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Role of the immune response in initiating central nervous system regeneration in vertebrates: learning from the fish

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ABSTRACT The mammalian central nervous system is not able to regenerate neurons lost upon injury. In contrast, anamniote vertebrates show a remarkable regenerative capacity and are able to replace damaged cells and restore function. Recent studies have shown that in naturally regenerating vertebrates, such as zebrafish, inflammation is a key processes required for the initiation of regeneration. These findings are in contrast to many studies in mammals, where the central nervous system has long been viewed as an immune-privileged organ with inflammation considered one of the key negative factors causing lack of neuronal regeneration. In this review, we discuss similarities and differences between naturally regenerating vertebrates, and those with very limited to non-existing regenerative capacity. We will introduce neural stem and progenitor cells in different species and explain how they differ in their reaction to acute injury of the central nervous system. Next, we illustrate how different organisms respond to injuries by activation of their immune system. Important immune cell types will be discussed in relation to their effects on neural stem cell behavior. Finally, we will give an overview on key inflammatory mediators secreted upon injury that have been linked to activation of neural stem cells and regeneration. Overall, understanding how species with regenerative potential couple inflammation and successful regeneration will help to identify potential targets to stimulate proliferation of neural stem cells and subsequent neurogenesis in mammals and may provide targets for therapeutic intervention strategies for neurodegenerative diseases.

KEY WORDS: *neuro-inflammation, injury, lipid mediator, cytokine, immune cell*

Introduction

Although continuous generation of new neurons occurs in the central nervous system during adulthood, mammals are not able to regenerate neurons lost upon traumatic injury, stroke or neurodegenerative diseases. In spite of extensive research, it is still not fully understood, why teleosts and amphibia such as axolotl and zebrafish, are capable of regenerating extensive parts of their body, while mammals such as human or mouse, can not (reviewed by (Kaslin *et al.*, 2008; Tanaka & Ferretti, 2009; Grandel & Brand, 2013; Alunni & Bally-Cuif, 2016; Fig. 1).

Some studies indicate that extensive neuronal regeneration has been lost in certain vertebrate species selectively and propose that this loss correlates with the development of a more complex immune system (reviewed by (Aurora and Olson, 2014). Whether or not this hypothesis holds true, remains to be experimentally addressed. Of note, zebrafish, which exhibit extensive neuronal regeneration, also possess a complex immune system (Renshaw and Trede, 2012). Until recently, inflammation following traumatic injury was considered to be mainly detrimental, especially through secondary damage to the wounded tissue mediated by a variety of inflammatory signaling molecules (recently reviewed by (Gadani *et al.*, 2015; McKee and Lukens, 2016). However, increasing evidence indicates that inflammation also has a strong pro-regenerative role in the nervous system. In this review, we discuss the emerging role of the immune system in initiating regeneration of the central nervous system, and highlight differences between non-regenerating and naturally regenerating organisms

Abbreviations used in this paper: CNS, central nervous system; COX, cyclooxygenase; CysLT, cysteinyl leukotriene; IL, interleukin; IFN, interferon; LT, leukotriene; NPC, neural precursor cell.

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in the context of their immune response to injury.

Constitutive and regenerative neurogenesis potentials differ between mammals and teleosts

The vertebrate central nervous system, consisting of the brain, the spinal cord and the retina, has long being considered a static organ system, with only limited generation of new neurons during adulthood (Rakic, 1985). This view has been extensively challenged and today it is well accepted that adult neurogenesis takes place in many different species, including mammals, where it is mainly found within two specific regions in the brain: the subventricular zone (SVZ) of the telencephalic lateral ventricle and the subgranular zone (SGZ) of the dentate gyrus in the hippocampus ((Altman and Das, 1965; Doetsch and Alvarez-Buylla, 1996); recently reviewed by ((Kempermann, 2015; Gage *et al.*, 2016)). Many factors capable of actively modulating adult neurogenesis are already known. For instance, stress and aging are stimuli that negatively affect neurogenesis (Cameron *et al.*, 1993; Kuhn and Gage, 1996; Garthe *et al.*, 2016), whereas environmental enrichment and physical exercise can increase formation of new neurons in the adult dentate gyrus of the hippocampus (Kempermann *et al.*, 1997; van Praag *et al.*, 1999). Adult neurogenesis was also confirmed in humans (Eriksson, 1998; Spalding *et al.*, 2013), creating some hope that upon better knowledge of the required signals to activate neural stem cells, neurodegenerative diseases and tissue loss due to injury could be overcome in the future. Until today, the phenomenon of adult neurogenesis has been extensively studied in many different species and is considered to be an evolutionarily conserved trait (Lindsey and Tropepe, 2006; Kaslin *et al.*, 2008; Kempermann, 2012; Kempermann, 2015). In contrast to mammals, teleost fish such as three-spined stickleback, gymnotiform and zebrafish possess abundant sources of neurogenesis (Zupanc *et al.*, 1996; Ekström *et al.*, 2001; Grandel *et al.*, 2006). In these species, numerous neurogenic niches are distributed along the entire rostro-caudal brain axis, where continuous turnover of neurons is found until adulthood (Zupanc *et al.*, 2005; Grandel *et al.*, 2006; Ganz and Brand, 2016). Remarkably, besides life-long constitutive neurogenesis, teleosts are also potent regenerators following a traumatic injury (Kroehne *et al.*, 2011; Baumgart *et al.*, 2012; Than-Trong and Bally-Cuif, 2015; Kaslin *et al.*, 2017).

Stem and progenitor cells contribute to tissue regeneration after traumatic injury in the anamniote vertebrate central nervous system

The regenerative potential of animals varies greatly between different species. In general, anamniote vertebrates have greater regenerative capacity compared to amniotes (reviewed by (Kaslin *et al.*, 2008; Grandel & Brand, 2013; Tanaka & Ferretti, 2009; Fig. 1). Despite the fact that adult neurogenesis occurs in mammalian species, regenerative capacity is very limited. Although constitutive neurogenesis can be significantly increased by physical exercise or environmental stimuli, the number of neurons generated is usually not sufficient to replace cells lost due to injury or neurodegenerative disease (Jessberger and Kempermann, 2003; Kronenberg *et al.*, 2003; Fabel *et al.*, 2009).

In areas where neurogenesis is normally absent, such as the cerebral cortex and the striatum, recent studies have indicated a certain degree of reactive neurogenesis following ischemic stroke (recently reviewed by (Lindvall and Kokaia, 2015)). To address the problem of insufficient regenerative neurogenesis, astrocytes and NG2 glia reacting to injury, have become an interesting target for neuronal reprogramming strategies (for recent reviews see (Péron and Berninger, 2015; Berninger and Jessberger, 2016; Gascón *et al.*, 2017)).

