked whether astrocyte-targeted IL-6 or IL-10 production were able to induce changes in the activation phenotype of microglial cells after FNA. We have shown that non-lesioned and axotomized WT, GFAP-IL6Tg

(Suppl. Fig. 3) and GFAP-IL10Tg animals (Article 2) did not express Ym-1. After FNA, they barely express Arginase-1 and CD150. These three markers are usually associated with alternative microglia/macrophage activation phenotype (Gordon and Martinez 2010). Our results indicated that the signals driving microglial activation during FNA evolution do not induce an alternative microglial phenotype at any time-point after lesion and, on the other hand, that neither transgenic production of IL-6 nor IL-10 have no effect promoting M1/M2 switching.

5.7 Lymphocyte recruitment is increased by both IL-6 and IL-10 production

Infiltration of T-cells without BBB disruption in the FN parenchyma and their aggregation around axotomized FMN is a key event following FNA (Olsson et al. 1992; Raivich et al. 1998b). In addition to the changes in the pattern of microglial activation, our results showed that astrocyte-targeted production of IL-6 and IL-10 induced a significant increase in lymphocyte recruitment into the lesioned FN (Article 1 and 2). How these cytokines increase lymphocyte infiltration is unknown. However, it should be pointed out that GFAP-IL6Tg mice show increased basal lymphocyte infiltration in specific areas of the CNS, such as the cerebellum that is concomitant with upregulation of the adhesion molecules VCAM-1 and ICAM-1 (Campbell et al. 1993; Milner and Campbell 2006) and the chemokines CCL5 and CCL12 (Quintana et al. 2009). These are key molecules involved in lymphocyte transmigration across BBB (Engelhardt 2008; Greenwood et al. 2002; Wilson et al. 2010). Furthermore, other authors reported that transgenic deletion of IL-6 caused a massive decrease in the recruitment of T-cells (Galiano et al. 2001). Regarding IL-10, potent down-regulatory effects on the expression of adhesion molecules in vascular cells and macrophages are well-accepted (Henke et al. 2000; Krakauer 1995) and supported also by upregulation of both VCAM-1 and ICAM-1 in IL-10 deficient mice (Kawachi et al. 2000). *In vitro*, IL-10 inhibits CCL5 production by both microglia (Hu et al. 1999) and astrocytes (Guo et al. 1998) and suppress CCL2 after β-amyloid and LPS stimulation of primary murine microglia (Szczepanik et al. 2001) and CXCL10 in citomegalovirus-stimulated microglia (Cheeran et al. 2003). Altogether these studies reflect the importance and necessity of a detailed analysis of the expression of these adhesion molecules and chemokines in this lesion model.

Nonetheless, a neuroprotective function has been attributed to infiltrated T-cells since the lack of functional mature T-cells has been correlated with a dramatic increase in neuronal death after FNA (Serpe et al. 2000). Moreover, the same research group demonstrated that the increase in neuronal death is prevented by reconstitution with functional T and B cells (Serpe et al. 1999). Later on, it was described that specifically the CD4+, Th2 cells, are the responsible for the neuroprotective effect (Serpe et al. 2003; Xin et al. 2008). In this context, our results showing higher T-lymphocyte infiltration in correlation with increased neuronal survival in GFAP-IL10Tg mice are in agreement with the putative protective role associated to T-cells in this paradigm. By contrast, the fact that GFAP-IL6Tg mice had an increase in lymphocyte infiltration correlating with a higher neuronal death caught our attention. A possible explanation could be that astrocyte-targeted production of IL-6 shifts the phenotype of infiltrating T-cells towards a pro-inflammatory Th17 phenotype, as it has been described in other neuroinflammatory conditions (Kimura and Kishimoto 2010). Thus the lack of the neuroprotective subtype Th2 and the prevalence of Th17 may be responsible of the increase in neuronal death we found in GFAP-IL6Tg mice. It is important to mention here that, so far, the exact subtypes of T-cells infiltrating the FN are unknown in part due to methodological difficulties since

the precise tissue dissection of FN and obtaining enough volume tissue for an accurate flow cytometry analysis is not an easy task. The few reports addressing this issue attempted to describe the different subtypes indirectly by analyzing the draining cervical lymph nodes (Deboy et al. 2006; Jones et al. 2005). These studies reported similar increase of CD4+ T cells expressing either IFN-γ or IL-4, i.e. Th1 and Th2 effector cells respectively. A better characterization of the specific T-cell subtypes infiltrating the FN along the different time-points after axotomy would be very useful to unravel the role of lymphocytes in this lesion paradigm.

