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Zebrafish as a translational regeneration model to study the activation of neural stem cells and role of their environment

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Abstract: The review is an overview of the current knowledge of neuronal regeneration properties in mammals and fish. The ability to regenerate the damaged parts of the nervous tissue has been demonstrated in all vertebrates. Notably, fish and amphibians have the highest capacity for neurogenesis, whereas reptiles and birds are able to only regenerate specific regions of the brain, while mammals have reduced capacity for neurogenesis. Zebrafish (*Danio rerio*) is a promising model of study because lesions in the brain or complete cross-section of the spinal cord are followed by an effective neuro-regeneration that successfully restores the motor function. In the brain and the spinal cord of zebrafish, stem cell activity is always able to re-activate the molecular programs required for central nervous system regeneration. In mammals, traumatic brain injuries are followed by reduced neurogenesis and poor axonal regeneration, often insufficient to functionally restore the nervous tissue, while spinal injuries are not repaired at all. The environment that surrounds the stem cell niche constituted by connective tissue and stimulating factors, including pro-inflammation molecules, seems to be a determinant in triggering stem cell proliferation and/or the trans-differentiation of connective elements (mainly fibroblasts). Investigating and comparing the neuronal regeneration in zebrafish and mammals may lead to a better understanding of the mechanisms behind neurogenesis, and the failure of the regenerative response in mammals, first of all, the role of inflammation, considered the main inhibitor of the neuronal regeneration.

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Introduction

The function and integrity of the organism depend tissue's tissue ability to produce new cells to substitute those eliminated by aging events. This mechanism is not only related to maintaining the homeostasis, but it also represents an answer to traumatic injury or pathologies. The central nervous system (CNS) has the capacity to produce functional neurons from precursors, in particular, niches of the brain and not only after traumatic events but also under physiological conditions (Yamashita et al., 2006; Tonchev, 2011). The process of generating functional neurons from precursors (neurogenesis) and from activated stem cells, or trans-differentiation of key elements, during regeneration has been demonstrated, even if the efficiency has been considerably different among vertebrates (Alvarez-Buylla and Lim, 2004; Kaslin et al., 2008; Grandel and Brand, 2013). The fish and partially also amphibians can renew/regenerate almost all parts of the nervous system by acting both on physiological neurogenesis and trans-differentiation of pre-existing elements (Bollaerts et al., 2017). Physiological and regenerative neurogenesis in reptiles has not been studied extensively (Pirotte et al., 2016), whereas some studies were performed in birds (Barnea and Pravosudov, 2011). A traumatic brain injury could be partially restored in specific brain areas. For instance, it is thought that the diversity of the behavior exhibited by the various species of birds, such as singing, migration, food catching, nest building and courtship rituals, is related to the maintenance of constitutive neurogenesis in several specific areas of the brain. However, this hypothesis is still to be confirmed (Barnea and Pravosudov, 2011). In songbirds, new neurons are constantly added to the high vocal centers (HVC) to play the newly learned sounds (Barnea and Pravosudov, 2011). Following a mechanical injury, only specific subtypes of neurons in the HVC, the

neurons from archeo-striatum and their interneurons, are repaired successfully (Scharff et al., 2000). In not-singing birds, these areas seem to be absent and different neurogenic regions are observed at the level of the telencephalon (Scharff et al., 2000). Even the damaged retina can be repaired by newborn neurons from Müller glia, as it was shown in chickens (Fischer and Reh, 2001).