In contrast to mammals, the zebrafish has remarkable regenerative capacity and is therefore an extremely valuable model for regeneration research (see review by (Kizil *et al.*, 2011; Gemberling *et al.*, 2013)). To study traumatic brain injuries various lesion paradigms have been established in rodents such as weight-drop models, fluid percussion or cortical stab wound injuries (reviewed

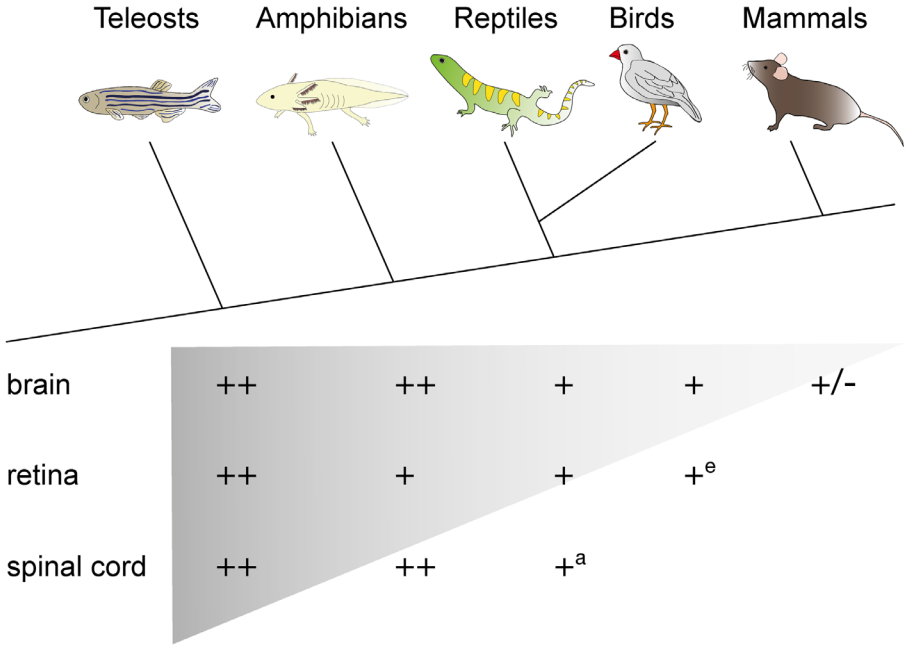

Fig. 1 Regenerative potential of the central nervous system differs across vertebrate classes. *The ability to regenerate the central nervous system (CNS) varies between different vertebrate species and relates to their phylogenetic distance from each other. Regenerative potential has declined throughout evolution; Teleosts, such as the zebrafish, show extensive regeneration of the brain, retina and spinal cord. Amphibians and reptiles possess the ability to regenerate certain areas of their CNS. In reptiles, spinal cord regeneration is limited to axonal regrowth, but no longer neurogenesis (+^{a}). In birds, retinae can regenerate during embryonic stages but no longer in the adult organism. Although some degree of reactive neurogenesis has been observed in the mammalian CNS, it is typically insufficient for regeneration of neurons lost to injury or disease. After Grandel and Brand, 2013, modified. ++ high regenerative potential, + regeneration, +^{a} axonal regrowth, +^{e} regeneration at embryonic stages, +/- neurogenesis insufficient for regeneration. Note that this denotes qualitative levels of CNS regeneration at the tissue level; regeneration competence may well differ for different cell lineages (e.g., Kaslin* et al.*, 2017).*

by (Xiong *et al.*, 2013); (Buffo *et al.*, 2005)). To create a stab wound injury in the adult zebrafish telencephalon, a small cannula is introduced through the nostril into the brain parenchyma without directly targeting the ventricular zone, where the neural stem cells (radial glial cells) reside (Kroehne *et al.*, 2011). Upon injury a quick cellular response of increased apoptosis and edema formation is observed. Radial glial cells react to injury and increase proliferation at the ventricular zone of the lesioned hemisphere, and genetic lineage tracing experiments confirmed that the daughters of radial glia differentiate into neurons that repopulate the lesion site. In addition, an increase of glial fibrillary acidic protein as well as hypertrophy of glial processes indicates reactive gliosis, however neither chronic inflammation nor scarring occurs in the adult zebrafish brain after injury (Kroehne *et al.*, 2011). Other studies have similarly shown that the zebrafish successfully regenerates after stab wound injuries to the telencephalon via increased proliferation of radial glial cells (Ayari *et al.*, 2010; März *et al.*, 2011; Baumgart *et al.*, 2012; Kishimoto *et al.*, 2012). More recently, it has been suggested, that the stem cell pool of the adult zebrafish telencephalon may be depleted during regeneration, as some of the stem cells may directly convert to neurons, rather than undergoing symmetric and asymmetric divisions (Barbosa *et al.*, 2015).

Similar regenerative events are reported to occur in the vertebrate retina (reviewed by (Lenkowski and Raymond, 2014; Wan and Goldman, 2016)). Mammals exhibit the lowest regenerative capacity, while non-mammalian vertebrates such as chick, amphibians and fish show higher potential. Similar to sites of continuous proliferation in the adult brain, the ciliary marginal zone (CMZ) of birds, amphibians and fish functions as stem cell niche, contributing both to adult growth of the retina and regeneration (reviewed by (Hamon *et al.*, 2016). In amphibian retinae neuronal progenitor cells are generated by transdifferentiation of pigmented epithelial cells. During homeostasis, zebrafish Müller glia give rise to rod photoreceptors only (Raymond *et al.*, 2006). This changes upon retinal damage: Müller glia partially de-differentiate, undergo interkinetic nuclear migration, re-enter the cell cycle and generate a single neuronal progenitor cell by asymmetric cell division. This progenitor undergoes subsequent cell divisions and forms a neurogenic cluster migrating towards the lesion site where the cells differentiate into the lost types of neurons (Nagashima *et al.*, 2013). During regeneration, various signals involved in stress response, inflammation, gliosis and cell adhesion are required and sufficient to stimulate Müller glia proliferation (see section 6. below for more details).

Reactive proliferation has also been observed following spinal cord injury in the zebrafish, where (ependymal-) radial glial cells start to proliferate and generate new motor neurons. Newly generated neurons mature and show signs of terminal differentiation and integration into the circuitry (Reimer *et al.*, 2008). Radial glia migrate to the transected area of the spinal cord, where they form a "glial bridge" which supports axonal regeneration across the lesion site (Goldshmit *et al.*, 2012). In addition, also large numbers of different types of interneurons are found after lesion. However, they are not generated from $Olig2^+$ precursor cells but a different $Pax6^+$ $Nkx6.1^+$ progenitor domain. Interestingly, new V2 interneurons are generated in a domain of the ependymal layer, which are normally not present in the unlesioned spinal cord (Kuscha, Frazer, *et al.*, 2012). Despite the fact that zebrafish show altered serotonergic and dopaminergic innervation, locomotor function is restored after 6 weeks, indicating a high plasticity of the adult spinal network (Kuscha, Barreiro-Iglesias, *et al.*, 2012).

Immune response following central nervous system injury in mammals and non-mammalian vertebrates

Inflammation is a rapid process following injury and involves activation of different types of immune cells. Responsive immune cells can be local, tissue-resident, self-renewing cells -such as microglia in the central nervous system- as well as peripheral monocyte-derived macrophages, neutrophils and cells of the adaptive immune system such as B cells and T cells. Circulating immune cells such as monocyte-derived macrophages, granulocytes and T cells can recruit additional immune cells to the site of injury via secretion of inflammatory mediators.