In the three experimental animal groups of our study, infiltrated CD3 positive T-cells are found closely related to microglial clusters, supporting the idea that, in these specific locations, MHC-II positive microglial cells might act as antigen presenting cells and regulate lymphocytic activity (Byram et al. 2004; Carson 2002). In this context, an impaired cross-talk between lymphocytes, neurons and microglia promoted by the transgenic production of IL-6 or IL-10 could be the reason for a higher or lower neuronal cell death. Molecular signaling involved in this cellular dialogue is not completely characterized, but one important adhesion molecule described in infiltrating T-cells after FNA and implicated in this cross-talk with microglia and neurons is CD44 (Raivich et al. 1998b). CD44 has been involved in intercellular and cell-matrix adhesion, cell migration and lymphocyte activation and homing (Goodison et al. 1999; Johnson and Ruffell 2009; Ponta et al. 2003) and is also a receptor for the osteopontin (OPN) which is expressed in FMNs (Weber et al. 1996; Zohar et al. 2000). We observed that while GFAP-IL10Tg mice showed higher numbers of CD3+/CD44+ lymphocytes than WT, most of the infiltrating lymphocytes in GFAP-IL6Tg failed to express CD44. This observation reinforces the hypothesis that the communication between neurons, lymphocytes and microglia is altered in GFAP-IL10Tg and GFAP-IL6Tg mice.

5.8 Altered kinetics of FMN loss in both GFAP-IL6Tg and GFAP-IL10Tg mice

In our studies, we showed that, astrocyte targeted IL-6 production led to an increase in neuronal death, whereas astrocyte-targeted IL-10 production induced a strong beneficial effect on neuronal survival (Articles 1 and 2). These quantitative studies have been performed at 21 days after axotomy. As previously discussed in detail above, these differences on neuronal survival may be due to the important changes observed in microglial reactivity, lymphocyte infiltration and altered cross-talk after FNA induced by the transgenic production of either IL-6 or IL-10. However, we cannot exclude the possibility that transgenic production of the mentioned cytokines also plays a direct effect on FMN survival as these neurons are known to express receptors for both IL-6 (Klein et al. 1997) and IL-10 (Xin et al. 2011). In this regard, a direct neurotoxic effect of IL-6 is not rare as chronic IL-6 treatment induced the death of cerebellar neurons in cultures (Conroy et al. 2004) and the deficiency of IL-6 in KO animals has been associated with increased motor neuron survival (Galiano et al. 2001). A possible mechanism that could explain this neurotoxicity comes from studies that showed alterations of both NMDA and glutamate receptors in cultured neurons after chronic IL-6 exposure (Nelson et al. 2004; Qiu et al. 1998). On the other hand, neuroprotective effects promoted by IL-10 were expected as administration of this cytokine has been described to improve the lesion outcomes after focal stroke (Spera et al. 1998), excitotoxic (Brewer et al. 1999) or traumatic (Bethea et al. 1999) spinal cord injury and after peripheral sciatic nerve transection (Atkins et al. 2007). As we observed an IL10R increase in FMNs of GFAP-IL10Tg mice, neuroprotective actions exerted by transgenic

IL-10 production could be explained by a direct effect on these motor neurons, either acting as a neurotrophic factor (Zhou et al. 2009) or preventing neuronal death (Sharma et al. 2011).
Another interesting result derived from this thesis is the putative use of OPN as a marker of the "endangered" motor neurons. Although in some CNS challenges OPN has been described in microglia and astrocytes (Choi et al. 2007; Fu et al. 2004; Hashimoto et al. 2003; Iczkiewicz et al. 2005; Jin et al. 2006; Kim et al. 2002; Shin et al. 2005), some authors also reported the expression of this molecule, in basal conditions, in mouse spinal cord motor neurons (Misawa et al. 2012) and in FMNs in the rat facial nucleus (Shin et al. 1999; Suzuki et al. 2012). Increased OPN has also been described in affected neurons after diverse kind of CNS pathologies such as spinal root avulsion (Fu et al. 2004), epilepsy (Borges et al. 2008), scrapie infection (Jin et al. 2006), cryolesion (Shin et al. 2005), oxygen-glucose-deprived hippocampal slices (Lee et al. 2010a), Alzheimer's disease (Wung et al. 2007), multiple sclerosis (Sinclair et al. 2005) and different EAE models (Chabas et al. 2001). In agreement, in our studies, OPN expression was not observed in microglial cells and astrocytes but found to be constitutively expressed by the FMNs in the non-lesioned WT, GFAP-IL6Tg (Article 1) and GFAP-IL10Tg mice (Suppl. Fig. 5). Increased OPN expression was found in lesioned FMNs in the three experimental groups. Both neurodegenerative and neuroprotective effects have been attributed to neuronal OPN expression (Braitch and Constantinescu 2010) (Carecchio and Comi 2011; Shin 2012). Although only GFAP-IL6Tg mice experienced a remarkable OPN increase at 14 dpi, when a peak of FMN death has been described (Dai et al. 2000; Raivich et al. 1998b), the exact role played by OPN after FNA could be tricky to establish, as both GFAP-IL6Tg and GFAP-IL10Tg showed less expression than WT at 21 dpi, the time-point when neuronal survival was analyzed.