Mammals, but especially primates, have lost much of the regenerative capacity of both the nervous system and other organs and tissues (Kaslin et al., 2008; Kizil et al., 2011; Grandel and Brand, 2013). Primary olfactory sensory neurons and other cells in the nose turn over constantly, and they are replaced over the animal's lifetime and represent an excellent model for investigating neural stem cell regulation *in vivo* (see above, Fletcher et al., 2011). Except for the olfactory tissue, traumatic brain injuries are followed by limited neurogenesis and poor axonal regeneration, often insufficient to functionally and morphologically restore the nervous tissue. Despite newly generated neurons from the harbor of adult neural stem cells, it is calculated that only 0.2% of the striatal cells lost by injury replaced and that from the survival, the number of new neurons is relatively low in some ventricular area (Arvidsson et al., 2002). The reason for that failure could be the absence of trans-differentiation of resident cells, as occurs for example in fish (Kyritsis et al., 2014). In adult rodents or humans, spinal injuries are not followed by neurogenesis or by axonal regeneration, which are prevented by gliosis, hypertrophy of astrocytes and inflammatory cells and the formation of the glial scar (Sofroniew, 2009; Lee-Liu et al., 2013), contrary to what happens in zebrafish where the inflammation process activates the regeneration program (Hui et al., 2010). Emerging in the field is the study of the environment of the neurogenic regions (Fernàdez-Hernàndez and Rhiner, 2015) that is able to drive and regulate the fate of the resident cells. Following the zebrafish model, the pro-inflammatory molecule activation and consequent neuroinflammation, classically considered harmful in mammal models, could represent instead a possible process to promote regeneration, when the appropriate molecular context is provided (Kyritsis et al., 2014; Bollaerts et al., 2017). Thus, for their high generative capacity, the anamnia can be very useful to understand the cellular and molecular mechanisms underlying the neuronal regeneration. Moreover, this may next offer the possibility of translating these findings to mammalian models, mostly consisting in rodents. In this way the zebrafish (*Danio rerio*) represents an excellent model for the study of the neuro-regeneration processes (Quian et al., 2005). Zebrafish are vertebrates and therefore share a high degree of genetic and functional homology with mammals, including humans. Due to the conservation of cell biological and developmental processes across all vertebrates, studies in fish can give great insight into biological processes.

The purpose of this review is to compare the different neuro-regenerative capacities between zebrafish and rodents/humans, analyzing both the cellular and molecular mechanisms that regulate the process. Here it will describe their neurogenic niches, the processes of neuronal regeneration in the forebrain and spinal cord in zebrafish compared to regenerative response in rodent brain. Finally, it will present some possible mechanisms involved in the failure of neuronal regenerative response in mammals, such as the inflammatory response and the expression of specific miRNAs as key molecules in trans-differentiation.

Constitutive neurogenic niches in fish versus mammals

Stem cells exhibit two defining characteristics: the capacity of self-renewal through cell division and the capacity of generating cell types that undergo specialization through the differentiation process (Gage, 2000). In neurogenesis, stem cells generating functional neurons have been defined as neuronal precursor cells (NPCs) (Figure 1). Traditionally, the neurogenesis has been only considered a

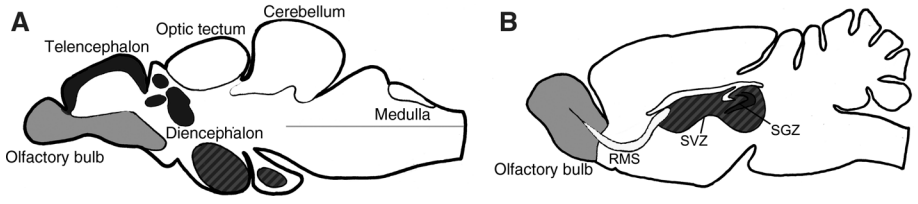

Figure 1: Schematic longitudinal section of the adult brain of (A) zebrafish and (B) mice, highlighting regions of NPC proliferation (light gray) and neurogenesis (gray).
SVZ, sub-ventricular zone; SGZ, subgranular zone; RMS, rostral migration stream. Image modified from Grandel et al. (2006).

process occurring during embryonic and prenatal stages. But some decades ago, studies providing the presence of newly generated neurons and their integration in the neuronal network in the CNS of adult rats and songbirds also have demonstrated that adults of all vertebrates share the process of neurogenesis (Altman and Das, 1965; Reynolds and Weiss, 1992; Arvidsson et al., 2002; Tonchev, 2011). The neurogenic activity of NPCs depends strongly on the microenvironment in which they reside, the so-called neurogenic niche, which houses the stem cells by regulating their survival and the delicate balance between maintaining a state of quiescence and production of an expanding and pro-differentiated progeny (Schofield, 1978; Bonfanti and Peretto, 2011). Extracellular matrix (ECM), astrocytes, microglia and neuronal precursors, basal lamina and epithelial cells such as endothelial cells are key components of the niche. Glial cells, endothelia and the ECM have been demonstrated of fundamental importance for the proper functioning of the neurogenic niche since they secrete soluble factors or express membrane molecules such as morphogens, cytokines and mitogenic factors that regulate the process of neurogenesis (Lim et al., 2000; Ma et al., 2005; Kazanis, 2012). Moreover, the same NPCs contribute by themselves to the creation and the maintenance of their microenvironment (Ortega-Perez et al., 2007; Kazanis, 2012).