Several mouse studies imply that inflammation is largely unfavorable for proliferation of neural precursor cells, a process indispensable for successful regeneration. Microglial activation in the brain reduced hippocampal neurogenesis and consistently, treatment with anti-inflammatory drugs was able to restore neurogenesis (Ekdahl *et al.*, 2003; Monje *et al.*, 2003). Similarly, immunosuppressive treatment was able to promote endogenous neural stem cell migration and subsequent tissue regeneration following ischemic injury. Mice recovered from cortical injury showed increased functional behavioral recovery (Erlandsson *et al.*, 2011). Particularly in mammals, secondary damage, such as edema, impaired metabolism, reactive oxygen species as well as excitotoxicity occurring after traumatic central nervous system injury are thought to be important factors causing poor recovery (Prins *et al.*, 2013; Corps *et al.*, 2015). Recently, however, a novel type of dormant neural stem cell, which becomes primed but still retains its quiescent state after TBI, has been proposed. These cells can be specifically activated via IFNγ-signaling following ischemic injury (Llorens-Bobadilla *et al.*, 2015). Interestingly, also in non-mammalian vertebrates, where regeneration occurs efficiently, a rapid inflammatory response is observed. This regenerative potential despite a strong inflammatory response appeared to be in contrast to mammals where strong, often persistent inflammation as well as formation of scar tissue from reactive astrocytes is considered one of the main obstacles for successful regeneration (Fitch and Silver, 2008; Buffo *et al.*, 2008; Sofroniew, 2009).

In contrast to the general understanding of inflammation, it was initially surprising that in zebrafish the immune response observed after traumatic brain injury is actually required for initiating the regenerative response (Kyritsis *et al.*, 2012). Upon drug-mediated immunosuppression, radial glial cell proliferation and subsequent regenerative neurogenesis is significantly reduced. Conversely, sterile inflammation via injection of Zymosan yeast particles into the ventricular zone of the telencephalon stimulates proliferation of radial glia and downstream generation of new neurons in the absence of injury (Kyritsis *et al.*, 2012). Interestingly, in a different study similar results were obtained using a mouse model of optic nerve injury. Stimulation of the immune system in addition to injury led to enhanced axonal regeneration. By using intraocular Zymosan injections, monocyte-derived macrophages, neutrophils and retina-resident microglia were stimulated and consequently increased axonal regeneration in a Dectin-1 receptor-dependent manner. The authors speculate that this specific additional activation of immune cells leads to the secretion of pro-regenerative

inflammatory mediators, which then stimulate axonal regeneration (Baldwin *et al*., 2015). Furthermore, immunosuppression also impaired motor neuron regeneration following spinal cord injury in the larval zebrafish (Ohnmacht *et al*., 2016). In the adult red spotted newt *Notophthalmus viridescens,* a model of neurotoxin-mediated injury selectively ablates dopaminergic neurons, triggering a strong inflammatory response with recruitment and activation of microglia. The salamander fully regenerates these lesions via activation of radial-glia like ependymoglial cells, which proliferate and regenerate lost dopaminergic neurons (Parish *et al*., 2007; Berg *et al*., 2010). Interestingly, upon immunosuppression using dexamethasone, more newly generated tyrosine hydroxylase neurons are found in response to injury (Kirkham *et al*., 2011). It will be important to carefully dissect the immune response also in a temporal manner, since correct timing is likely one of the key factors influencing regenerative outcome. In addition, it will be crucial to further investigate underlying cellular and molecular inflammatory cues that act on neural stem cells.

Immune cell types and their function during regeneration

Microglia

Microglia, the central nervous system-resident macrophages, descend from the myeloid lineage of the hematopoietic system and colonize the brain already at early stages of development (for recent reviews, please refer to (Ginhoux and Jung, 2014; Dey *et al*., 2015). Despite the common progenitor origin, their developmental source seems to differ among vertebrates. In mice microglia were suggested to derive solely from the yolk sac, whereas two distinct zones of origin have been identified in the zebrafish: the rostral blood island at embryonic stages, and the ventral wall of the dorsal aorta in adulthood (Ginhoux *et al*., 2010; Xu *et al*., 2015).

Similar to other mononuclear phagocytes, such as peripheral macrophages, microglia contribute to homeostasis of the resident tissue by clearance of dying/dead cells and phagocytosis of debris and infectious agents. Under physiological conditions, although not activated, they constantly survey their microenvironment by dynamically extending processes from their cell body and show a characteristic ramified morphology. Upon detection of infection or injury, microglia undergo functional activation with morphological transformation towards an amoeboid shape. They migrate towards the infection/injury center, phagocytose infectious agents and dying cells and secrete various inflammatory mediators (for an extensive review, see (Kettenmann *et al*., 2011).

In a recent zebrafish study, slc7a7, a Leu/Arg transporter, has been identified to mark a specific subset of primitive macrophages, which colonize the brain and give rise to microglia during development (Rossi *et al*., 2015). In addition, the phosphate exporter xpr1b is required to generate microglia, also shown through a zebrafish knock-out model (Meireles *et al*., 2014). Mechanistically, microglial cells within the site of injury act through a variety of signals, including a wave of Ca^{2+} (Sieger *et al*., 2012). Using live-imaging, two phosphatidylserine receptors, BAI1 and TIM-4, were identified as crucial participants in the engulfment and clearing of dying neurons. BAI1 controls the formation of phagosomes around dying neurons, whereas TIM-4 is required for phagosome stabilization (Mazaheri *et al*., 2014). More recently, an important role of the sigma-1 receptor was suggested in microglia de-activation. The authors could show that the sigma-1 receptor is crucial to allow microglia to leave the site of injury and become inactivated (Moritz *et al*., 2015).

Monocyte-derived macrophages

Monocytes derive from hematopoietic stem cells, which are located in the bone marrow in mammals and in the kidney marrow of zebrafish. For detailed reviews on their developmental origin in mouse and zebrafish please refer to recent reviews by (Chen and Zon, 2009; Paik and Zon, 2010; Perdiguero and Geissmann, 2015). Monocytes from the blood stream can differentiate into macrophages and hence are termed monocyte-derived macrophages. Under central nervous system inflammatory conditions they can cross the blood brain barrier and invade the tissue. It has been shown that in mice activated macrophages can promote central nervous system repair following drug-induced demyelination by providing neurotrophic and growth factors (Miron *et al*., 2014). Furthermore, a population of macrophages was identified to promote regenerative axonal growth in the injured mouse spinal cord (Kigerl *et al*., 2009). These different phenotypes could potentially be explained by different macrophage polarization, often also referred to as activation states. Different polarization states of macrophages can be discriminated by presence of certain marker proteins. Historically, two major classes of macrophages have been proposed: "classically-activated M1" macrophages, which show increased antigen presentation capacities and expression of tumor necrosis factor-α (TNF-α), reactive oxygen species and interleukin-1β (IL-1β) (Block *et al*., 2007) and "alternatively activated M2 macrophages", which show increased phagocytic activity and secrete neurotrophic, growth and neuroprotective factors such as IL-4 and IL-13 (Ponomarev *et al*., 2007; Colton, 2009). Therefore, M1 and M2 macrophages could be regarded as anti- (neurotoxic) and pro-regenerative (neurotrophic) states, respectively (Tang and Le, 2016). Polarization is reversible and polarized macrophages can shift dynamically between different states. Indeed, increasing evidence suggests that there are various macrophage subsets rather than just two exclusive polarization states (reviewed by (Hu *et al*., 2014; Murray *et al*., 2014; Prinz and Priller, 2014)). With the zebrafish becoming a more widely used model system to study inflammation and immune processes, two different subtypes of macrophages have been reported in zebrafish as well (Nguyen-Chi *et al*., 2015). Furthermore, additional markers to better classify murine macrophage subtypes have been suggested recently (Jablonski *et al*., 2015). However, as already mentioned, this strict binary classification might be overly simplistic and not account for the true spectrum of macrophage subtypes *in vivo*. A recent single-cell gene expression profiling study in mice subjected to traumatic brain injury provides evidence that monocyte-derived macrophages can not be strictly categorized into either of these classes, but rather adopt diverse polarization states simultaneously (Kim *et al*., 2016). In addition, great phenotypical differences in macrophage behavior have been observed between *in vitro* systems and *in vivo* studies. Hence, better nomenclature and experimental guidelines for studying macrophage activation and polarization states may help to generate comparable results (Murray *et al*., 2014).