Although the peak of FMN death after FNA has been described to occurs around 14 dpi (Dauer et al. 2011; Fendrick et al. 2005; Mignini et al. 2012; Raivich et al. 1998b), it has been reported that the number of FMNs continues to decline gradually after FNA (Serpe et al. 2000). Therefore, we analyzed long-term neuronal survival at 42 dpi and, in contrast to the variations observed at 21 dpi, we found that the number of surviving FMNs in the three groups of animals was similar with approximately 55% of FMN death (Suppl. Fig. 6). These findings indicate that transgenic IL-6 and IL-10 production exerted temporal neurodegenerative or neuroprotective effects. The fact that neither IL-6 nor IL-10 transgenic production affected the long-term FMN survival suggests that more factors might be required to maintain these neurodegenerative/neuroprotective effects for long time periods. In fact, the successful regeneration-associated-genes expression in the FMN body and the expression of growth factors in the surrounding parenchyma are both essential for proper axonal regeneration; the main requirement for prolonged neuronal survival (Hottinger et al. 2000; Zhao et al. 2004).

5.9 Impaired nerve regeneration in GFAP-IL6Tg but not in GFAP-IL10Tg mice

The study of neuronal regeneration was assessed by the injection of the retrograde fluorescent marker Fluorogold® (FG) into the both whiskerpads 7 days prior to the sacrifice at 42 dpi. Our results showed that while both WT and GFAP-IL10Tg mice had a similar regeneration index (WT= 23.22% ± 3.941, GFAP-IL10Tg= 16.20% ± 8.765), GFAP-IL6Tg mice had significantly impaired regeneration (9.936% ± 4.488) (Suppl. Fig. 7). As already stated in the previous section, the percentage of FMN survival at 42 dpi is around 45% whereas the regeneration index is comparably lower, in all experimental groups. Such difference may be due to the methodology, as we are evaluating the amount of FMNs regenerating an axon that arrived to the anatomic area injected with the retrograde

marker FG. Therefore, it might be that part of the surviving neurons were able to regenerate an axon, which might reach other targets nearer to the transection area; i.e. it would not be detected with FG tracing injected in the whiskerpads. In this sense, it has been reported that facial nerve transection leads to misdirection and excessive branching of regenerating axon fibers (Aldskogius and Thomander 1986; Asahara et al. 1999; Choi and Raisman 2002; Dohm et al. 2000; Ito and Kudo 1994; Popratiloff et al. 2001).

In the case of GFAP-IL6Tg mice, the low regenerative index we found in comparison to WT may be explained taking into account the increased neuronal death in these animals after FNA but also the putative role attributed to IL-6 in promoting axonal regeneration, which can lead to higher amounts of misdirected axons. In this regard, it has been reported that, after hypoglossal nerve transection, transgenic mice constitutively expressing IL-6/IL-6R had increased nerve regeneration (Hirota et al. 1996), whereas IL-6 deficient mice demonstrated a delayed functional recovery after sciatic nerve crush and a moderate reduction in regeneration after FNA (Galiano et al. 2001; Zhong et al. 1999). It has been shown that *in vitro,* administration of IL-6 promotes sprouting, functional recovery and neurite outgrowth in lesioned organotypic hippocampal slices (Hakkoum et al. 2007; Yang et al. 2012). Moreover, *in vivo* administration of IL-6 stimulates neurite regeneration after nerve transection of the dorsal root ganglion (Shuto et al. 2001) and improves functional recovery after cortical spinal tract injury (Yang et al. 2012). Conversely, some studies reported a detrimental role of IL-6 in nerve regeneration (Armstrong et al. 2008) (Koulaxouzidis et al. 2015).