The presence of constitutive neurogenic niche has been demonstrated in zebrafish (Ekstrom et al., 2001; Zupanc, 2001; Grandel et al., 2006; Grandel and Brand, 2013) as well as in adult rodents (rabbit and mouse; Alvarez-Buylla and Lim, 2004) and humans (William, 2014). In zebrafish, about six brain areas have been identified (Figures 1A and 2) as neurogenic niches (two of them localized along the ventricular side of the pallium and along the dorsal-lateral surface of the subpallium) (Liem et al., 2002; Grandel et al., 2006; Grandel and Brand, 2013; Schmidt et al., 2013). Moreover, within these areas, 10 regions seem to be characterized by an active proliferation of NPCs (the olfactory bulb, telencephalon, thalamus, epithalamus, preoptic region, hypothalamus, optic tectum and hindbrain) (Zupanc and Horschke, 1995; Clint and Zupanc, 2001; Ekstrom et al., 2001; Grandel et al., 2006; Zupanc and Zupanc, 2006).

In contrast, in mice next to the olfactory bulb, only two specific regions of the forebrain with neuro-regenerative capacity have been identified: the sub-ventricular zone (SVZ) and sub-granular zone of the dentate gyrus in the hippocampus (SGZ) (Altman and Das, 1965; Altman, 1969; Gage et al., 1995; Alvarez-Buylla and Lim, 2004) (Figures 2 and 3). In fact, the pseudostratified olfactory epithelium maintains for a long time the regeneration capacity from perinatal stages (Figure 1B). Multipotent globose basal cells (GBCs) in the olfactory epithelium (Graziadei and Graziadei, 1979; Chen et al., 2004; Gokoffski et al., 2011) express specific markers and revealed a function of support of normal turnover of fast replacing

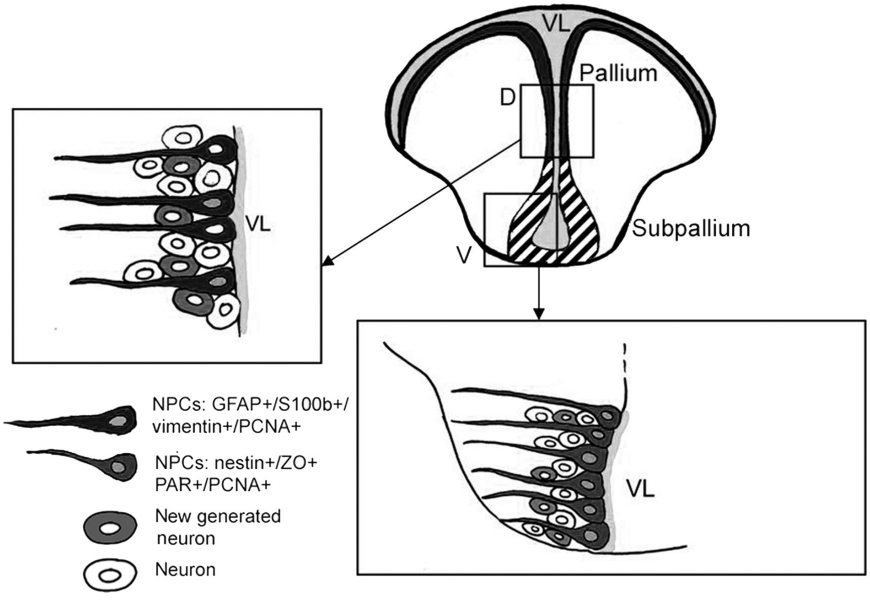

Figure 2: Schematic cross-section of the forebrain of adult zebrafish, which shows the two neurogenic regions: the pallial neurogenic zone (D) and subpallial neurogenic zone (V).
VL, ventricular lumen. Image modified from Grandel and Brand (2013).