A further technical limitation in studies of macrophage/microglia responses within the nervous system -both in mammals and zebrafish- has been the lack of exclusive markers to distinctly differentiate between tissue-resident microglia and monocyte-derived macrophages recruited from the blood stream. As a consequence,

these cell types have been considered to be functionally homogenous in nervous system repair (London *et al.*, 2013; Raposo and Schwartz, 2014). Interestingly, recent mouse transcriptome studies uncovered distinct profiles of gene expression between microglia and monocyte-derived macrophages (Gautier *et al.*, 2012; Hickman *et al.*, 2013; Butovsky *et al.*, 2014; Grabert *et al.*, 2016). In terms of the ability to experimentally differentiate between microglia and monocyte-derived macrophages, transmembrane protein 119 (tmem119) was identified as unique marker for microglia during homeostasis and injury-induced inflammation (Bennetta *et al.*, 2016; Satoh *et al.*, 2016).

A novel anti-inflammatory role has been attributed to a unique subset of infiltrating monocyte-derived macrophages in mouse spinal cord injury, which cannot be provided by activated resident microglia (Shechter *et al.*, 2009; London *et al.*, 2013; Shechter *et al.*, 2013). A different study reported that M1 macrophages predominantly reside at the inflammatory site at early stages following central nervous system trauma and only later shift towards the M2 state (Miron *et al.*, 2013). In a murine experimental autoimmune encephalitis model, a commonly used model for multiple sclerosis, disease progression was triggered by infiltration of monocytes. Interestingly, inhibition of monocyte recruitment blocked further progression (Ajami *et al.*, 2011). These findings harbor a clinical implication as modulation of M1:M2 ratios could potentially improve regenerative capacity of the human nervous system.

In the zebrafish less is known about the importance of microglia and macrophage subtypes during regeneration of the central nervous system. However, a contribution of macrophages to regeneration has also been reported for other organs. In the zebrafish fin macrophages are required during regeneration as depletion of macrophages greatly impairs regenerative growth. Macrophages accumulate at the transected area at around 4 days post amputation (dpa). In addition, the study provides evidence that macrophages are crucial early mediators of blastema formation (Petrie *et al.*, 2014). Furthermore, a recent zebrafish study showed, that immune-suppressive treatment using prednisolone leads to decreased bone growth as well as impaired regeneration (Geurtzen *et al.*, 2017). In a zebrafish model of peripheral axonal nerve injury, macrophages rapidly arrive at the lesion site where they engulf axonal debris and invade into the nerve following axon fragmentation (Rosenberg *et al.*, 2012). Interestingly, macrophages are also important for mediation of heart regeneration in neonatal mice, which implies their functional relevance for regenerative processes also in mammalian systems (Aurora *et al.*, 2014).

Additional research is needed to further characterize functional differences between resident microglia and blood-derived macrophages during health and disease. Zebrafish will serve as a valuable model with great intrinsic regenerative capacity and an immune system that appears to be very similar to the mammalian one.

Neutrophils

Similarly to monocyte-derived macrophages, neutrophils originate from the myeloid lineage in the bone marrow in mammals and the kidney marrow in zebrafish. Neutrophils in zebrafish also express myeloperoxidase and quickly respond to injuries such as tail transection (Lieschke *et al.*, 2001).

Neutrophils are circulating in the blood stream under physiological conditions, but are recruited to sites of inflammation by crossing the endothelial barrier. They are amongst the earliest circulating immune cells to arrive at the injury site. Generally, they phagocytose infectious agents and lethally damaged cells as well as secrete inflammatory molecules (for a recent review see (de Oliveira *et al.*, 2016). Compared to monocyte-derived macrophages and microglia, less is known about the functions of neutrophils during central nervous system inflammation and regeneration.

Due to their immune cell attracting properties, neutrophils are largely considered pro-inflammatory. Deleterious effects in central nervous system regeneration, damage of inflamed tissue by reactive oxygen species, disruption of extracellular environment by release of proteases and physical blocking at the epicenter of lost tissue have been attributed to neutrophils (reviewed by (Neirinckx *et al.*, 2014)). Indeed, several studies have highlighted evidence for their detrimental effects. Co-culture experiments suggested neurotoxicity induced by cell-cell interactions between neutrophils and neurons (Dinkel *et al.*, 2004). An antibody-based neutrophil depletion experiment in mice led to reduced edema formation and tissue loss after traumatic brain injury (Kenne *et al.*, 2012). These studies indicate that neutrophils are negative effectors during regeneration. However, increasing evidence also suggests their -at least indirect- beneficial roles. In a different study, antibody-mediated neutrophil-depletion caused elevated levels of macrophage inflammatory protein 1-γ and worsened behavior outcome after spinal cord injury in mice, potentially by interfering with infiltration of other immune cells (Stirling *et al.*, 2009). Another study found the importance of secreted leukocyte protease inhibitor for recovery of spinal cord injury (Ghasemlou *et al.*, 2010). The many different roles for neutrophils during zebrafish regeneration as well as available tools to study their function have been thoroughly reviewed elsewhere (Keightley *et al.*, 2014). Zebrafish *in vivo* studies have not only shown that neutrophils migrate to the site of injury or inflammation in a directed manner but also undergo reverse migration to find their way back to the vasculature in order to resolve acute inflammation (Mathias *et al.*, 2006; Starnes and Huttenlocher, 2012). Interestingly, macrophages interact with neutrophils at the wound site. Redox-regulated Src family kinase signaling leads to macrophage attraction and triggers subsequent reverse migration of neutrophils through direct interaction with each other, indicating their role in regulating resolution of inflammation (Tauzin *et al.*, 2014). Experiments using intravital imaging and electron microscopy showed that neutrophils were absent in the brain under physiological conditions as well as after neuron-specific cell ablation, leading to the conclusion that neutrophils do not contribute to brain inflammation in the larval zebrafish (van Ham *et al.*, 2014). Their contribution to adult zebrafish brain regeneration has not been investigated so far. During optic nerve regeneration in zebrafish, neutrophils were identified as a source of oncomodulin, a mediator actively promoting regeneration. Interestingly, although macrophages are also recruited to the injury site at later stages, in absence of neutrophils they remained insufficient for regeneration (Kurimoto *et al.*, 2013).

In light of these findings, the context-dependent role for neutrophils in regeneration of nervous system injuries remains to be further studied to better understand their potential contribution to tissue regeneration.

T lymphocytes

T lymphocytes or T cells are part of the adaptive immune system and participate in central nervous system inflammation after trauma.

In contrast to their presence in peripheral inflammatory tissues, presence in the central nervous system is considerably lower (Moalem *et al*., 1999; Stirling and Yong, 2008; Beck *et al*., 2010). Increasing evidence suggests a functional correlation between T lymphocytes and the nervous system, both during homeostasis and pathology (Ellwardt *et al*., 2016). T cells are important for adult neurogenesis and learning in rodents. Severe combined immune deficient mice (SCID mice) show poor hippocampal neurogenesis, a deficit that is restored following $CD4^+$ T lymphocyte transplantation (Ziv *et al*., 2006; Wolf *et al*., 2009).