Regarding GFAP-IL10Tg mice, we could expect an increase in axonal regeneration since the number of surviving neurons is greater at least during the first weeks, however the regenerative index we found was not higher than in WT. These results draw attention taking into account the studies attributing a role to IL-10 in promoting nerve regeneration (Atkins et al. 2007; Jancalek et al. 2010; Sakalidou et al. 2011; Siqueira Mietto et al. 2015). Thus, considering the direct effects of IL-10 in maintaining neuronal survival (Sharma et al. 2011; Zhou et al. 2009), it seems plausible that FMNs survive for a long period, though they were not able to successfully regenerate the axon or, as discussed before in the case of GFAP-IL6Tg, regenerating axons in GFAP-IL10Tg could be also misdirected to a different targets and therefore remain undetectable with the FG method.

For a better understanding of the regenerative status of FMNs, we also assessed the neuronal expression of CD44. Apart from its functions on the immune cells previously described, neuronal CD44 is also known as one of members of the so-called "regeneration-associated-molecules" (Dzwonek and Wilczynski 2015; Raivich and Makwana 2007). , In our studies, *de novo* CD44 expression was found in FMNs after FNA. When compared to WT, GFAP-IL10Tg mice showed an important increase in neuronal CD44 expression at 14 and 28 dpi (Suppl. Fig. 8), whereas GFAP-IL6Tg mice presented a marked decrease in CD44 expression from 7 to 28 dpi (Article 1). An elegant study using electron microscopy showed CD44 in the outer part of the plasmalemma of the FMN bodies and their dendrites and axon after FNA (Jones et al. 1997). Although the exact function played by CD44 in motor neurons is not clear, there is evidence suggesting that its presence in regenerative neurons play a role in regulation of axonal outgrowth (Lin and Chan 2003; Makwana et al. 2010; Ries et al. 2007). Being that the case, the drastic CD44 reduction we found in GFAP-IL6Tg animals could explain the impairment in successful axonal regeneration in these mice. In contrast, the slight increase in CD44 expression observed in GFAP-IL10Tg mice may be related to an increased attempt

of axonal growth, yet regeneration is ultimately unsuccessful. Probably, other regeneration-associated molecules must be upregulated to promote a more robust effect.

Figure 1 has been prepared in order to highlight the main findings in this thesis.