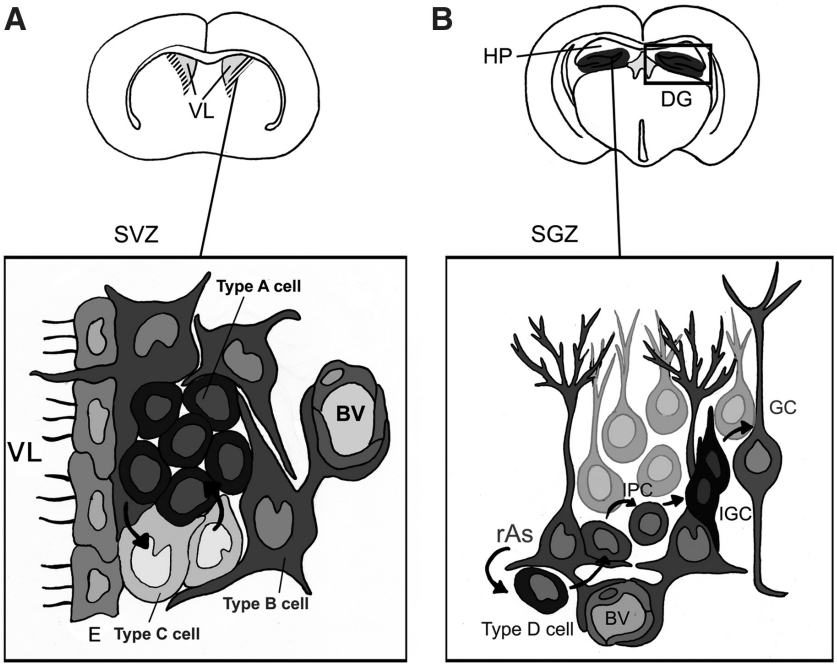

Figure 3: Schematic cross-sections of the adult mouse forebrain that highlight the neurogenic niches: (A) the sub-ventricular zone (SVZ) and (B) the subgranular zone of the dentate gyrus (SGZ).
BD, blood vessel; DG, dentate gyrus; E, ependymal layer; rAS, radial astrocyte; IGC, immature granule cells; GC, granule cells; HP, hippocampus; IPC, intermediate progenitors; VL, ventricular lumen. Image composed by the indications of Alvarez-Buylla and Lim (2004) and Fuentealba et al. (2012).

neurons after damage during the life (Iwai et al., 2008). The other olfactory tissue called horizontal basal cells (HBCs) instead result in a reserve of stem cells that can generate the GBCs as well as non-neural cells (Carter et al., 2004; Fuchs, 2009; Li and Clevers, 2010). During the injury-induced regeneration, in transgenic mice, HBCs give rise to differentiated cells of olfactory epithelium by P53 promoting factor, whereas delta-NSp63 is the necessary factor to maintain the undifferentiated cells (Fletcher et al., 2011).

In the olfactory bulb there is 'persistent neurogenesis,' namely a constitutive neurogenic process that decreases in intensity but does not come to an end (Bonfanti, 2011). In other CNS parts, such as SVZ and SGZ, it is possible to make a different distinction as persistent neurogenesis, whereas non-neurogenic regions (parenchymal neurogenesis) have been part of the protracted neurogenesis in rodent adulthood (Spalding et al., 2013). It has been localized to other parenchymal regions as candidate regions of possible constitutive neurogenesis: the area CA1 of the hippocampus (Nakatomi et al., 2002; Xu et al., 2005), the neocortex (Gould et al., 1999), the amygdala (Bernier et al., 2002), spinal cord (Yamamoto et al., 2001; Lee-Liu et al., 2013) and the cerebellum (Lee et al., 2005). Histological and carbon-14-dating approaches, recently have demonstrated that also striatum was able to integrate new neurons (Ernst et al. 2014).

The rate of proliferation of the NPCs and fate of the new neurons within brain areas have been used for neurogenic niche comparison between zebrafish and mammalians. The low rate of proliferation and the generation of neurons that migrate a short distance into the parenchyma (Grandel et al., 2006) could associate the pallium ventricular zone of the zebrafish with the SGZ of mammalians. The pallium area of zebrafish is characterized by an alternating pattern of dividing cells, positive for the proliferatin cell nuclear antigen ($PCNA^+$) and quiescent cells ($PCNA^-$) (Kroehne et al., 2011; Grandel and Brand, 2013). About two-thirds of the $PCNA^+$ cells have been phenotyped as radial glia, both in morphology and in positivity to markers such as glial fibrillary acidic protein (GFAP), vimentin, the S100B protein, the target gene of Notch HER4, glutamine synthetase, the glutamate transporter specific astrocytes and fatty acid binding protein (Götz and Huttner, 2005; Grandel et al., 2006; Kroehne et al., 2011; Schmidt et al., 2013). One-third of $PCNA^+$ cells have been characterized as neuroblasts in differentiation, since they expressed the adhesion protein polysialylated-neural cell adhesion molecule (PSA-NCAM) (März et al., 2010, 2011; Kroehne et al., 2011; Grandel and Brand, 2013). In