Similar to other immune cells, effects of T cells on neural repair seem to be contradictory: both deleterious and beneficial roles have been reported. T cells isolated from spinal cord-injured rats induced neurological deficits and histopathologic alterations in recipient animals (Popovich *et al*., 1997). Transgenic mice immunized against a central nervous system-derived antigen show increased neurogenesis in the hippocampus and improved learning (Ziv *et al*., 2006). Targeted depletion of $CD8^+$ T cells in mice caused elevated recovery of motor function in a neurodegenerative multiple sclerosis model (Howe *et al*., 2007). In contrast to these studies, pro-regenerative/neuroprotective roles for T cells have been reported both *in vitro* and *in vivo*. Organotypic murine hippocampal slice cultures showed that $CD4^+$ and $CD8^+$ T lymphocytes isolated from peripheral lymph nodes protect neurons from excitotoxic damage and after glucose/oxygen depletion (Shrestha *et al*., 2014). T cells have been reported to produce neuroprotective molecules such as brain derived neurotrophic factor (Kerschensteiner *et al*., 1999). There is also an indirect effect of T cells likely to be mediated via interaction with monocyte-derived macrophages or astrocytes (Garg *et al*., 2009; Walsh *et al*., 2014). Increasing evidence suggests that peripheral immune cells coming to the brain via the blood stream positively influence adult neurogenesis in the rodent hippocampus (recently reviewed by (Leiter *et al*., 2016)). As discussed above, monocyte-derived macrophages and microglia have functionally different subtypes. The peak of alternatively activated macrophages coincides with that of T cell infiltration into the murine nervous system (Popovich *et al*., 1996; Miron *et al*., 2013). In addition, one of the key factors triggering the alternative activation of monocyte-derived macrophages is IL-4, a prototypical T cell-derived cytokine. It has been reported that IL-4 helps to improve survival of primary murine cortical neurons under oxidative stress. IFN-γ secreted by T cells also plays a neuroprotective role through stimulating astrocytes to clear neurotoxic glutamate under oxidative stress. Therefore, these findings suggest that T cells activate and lead macrophages towards an anti-inflammatory phenotype, thus promoting nervous system recovery (Garg *et al*., 2009). Along these lines, 'protective autoimmunity' has been proposed as a central physiological mechanism for protection, repair and maintenance. The choroid plexus has been described as unique neuro-immunological gate allowing controlled entry of immune cells into the brain parenchyma (Schwartz and Baruch, 2014). As discussed above, central nervous system-specific T cells also show the ability to recruit monocyte-derived macrophages to the injured murine spinal cord where they secrete anti-inflammatory mediators to limit spread of tissue damage (Shechter *et al*., 2009). Although T cells have been identified in the zebrafish, their functional role in mediating regenerative processes remains unclear and warrants future research (Langenau *et al*., 2004; Langenau and Zon, 2005). The recent development of an immune-deficient zebrafish line similar to existing immune-compromised models in mice will be of major help in delineating the role of T cells during regenerative processes (Moore *et al*., 2016). Taken together, T cells have a multi-faceted role in nervous system injury and they remain an interesting target for future scientific investigations to enhance tissue regeneration.

Molecular cues and inflammatory mediators after injury and during regeneration

In order to understand regeneration, not only cellular responses, but also underlying molecular mechanisms and signals triggering inflammation have to be investigated. Upon injury of the central nervous system, the immune system quickly responds, leading to activation and proliferation of microglia and attraction of additional immune cells from the blood stream. Recruitment of different inflammatory cell types as well as stimulation of cell proliferation is mediated via a variety of different secreted mediators, such as cytokines and chemokines as well as lipid mediators, which will be discussed in the following sections. Important immune-derived factors already known to stimulate neural stem cell proliferation and neuronal differentiation have been summarized in Table 1.

TABLE 1

INFLAMMATORY MEDIATORS AFFECTING CENTRAL NERVOUS SYSTEM PROLIFERATION

Mediator	Cell type / tissue	Organism	Effect	Reference
IL-1β	astrocytes	mouse	increased proliferation	(Liberto *et al*., 2004)
TNF-α	neural precursor cells, hippocampus Müller glia, retina	mouse zebrafish	deletion of TNF-receptor 1 increases neural precursor cell proliferation induces proliferation	(Iosif *et al*., 2006) (Nelson *et al*., 2013)
IFN-γ	neural precursor cells	mouse	activation of dormant quiescent cells in response to injury	(Llorens-Bobadilla *et al*., 2015)
IL-6	Müller glia, retina retinal ganglion cells spinal cord	zebrafish mouse mouse	increased proliferation axon regeneration optic nerve improved functional recovery	(Zhao *et al*., 2014; Elsaeidi *et al*., 2014) (Leibinger *et al*., 2013) (Yang *et al*., 2012)
CNTF	Müller glia, retina	zebrafish	induces proliferation	(Elsaeidi *et al*., 2014; Zhao *et al*., 2014)
SDF-1	spinal cord	rat	decreased apoptosis, increased proliferation, increased functional recovery	(Zendedel *et al*., 2012)
IL-4	radial glial cells, telencephalon subventricular zone, brain	zebrafish mouse	increased proliferation keeps neural precursor cells in undifferentiated state	(Bhattarai *et al*., 2016) (Perez-Asensio *et al*., 2013)
CCL11	hippocampus	mouse	decrease of neural precursor cells proliferation, impaired learning/memory	(Villeda *et al*., 2011)
LTC_4	telencephalon	zebrafish	increased radial glial cell proliferation	(Kyritsis *et al*., 2012)
CysLT	neural precursor cells, hippocampus	mouse	inhibiting proliferation, improved learning and memory upon inhibition	(Marschallinger *et al*., 2015)

The table summarizes important inflammatory mediators that have been shown to affect proliferation within the central nervous system. Abbreviations: IL – interleukin; TNF – tumor necrosis factor; IFN – interferon; CNTF – ciliary neurotrophic factor; SDF – stromal cell-derived factor (also known as CXC motif chemokine 12); CCL – CC motif chemokine; LTC_4 – leukotriene C_4; CysLT – cysteinyl leukotrienes.

Cytokines, chemokines and their receptors

One important property of cells in general, but immune cells in particular, is their ability to secrete small molecules such as growth factors, chemokines and cytokines. Cytokine signaling appears to be evolutionary conserved, with high degrees of homology between different mammalian species, but a relatively low sequence-based homology between fish and mammals. Still, most factors do have functionally equivalent orthologs in fish (reviewed by (Savan and Sakai, 2005)). Cytokines can have a variety of functions, depending on amount, but also location and timing of production. Upon any inflammatory response several key cytokines are rapidly secreted, such as Interleukin-1β (IL-1β), tumor necrosis factor alpha (TNF-α), CXCL8/interleukin-8 (IL-8). Il-1β reduces murine neural stem cell proliferation both *in vitro* and *in vivo* (Wang *et al.*, 2007; Mathieu *et al.*, 2010). Upon injury of the brain, IL-1β is quickly produced by activated microglia. Subsequently, mammalian astrocytes become reactive and increase their proliferation (Liberto *et al.*, 2004). In zebrafish, where inflammation is required for initiating the regenerative response, up-regulation of IL-1β is observed very early following a traumatic brain injury (Kyritsis *et al.*, 2012).