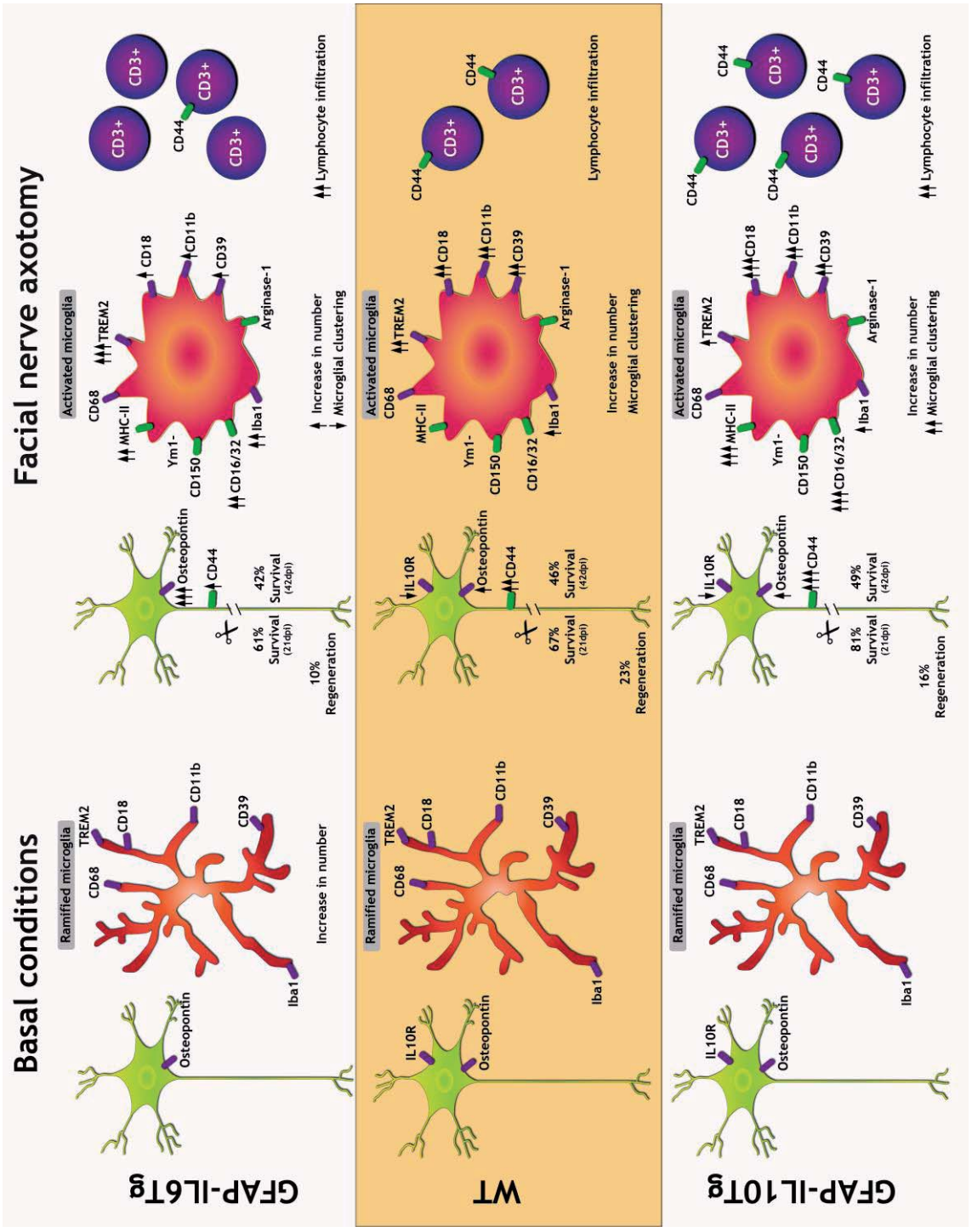

Figure 1. Schematic representation of the main changes after FNA in WT, GFAP-IL6Tg and GFAP-IL-10Tg mice. On the left side, molecules expressed in neurons and microglia in basal conditions in WT, GFAP-IL6Tg and GFAP-IL10Tg are depicted. After FNA (right side), changes in the expression (purple) and "de novo" expression (green) of several molecules are depicted in axotomized neurons, activated microglia and infiltrated lymphocytes. See the text for details.

6. CONCLUSIONS

The results obtained in this thesis indicate that astrocyte-targeted production of IL-6 and IL-10 induces important alterations in glial activation and lymphocyte recruitment after FNA that correlates with modifications in short-term neuronal survival and axonal regeneration.

More specifically:

- The pattern of microglial activation after FNA is substantially modified by astrocyte-targeted production of IL-6 and IL-10 and correlates with changes in neuronal survival. The alterations in the microglial response determine the outcome of the lesion.

- Astrocyte-targeted production of IL-6 and IL-10 increase the number of microglial cells in basal conditions as well as throughout the different time-points after FNA. In GFAP-IL6Tg mice, microglial increase is related to changes in the microglial proliferation rate, whereas in GFAP-IL10Tg is linked to a protective role of IL-10 against programmed cell death.

- While microglial wrapping is not affected in GFAP-IL10Tg mice, in GFAP-IL6Tg mice this mechanism is impaired. These changes in microglial wrapping are related to a downregulation of integrin expression.

- The number of microglial clusters is lower in GFAP-IL6Tg and higher in GFAP-IL10Tg mice, being inversely proportional to the FMN death observed at short-term. In both transgenic mice, microglial clusters display higher MHC-II expression than WT.

- Astrocyte-targeted production of IL-6 and IL-10 induces changes in the phagocytic machinery of microglia and in the expression of the "eat-me" signal TREM2.

- In WT, activated microglia do not acquire an alternative activation phenotype at any time after FNA. Neither astrocyte-targeted production of IL-6 nor IL-10 are capable of induce an alternative activated phenotype of microglia in this paradigm.

- In terms of astrocytic response, only GFAP-IL6Tg mice presents down-regulation of GFAP expression along the evolution of the lesion.

- Astrocyte-targeted production of IL-6 and IL-10 increases the recruitment of lymphocytes to the facial nucleus parenchyma. Infiltrated lymphocytes in GFAP-IL6Tg mice fail to express the cell adhesion molecule CD44, whereas in GFAP-IL10Tg animals their expression is higher.

- At 21 days post axotomy, astrocyte-targeted production of IL-6 induces an increase in neuronal death, whereas astrocyte-targeted production of IL-10 reduces neuronal death, due to a direct action of these cytokines on the axotomized FMNs as well as an indirect effect derived from the altered glial reactivity and lymphocyte recruitment. Changes induced in neuronal survival by these cytokines are not maintained at 7 weeks post injury.

- Effective functional regeneration was not altered in GFAP-IL10Tg mice, whereas, it was impaired in GFAP-IL6Tg mice.

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