mouse, the SGZ is localized at the interface between the granular cell layer and the hilus (Martino et al., 2011), and can continuously generate new neurons that integrate in the neural network of the granular layer of the hippocampus (Curtis et al., 2012). The analysis of the number of the neuronal progenitor cells could give an indirect indication of the possible extent of neurogenesis. However, it does not provide information as to whether the neuroblasts differentiate and integrate as mature neurons. Recently, the generation of hippocampal cells has been assessed in human adulthood by measuring the concentration of nuclear-bomb-test-derived [^{14}C] in genomic DNA, and an integrated model of the 'cell turnover dynamics' suggested: 700 new neurons have been added in each hippocampus per day, corresponding to an annual turnover of 1.75% of the neurons within the renewing fraction, with a modest decline during aging (Spalding et al., 2013). *Post-mortem* studies in healthy older humans, subjects without cognitive impairment, neuropsychiatric disease, reported preserved neurogenesis in the hippocampal region (Boldrini et al., 2018). It is possible that ongoing hippocampal neurogenesis sustains human-specific cognitive function throughout life when angiogenesis is still present (Boldrini et al., 2012). The term 'turnover of neurons' does not imply that individual lost neurons are replaced by new neurons but as an exchange of neurons at the population level. The turnover modeling proposed by Spalding et al. (2013) consisted in the observation that adult-born neurons in mice seemed to be preferentially lost and do not survive as long as neurons generated during development.

The neurogenesis in the dentate gyrus of SGZ, associated with the processes of learning and memory (Deng et al., 2010), has evidenced two types of hippocampal progenitors (Boldrini et al., 2012). Type 1 cells have a radial process spanning the entire granule cell layer and ramifying in the inner molecular layer (Zhao et al., 2008). These cells express nestin, GFAP and the Sry-related HMG box transcription factor, Sox2 (Fukuda et al., 2003; Garcia et al., 2004; Suh et al., 2007). Although expressing the astrocyte marker GFAP, these cells are morphologically and functionally different from mature astrocytes (Garcia et al., 2004). Type 2 cells have only short processes and do not express GFAP. Type 2 cells may arise from type 1 cells (Zhao et al., 2008). In SGZ, proliferating radial and non-radial precursors, which also have the property of self-renewal, generate intermediate progenitors, which turn into neuroblasts. Moreover, the number of proliferating progenitors and young neurons in the dentate gyrus declines sharply during the first year of life and only a few isolated young neurons are observed by 7 and 13 years of age in humans, and in the first 2 years of life in *Macaca macaca*, indicating that in primates the early decline in hippocampal neurogenesis raises questions about how the function of the dentate gyrus differs among species (Sorrells et al., 2018). Immature neurons after migrating in the inner granule cell layer of hippocampus differentiate into dentate granule cells. Within days, newborn neurons extend their dendrites toward the molecular layer and project axons through the hilus toward the CA3 (Zhao et al., 2006). New neurons follow a stereotypic process for synaptic integration into the existing framework (Alvarez-Buylla and Lim, 2004; Martino et al., 2011; Fuentealba et al., 2012; Kazanis, 2012). These cells progressively express PSA-NCAM and double-cortin (DCX, a marker for neuronal precursors), NeuroD, Prox1 and NeuN (markers for neurons in the more advanced stage of differentiation) (Seri et al., 2001; Martino et al., 2011). Newborn neurons in the SGZ have migrated only a short distance into the granule cell layer. A recent study has suggested that the protein disrupted-in-schizophrenia (DISC1) may be involved in newborn neuron migration in the SGZ, as cells with less DISC1 migrate further into the granule cell layer and even into the molecular layer of the dentate gyrus (Duan et al., 2007). The migration of newborn neurons in the dentate gyrus may also be controlled by guidance cues, as these cells migrate only to the hilus or the molecular layer under pathological conditions, such as in animal models of temporal lobe epilepsy (Duan et al., 2007). Signaling through the Reelin pathway may be involved in such regulation (Gong et al., 2007).