Traditionally, cytokines have been grouped into being pro- or anti-inflammatory correlating with different states of macrophage activation. However, recent studies indicate that depending on the specific context this categorization might be overly simplistic. IL-6, initially classified as pro-inflammatory cytokine, also has anti-inflammatory properties depending on the type of receptor being expressed either in a membrane-bound or soluble form (Scheller *et al.*, 2011). IL-6 is a pleiotropic cytokine, with multiple inflammatory effects. In the mammalian central nervous system, IL-6 as well as its receptors are found expressed by both neuronal and glial cell populations (Erta *et al.*, 2012; Gruol, 2015). IL-6 is part of the neuropoietic family of cytokines, including other factors such as ciliary neurotrophic factor (CNTF), leukemia inhibitory factor, oncostatin M, cardiotrophin-1 and IL-11 (Taga and Kishimoto, 1997). Importantly, members of this family are involved in different biological processes and responses elicited by different members can be very similar. This is possible due to a very high similarity in their three-dimensional conformation, rather than primary structural similarity, which is as low as 30% (Gadient and Otten, 1997). *In vitro* experiments showed that IL-6 greatly reduces murine neurogenesis and that blocking IL-6 can fully restore hippocampal neurogenesis (Monje *et al.*, 2003). Despite the fact that zebrafish IL-6 shows a low sequence homology with other species, it has a high structural similarity to human IL-6. IL-6 family cytokines together with leptin are potent stimulators of Müller glia cell reprogramming and retina regeneration in zebrafish. It was shown that leptin, in conjunction with the gp130-coupled cytokine receptor, activate JAK/STAT signaling, which triggers Müller glia cell proliferation in the retina. Importantly, IL-6 as well as IL-11 and CNTF synergize to induce Müller glia cell proliferation also in the uninjured retina (Zhao *et al.*, 2014). Furthermore, the same family of cytokines also stimulates activation of JAK/STAT signaling in retinal ganglion cells to facilitate optic nerve regeneration (Elsaeidi *et al.*, 2014).

TNF-α is rapidly produced following traumatic injury. TNF-α exists in two different isoforms in the nervous system: a soluble and a transmembrane form (McCoy and Tansey, 2008; Probert, 2015). It signals via the TNF receptors 1 and 2 (TNFR-1, TNFR-2) and can activate multiple downstream signaling pathways such as NFκB, JNK, MAPK or caspase-mediated death signaling (reviewed by (Wajant *et al.*, 2003)). A recent study found that induced inflammation via exogenous supply of TNF-α to mammalian astrocytes promotes their conversion to neural precursor cells via activation of NFκB signaling *in vitro* (Gabel *et al.*, 2015). In a zebrafish model of retinal injury, TNF-α signaling is an important mediator. Dying cells secrete TNF- α, which stimulates Müller glia to proliferate and regenerate the injured tissue (Nelson *et al.*, 2013). In addition, factors such as TGF-β also trigger Müller glia cell proliferation (Lenkowski *et al.*, 2013). Based on RNA sequencing analysis of lesion stimulated Müller glia, NFκB signaling shows a high activity during zebrafish retina regeneration (Sifuentes *et al.*, 2016). In chicken, the activation of glucocorticoid receptors using Dexamethasone was also shown to reduce the number of Müller glia derived progenitor cells after neurotoxic ablation of neurons, further demonstrating an involvement of inflammation in regeneration (Gallina *et al.*, 2014).

IL-10 is well known for its anti-inflammatory actions, which are mediated via STAT3 activation (Murray, 2005; Bazzoni *et al.*, 2010). IL-10 is a potent inhibitor of IL-1, IL-6, IL-10 itself, IL-12, IL-18 and TNF-α. It not only inhibits the production of pro-inflammatory, but also augments the production of anti-inflammatory mediators including soluble TNF-α receptors and IL-1 receptor antagonist. Using a rat model of traumatic brain injury, exogenously administered IL-10 improved neurological outcome and reduced TNF-α expression. It was suggested that IL-10 is anti-inflammatory due to its regulatory effect on pro-inflammatory cytokine expression (Knoblach and Faden, 1998). IL-10 reduces neuronal differentiation and keeps precursors in an immature state. Consistently, blockage of IL-10 *in vivo* results in increased incorporation of newly formed neurons in the olfactory bulb of mice (Perez-Asensio *et al.*, 2013). This indicates again that precise timing of cytokine secretion during regeneration is very important as IL-10 is required during the phase of stem cell proliferation but needs to be down-regulated to allow newly generated cells to differentiate into neurons.

The cytokine IL-4 is involved in wound healing and induction of alternatively activated macrophages (M2), which promote tissue remodeling and healing (reviewed by (Mosser & Edwards, 2008)). IL-4 signals through its cognate receptor propagating the signal through a series of phosphorylation steps via receptor-associated kinases. The IL-4Rα chain can also function in complex with the IL-13Rα (Nelms *et al.*, 1999). IL-4, which can be secreted by meningeal T cells, has been positively correlated with cognitive performance. IL-4 deficient mice show cognitive deficits and impaired learning (Derecki *et al.*, 2010). Furthermore, genetic knockout of IL-4 leads to worse outcome after stroke accompanied by larger lesion volumes. Administration of exogenous IL-4 reverses this effect (Xiong *et al.*, 2011). Recently, using a zebrafish model of amyloid deposition in the brain, IL-4 was identified to stimulate radial glial cell proliferation and subsequent neurogenesis (Bhattarai *et al.*, 2016). These studies indicate a beneficial role for IL-4 signaling in the context of traumatic brain injury, neural precursor cell proliferation and neurogenesis.

Chemokines are small cytokines usually involved in the induction of chemotaxis of cells. The chemokine network is very well conserved in evolution. A large comparative study investigated the evolution and development of the chemokine system in important model organisms including the zebrafish. In comparison to other species, zebrafish have a high number of chemokines and receptors, 63 and 24 respectively, probably as a result of ancient genome duplication (DeVries *et al.*, 2006).

The chemokine CXCL8, also known as IL-8, is one of the cardinal pro-inflammatory cytokines up-regulated during inflammation and after injury. It is secreted by glial cells, macrophages and endothelial cells and mediates activation and chemotaxis of neutrophils (Hammond *et al.*, 1995). It is also rapidly detected in cerebrospinal fluid of TBI patients together with elevated levels of IL-6, IL-10 and TGF- β (Kossmann *et al.*, 1997; Mussack *et al.*, 2002). In zebrafish, two homologs for IL-8 exist, CXCL8a and CXCL8b. Using an *in vivo* imaging approach, it was shown that in the absence of CXCL8, neutrophil migratory speed towards a peripheral wound was increased, directionality of movement however was not affected (Oehlers *et al.*, 2010; de Oliveira *et al.*, 2013).

The chemokine C-C motif ligand 2 (CCL2), also referred to as monocyte chemoattractant protein 1, has been identified as a neuron-derived pro-regenerative chemokine in the dorsal root ganglion in rodents (Kwon *et al.*, 2015). CCL2 can activate macrophages through interaction with its primary receptor CCR2 to produce pro-regenerative factors that can promote neurite outgrowth of cultured dorsal root ganglion neurons (Kwon *et al.*, 2013; Kwon *et al.*, 2016). Overexpression of the chemokine in uninjured murine dorsal root ganglion leads to accumulation of macrophages and promotes neurite outgrowth in dorsal root ganglion explants. The observed regenerative response is regulated in a STAT3-dependent manner (Niemi *et al.*, 2016).

Both the chemokine receptor CXCR4 and its ligand CXCL12, also known as stromal cell-derived factor 1 (SDF-1), are expressed in the ventricular zone of the adult zebrafish brain and have been suggested to play a role during homeostatic neuronal migration (Diotel *et al.*, 2010). SDF-1 can be induced by a variety of pro-inflammatory stimuli, such as bacterial toxins, TNF or IL-1. Also, the SDF-1/CXCR4 receptor pathway is important for homing of neural stem cells towards an injury site within the mammalian brain (Imitola *et al.*, 2004). Our own previous research identified *cxcr5* as important chemokine receptor involved during zebrafish telencephalon regeneration. In the adult zebrafish telencephalon *cxcr5* is expressed by proliferating and non-proliferating radial glial cells, as well as by neurons in the periventricular region. *Cxcr5* mediates neuronal differentiation of newly generated precursor cells following a stab lesion (Kizil *et al.*, 2012). Regulation of TGF-β has recently been demonstrated as an important aspect during zebrafish retinal regeneration. TGF-β is rapidly induced after acute light lesion, but also very quickly down-regulated. From 8-36 hours post lesion the suppressor transforming growth-interacting factor is up-regulated. Conversely, disruption of TGF-β co-repressors leads to reduced proliferation and decreased cone photoreceptor regeneration (Lenkowski *et al.*, 2013). Similarly, a recent study also showed that pharmacological suppression of the TGF- β pathway could accelerate zebrafish retinal regeneration (Tappeiner *et al.*, 2016). Both studies indicate that temporally and spatially controlled expression of mediators is crucial for proper regeneration.

Non-protein and lipid-derived inflammatory mediators

In addition to cytokines and growth factors, lipid-derived molecules are important mediators of inflammation (reviewed by (Serhan *et al.*, 2008). Lipid mediators are involved in many different inflammatory responses, both during infection and following injury. These mediators are mostly synthesized from arachidonic acid, which is derived from cell membranes via the action of phospholipase A_2 (Farooqui *et al.*, 2000). Subsequently, arachidonic acid can undergo a variety of reactions yielding different classes of lipid mediators. Arachidonic acid can be further oxidized via different enzymatic routes: Cyclooxygenases-1 and -2 (COX-1, COX-2) form prostaglandins and thromboxanes, lipoxygenases (LOX) form leukotrienes and lipoxins and cytochrome P450 enzymes (CYP450) form eicosatrienoic acids (EETs) (reviewed by (Dennis and Norris, 2015)). A further type of lipid mediators are protectins and resolvins, which exert neuroprotective effects both in the mammalian brain and retina (Bazan, 2005b; Bazan, 2014; Dyall, 2015).

In general, COX-1 is required for homeostatic and housekeeping functions, whereas COX-2 becomes rapidly activated upon inflammation and is induced by growth factors, cytokines or bacterial toxins. However, COX-2 is also constitutively found in kidney and brain (Rouzer and Marnett, 2008). COX-1 and COX-2 share approximately 60% homology at the cDNA and amino acid level. They have very similar structural and kinetic properties, the conformation of substrate binding sites and catalytic centers are highly similar. Multiple putative regulatory sites have been proposed for inducible COX-2, including the cyclic AMP, IL-6, NFκB, Sp-1, GATA-1 and glucocorticoid response elements (Phillis *et al.*, 2006). Furthermore, expression can also be induced via IL-1β resulting in elevated levels of prostaglandin E_2 (PGE_2) in the central nervous system (Bazan, 2001). Prostaglandin-mediated signaling is propagated through specific receptors leading to activation of multiple intracellular signaling cascades (reviewed by (Ricciotti and Fitzgerald, 2011)). COX-2 expression in the brain has been linked to regulation of synaptic activity, but also the perception of pain (Bazan, 2005a; Phillis *et al.*, 2006). Inhibition of COX-2 improves cognitive function in a rat model of diffuse traumatic brain injury (Cernak *et al.*, 2002). In contrast, in a different study treatment with a selective COX-2 inhibitor following trauma worsened motor behavior (Dash *et al.*, 2000). Using a rat model of peripheral nerve injury, treatment with a selective COX-2 inhibitor accelerated functional recovery (Cámara-Lemarroy *et al.*, 2008). Such seemingly contradicting studies show that the specific role of COX-2 in the context of traumatic brain injury is complex and only incompletely understood. Cyclooxygenases have been attractive drug targets for a variety of indications due to the plethora of roles they fulfill during physiologic as well as pathologic processes. Many different drugs already exist, however their potentially beneficial role in mediating neuro-inflammation following TBI is currently revisited in several pre-clinical and clinical studies (Hurley *et al.*, 2002; Gopez *et al.*, 2005).

Importantly, COX genes were found to be evolutionarily conserved in vertebrates. In zebrafish, COX-2 has two paralogs, COX-2a *(ptgs2a)* and COX-2b *(ptgs2b)* (Grosser *et al.*, 2002) and studies indicate that both genes generate functional and inducible enzymes upon inflammatory stimulation and have similar functions (Ishikawa *et al.*, 2007). Prostaglandins, in particular prostaglandin E_2 (PGE_2), was investigated regarding its role in hematopoietic stem cells and found to be an important modulator of Wnt signaling (North *et al.*, 2007; Goessling *et al.*, 2009). This interaction is also conserved in other species, such as mice, where PGE_2 is involved in hematopoietic stem cell homing and bone marrow repopulation following irradiation. In addition, the modulatory function of prostaglandins is required during liver regeneration (Goessling *et al.*, 2009). Prostaglandins have also been proposed to exert a regulatory effect on cytokine synthesis, because PGE_2 and PGI_2 reduced TNF-α and increased IL-10 levels in murine peritoneal macrophages (Shi-

nomiya *et al.*, 2001). A recent mouse study reported the beneficial effect of increased prostaglandin synthesis during regeneration by blocking 15-hydroxyprostaglandin dehydrogenase (15-PGDH), a prostaglandin-degrading enzyme. Interestingly, several organs, such as bone marrow, liver and colon showed increased ability to sustain damage as well as enhanced regenerative responses. Hence, 15-PGDH negatively regulates regenerative capacity in multiple organs and presents an attractive drug target for future therapies (Zhang *et al.*, 2015). However, its role during central nervous system regeneration remains to be addressed.

The other important branch of the arachidonic acid pathway results in the production of leukotrienes. Lipoxygenases can generate the intermediate leukotriene A_4 (LTA_4), which is metabolized to LTB_4 or LTC_4, LTD_4, LTE_4, collectively known as cysteinyl leukotrienes (Funk, 2001). Cysteinyl leukotrienes are rapidly produced in excess following traumatic brain injury, mainly by neutrophils but also by glial and neuronal cell types (Farias *et al.*, 2009). Pharmacological inhibition of cysteinyl leukotriene synthesis, leads to a reduction of secondary injury and cognitive impairments (Corser-Jensen *et al.*, 2014). Blocking cysteinyl leukotriene receptors increases neural precursor cell proliferation *in vitro* (Huber *et al.*, 2011) and significantly increased hippocampal neurogenesis leading to improved learning and memory in aged mice. Knock-down experiments identified the GPR17 receptor to be critical for mediating this effect (Marschallinger *et al.*, 2015).

Our own studies identified cysteinyl leukotriene receptor 1 (CysLTR1)–LTC_4 signaling as a crucial component of the neuroregenerative response in the zebrafish telencephalon. Using a selective receptor antagonist, both radial glial cell proliferation as well as subsequent neurogenesis in the brain parenchyma are diminished. Conversely, supply of exogenous LTC_4 in complete absence of injury increases both stem cell proliferation as well as neurogenesis in the adult zebrafish telencephalon. Furthermore, LTC_4 supply alone is sufficient to activate the regeneration specific transcription factor *gata3* in radial glial cells of the ventricular zone (Kyritsis *et al.*, 2012). A different study also reported that immunosuppressive treatment using dexamethasone significantly reduces cardiac repair after injury in the adult zebrafish (Huang *et al.*, 2013).