Other two neurogenic niches might be compared between zebrafish and mouse, the subpallium area of zebrafish and the SVZ of rodents (Grandel et al., 2006; Ganz et al., 2010; Kroehne et al., 2011; Schmidt et al., 2013). Both these neurogenic areas showed a higher rate of proliferation with respect to two previous neurogenic areas, the pallium and SGZ. The subpallium area in zebrafish is characterized by a higher rate of division and by nestin-expressing proliferating cells (Grandel et al., 2006; Ganz et al., 2010; Kizil et al., 2011). These cells show characteristics of neuroepithelial cells as interkinetic nuclear migration, expression of apical markers such as the area occludens (ZO1) and PAR proteins (Götz and Huttner, 2005). The subpallium area does not show quiescent cells and it generates neurons that migrate to the olfactory bulb and differentiate into GABA-ergic and TH$^+$ interneurons in the granular and periglomerular layer (Adolf et al., 2006; Grandel et al., 2006). As in zebrafish, the SVZ in adult mouse is characterized by high rate of neurogenesis by populations of astrocytes (type B cell) that act as CNS stem cells (Doetsch et al., 1997). These kinds of cells are characterized by a long basal process in contact with

the endothelium of blood vessels and an apical cilium that contact the ventricular lumen (Doetsch et al., 1997; Mirzadeh et al., 2008). Probably, this cellular expansion possesses special receptors for growth factors including Sonic Hedgehog (Shh) (Singla and Reiter, 2006). Type B cells show high proliferative capacity and retain important properties of radial glia cells, like the expression of high levels of GFAP, vimentin and nestin (Doetsch et al., 1997). The stage of maturation of these cells has been represented by another typology of cells called type C, which act as rapid amplifying population, express nestin and exhibit an intermediate phenotype between radial glia cells and neuroblasts (Doetsch et al., 1997). The last stage is represented by the neuroblast differentiation (type A cells) that present migratory capacity toward the olfactory bulb and express migratory-neuroblast typical markers like PSA-NCAM and tubulin βIII (Altman, 1969; Doetsch et al., 1997; Alvarez-Buylla and Lim, 2004).

In rodents newborn neurons in the SVZ migrate to the olfactory bulb in long chains enveloped by type B cells, in a structure called rostral migratory stream (RMS). However, only a small fraction of neuroblasts differentiate into dopaminergic, glutamatergic neurons and GABAergic interneurons, contributing to the continuous change of interneurons (Altman, 1969; Lois and Alvarez-Buylla, 1994; Alvarez-Buylla and Lim, 2004; Kaslin et al., 2008). In humans, the SVZ of the lateral ventricle is characterized by a continuous ribbon of proliferative astrocytes without forming an RMS, as observed in rodents (Sanai et al., 2004; Grandel and Brand, 2013), but neurogenesis within the olfactory bulb has been demonstrated, even if extremely limited (Bedard and Parent, 2004). The migration through the RMS is not driven by radial glia or existing axon fibers but through a 'chain migration,' composed of elongated cell aggregates that are sheathed by astrocytes (Grandel and Brand, 2013). Although astrocytes do not appear to play an essential role in this chain migration, they may be involved in modulating the level of GABA, which has a negative effect on the speed of neuroblast migration (Zhao et al., 2008). The cell-cell and cell-extracellular matrix interactions regulate the migration along the RMS and in the olfactory bulb (Lledo and Saghatelyan, 2005). For example, disruption of EphB2/ephrin-B2 or neuregulin/ErbB4 pathways leads to severe defects in the chain migration of SVZ neuroblasts (Lledo and Saghatelyan, 2005). The NCAM protein is required for the proper organization of the rostral migratory stream (Lledo and Saghatelyan, 2005). Radial migration in the olfactory bulb is partially dependent on the extracellular matrix protein tenascin-R and the glycoprotein Reelin (Zhao et al., 2008).

The regenerative capacity of the CNS between fish and mammals

The telencephalon regeneration in zebrafish and rodents

The capacity to regenerate part of the nervous system has been shown modest in rodents (mice, rabbit) and humans, and still debated until now (Boldrini et al., 2018; Sorrells et al., 2018), while it is high in zebrafish (Table 1). Zebrafish, on the contrary, can regenerate the telencephalon very efficiently following experimentally induced lesions (März et al., 2010; Kroehne et al., 2011; Kishimoto et al., 2012). The protocol used in these studies, characterized by the insertion of a needle in one of the two hemispheres, to injure an hemisphere leaving the other one intact, has permitted us to study at the same time the

Table 1: Comparative summary of the neuro-regenerative response in telencephalon in zebrafish and mammals.