Many studies suggest that inflammation is beneficial for healing and regeneration only if the initial inflammatory response does not persist or becomes chronic but is rapidly resolved. Many studies investigate the role of pro-resolving lipid mediators such as lipoxins, resolvins and protectins and their role in actively terminating an inflammatory response (for a review see (Serhan *et al.*, 2008)). It is important to emphasize that these mediators are not anti-inflammatory or immunosuppressive but rather activate specific mechanisms required to regain tissue homeostasis. Pro-resolving mediators increase monocyte recruitment to help faster clearing of cell debris and dead cells by phagocytosis. In a mouse stroke model, neuroprotectin D1 exerts neuro-protective effects both *in vivo* and *in vitro* via inhibition of leukocyte infiltration, NFκB signaling and COX-2 induction (Marcheselli *et al.*, 2003). Furthermore, this mediator also has protective functions in a model of corneal injury, where it potently increased nerve regeneration (Cortina *et al.*, 2013). Upon traumatic brain injury, lipoxin A_4 is a potent negative regulator of pro-inflammatory cytokine secretion. In addition, lipoxin A_4 treatment attenuates blood brain barrier breakdown, brain edema and lesion volume (Luo *et al.*, 2013).

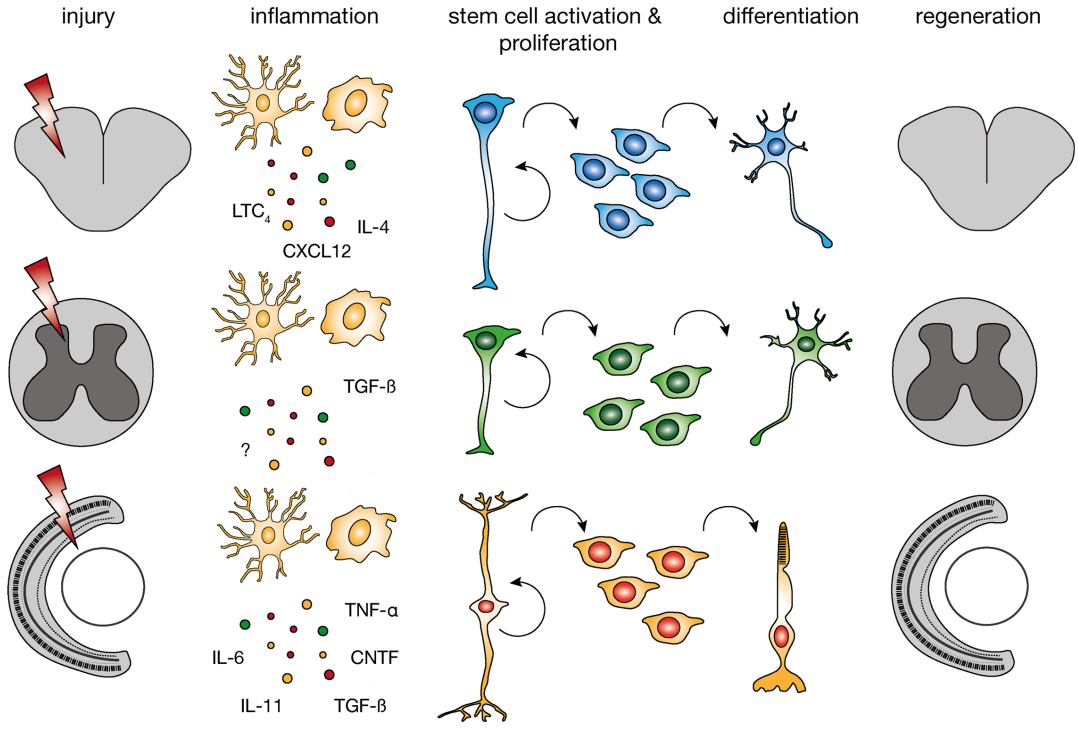

Fig. 2. Immunity related signals involved in the regenerative response in zebrafish CNS. *Injury of the zebrafish central nervous system (telencephalon, spinal cord, retina) elicits a rapid and strong inflammatory response characterized by immune cell activation, proliferation and infiltration as well as secretion of inflammatory mediators (cytokines or lipid-derived factors). These are potent to stimulate and increase stem cell proliferation. In the zebrafish retina and telencephalon several inflammatory mediators have already been identified, whereas less is known about inflammatory regulators in the spinal cord after injury. Radial glial cells of the telencephalon are the source of newly generated neurons after injury, whereas in the spinal cord ependymal-radial glia contribute to regeneration of lost motor neurons in response to damage. In the retina Müller glia cells are activated after lesion and proliferate to give rise to intermediate progenitors, which continue to proliferate and eventually differentiate to replenish lost photoreceptors. Abbreviations: IL, interleukin; TNF, tumor necrosis factor; CNTF, ciliary neurotrophic factor; SDF, SDF – stromal cell-derived factor (also known as CXCL12); CCL, CC motif chemokine; LTC_4, leukotriene C_4; CysLT, cysteinyl leukotriene.*

Collectively, all these studies show that in organisms with high intrinsic regenerative potential of the central nervous system, inflammation is a very important part of the response. Increasing evidence further suggests that also in mammals certain aspects of the inflammatory response within the nervous system are important to allow tissue healing and restoration. In a naturally regenerating organism such as the zebrafish, the inflammatory response is required for successful regeneration. Immune cell activation, infiltration and secretion of inflammatory mediators stimulates central nervous system stem cells to proliferate and subsequently differentiate into cell types lost to injury (Fig. 2).

Despite great research efforts and increased understanding of regenerative mechanisms, many open questions are still remaining. We know about the general requirement of an inflammatory response in animals with great regenerative capacity, however, contribution of specific inflammatory mediators is still incompletely understood. Furthermore, the function of specialized immune cell subtypes needs to be evaluated in greater detail, with special focus on the specific spatio-temporal regulation of the inflammatory and regenerative response. With rapid progress being made in single cell sequencing, gene editing, live imaging technologies as well as drug screening methods, it is now possible to gain a more complete and detailed understanding of complex molecular and cellular events during regeneration, eventually allowing to target these in a specific manner also therapeutically.

Taken together, as the field moves towards a more differentiated view on neuro-inflammation after injury, future research should reveal the knowledge required for the design of novel immune-modulatory therapies to enhance central nervous system regeneration also in mammals.

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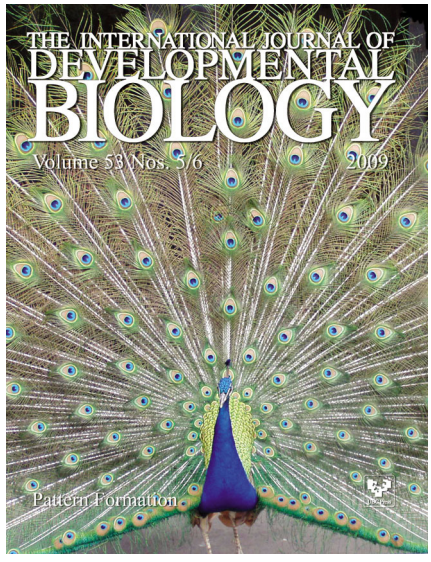

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