	Zebrafish	Mammals
Regenerative capacity	High	Low
Neurogenic niches	Extended, throughout the rostro-caudal axis of the brain	Limited, sub-ventricular zone (SVZ) and sub-granular zone of the dentate gyrus in the hippocampus (SGZ)
Neurogenesis	Ventricular radial glia S100β/*her4.1*$^+$ serves as NPCs Progenitors give rise to both neurons and glia	SVZ: Glia-like astrocytes (type B cells) serve as NPCs and give rise to neurons to restore the lesion site (80% of new generated neurons die for apoptosis) SGZ: Radial astrocytes (type B cells) serve as NPCs and give rise to new neurons in the granular layer of the hippocampus
Inflammatory/Immune response	Limited. Acute phase: 1–7 days post-injury Promotes neurogenesis	Prolonged, positive (first hours post-injury, neuroprotection) and negative effects (days and months post-injury; neurodegeneration)
Glial scar	No glial scar is observed	Glial scar is formed and prevents neurogenesis and axonal regrowth

constitutive neurogenesis and the regenerative response (Kroehne et al., 2011; Kishimoto et al., 2012; Grandel and Brand, 2013). Results showed that brain injury triggers a series of cascade events characterized by edema, death of damaged neurons with loss of neuronal processes, glial hypertrophy and an acute inflammatory response that reaches its peak 4 days after the lesion (Kroehne et al., 2011). From 3 days post-lesion an intense cell proliferation both in neurogenic regions and in the parenchyma has been observed (März et al., 2010; Kroehne et al., 2011; Kishimoto et al., 2012) with high expression of mitotic markers such as PCNA in the SVG zone (Kishimoto et al., 2012) and in the dorsal region with GFAP+/S100B+/her4.1+ radial glial cells (März et al., 2010; Kroehne et al., 2011). Furthermore, parenchymal proliferation of microglia and leukocytes (L-plastin+), endothelial cells (FLI+) and precursors of oligodendrocytes (OLIG2+) (Kroehne et al., 2011) has been described.

It has been demonstrated that in zebrafish the neuroinflammation, triggered by the activated microglia in the injured site, leads to the regeneration program by emitting key factors that trigger leukocyte chemotaxis and NSPC activation (Sieger and Peri, 2013; Kyritsis et al., 2014). Characterizing these secreted factors is determinant for understanding the difference in the regeneration mechanisms in fish and mammals (Deierborg et al., 2010). The neuroinflammation is reduced from the seventh day after the injury and in 30 days the neuronal tissue is almost restored (März et al., 2010; Kroehne et al., 2011). The NPC proliferation is followed by neuronal differentiation of the radial glial in neuroblasts that, after an intense proliferation, migrate to the injury site along the radial glia processes as a scaffold and completing the differentiation into neurons (Kroehne et al., 2011; Kishimoto et al., 2012). Stainings against typical neuronal markers, such as HuC/D, NeuroD, parvalbumin and Prox1 have shown that one-third of the newly generated cells differentiate correctly into mature neurons in the lesion site (März et al., 2010; Kroehne et al., 2011; Kishimoto et al., 2012). Furthermore, the newborn neurons survive and integrate into the existing neuronal network creating functional synapses, as demonstrated by the expression of synaptic markers such as synaptic vesicle glycoprotein 2 (SV2), Map2a+b and mGluR2 (Kroehne et al., 2011). How efficiently the neural network is also functionally restored requires further investigation, but a study has shown that the newborn neurons are able to generate spontaneously action potentials (Rothenaigner et al., 2011).

Differently to zebrafish, the ability of mammals to regenerate lesions in telencephalon is reduced. It was shown in rodents that an ischemic cerebrum injury stimulates the proliferation of neuronal precursors and neurogenesis both in the SVZ and SGZ (Liu et al., 1998; Jin et al., 2001; Yagita et al., 2001; Arvidsson et al., 2002; Parent et al., 2002; Zhang et al., 2004; Thored et al., 2006; Yamashita et al., 2006). The lesion-induced neurogenesis has also been attested even in regions such as the area CA1 of the hippocampus and the striatum in rodents (Arvidsson et al., 2002; Nakatomi et al., 2002; Xu et al., 2005) and the neocortex of primates (Gould et al., 1999). Even if the proliferation of NPC and neuroblast differentiation is observed, the regeneration program fails to fully restore the neuronal tissue. One reason is represented by an intense and prologued inflammatory response that hinders neuronal regeneration. In mammals, the role of neuroinflammation seems to have a diverse impact on NPCs compared to zebrafish (Table 2). Many chemokines issued by microglia have been shown to affect NPCs'

Table 2: Comparative summary of the neuro-regenerative response in the spinal cord in zebrafish and mammals.

	Zebrafish	Mammals
Regenerative capacity	High, locomotory functionality is completely restored	Neuronal regeneration is absent; limited axonal regeneration ability
Neurogenesis	Ependymal radial-glia progenitors $OLIG^+$ serve as NPCs Progenitors give rise to both neurons and glia	Progenitors give rise to glia only
Axonal regeneration	Radial glia cells give rise to the glial bridge that guides the axonal regrowth	No glial bridge is observed
Inflammatory/ Immune response	Limited: 15–30 days post-injury Promotes neurogenesis	Prolonged, positive (first hours post-injury, neuroprotection) and negative effects (days and months post-injury; neurodegeneration)
Glial scar	No glial scar is observed	Glial scar is formed and prevents neurogenesis and axonal regrowth
Extracellular matrix (ECM)	ECM does not inhibit neuronal regeneration and axonal regrowth	ECM components inhibit neuronal regeneration and axonal regrowth

properties, such as proliferation, migration, survival and maturation (Kyritsis et al., 2014).

In more detail, in SVZ, proliferation of type C cells and neuroblasts remains elevated for 3–4 weeks, as evidenced by the high expression of GFAP and DCX (Arvidsson et al., 2002), neuroblasts migrate to the site of the lesion at the level of the striatum and cortex (Zhang et al., 2004; Yamashita et al., 2006) and differentiate into neurons, as evidenced by the expression of NeuN, HuC/D, microtubule-associated protein 2 (MAP-2), choline acetyltransferase (ChAT) and proteins associated with synaptic vesicles such as synaptophysin and synapsin (Hou et al., 2008). But the newborn neurons lack proper integration in the neuronal network as more than 80% of neuroblasts die by apoptosis, probably due to the environment inflammation signals (Kyritsis et al., 2014).

In SGZ, the trauma triggers an intense proliferation of NPCs for 3–5 weeks, followed by migration of neuroblasts and neuronal differentiation, as demonstrated by the expression of β-III tubulin, NeuN and MAP-2 (Parent et al., 1997; Liu et al., 1998; Jin et al., 2001; Yagita et al., 2001). However, newborn neurons do not migrate to the injury site, but they stop in the granular layer of the dentate gyrus (Liu et al., 1998). Also in primates, global ischemia experiments on macaque monkeys (*Macaca fuscata*) have been carried out. They showed a rate of proliferation and neuronal differentiation in the SGZ significantly lower than rodents (Tonchev, 2011). These findings suggest that the rodents and primate CNS environment do not provide the necessary cues to support survival and integration in the neural circuitry of newborn neurons after injury. In this context the study of the pro-inflammatory and anti-inflammatory pathways that occur in the neuro-regenerative response in zebrafish can be useful to actuate a possible pharmacological modulation of the inflammation in the mammalian models. On the other hand, we still need to investigate more into the elucidation of the inflammatory process in zebrafish. Thus, better knowledge and characterization of chemokines, cytokines and immune cells, participating in the acute inflammatory response, can allow us to understand how the immune system and the inflammation could support the regeneration process.

The spinal cord regeneration in zebrafish and mammals

As for telencephalon, in mammal the ability to regenerate the spinal cord is limited to the axonal regrowth during embryonic and postnatal development (Keirstead et al., 1995). During adult life, only certain types of neurons are able to regenerate their axons in particular conditions (Coumans et al., 2001; Bareyre et al., 2004; Alto et al., 2009). Cases of motor function recovery following spinal cord injury are mainly due to remodeling ('sprouting') of the existing neural network (Weidner et al., 2001). Also in this context zebrafish is an excellent model system for the study of spinal cord regeneration (Table 3). Several experiments demonstrate that neurogenesis and axonal regeneration can be induced experimentally with spinal cord injuries such as compression or complete cross-section (Reimer et al., 2008; Hui et al., 2010; Goldshmit et al., 2012). The injury causes the paralysis of the fish and the efficiency of the regenerative response can be easily assessed by the degree of swimming-ability recovered (Hui et al., 2010). Spinal cord injuries are followed by edema, neuronal death, degeneration of damaged axons, significant loss of white and gray matter and infiltration of blood cells (Hui et al., 2010; Goldshmit et al., 2012). The edema progressively decreases with the activation of the regeneration process (Becker and Becker, 2001; Hui et al., 2010). In fact, intense proliferation of GFAP+ radial glial

Table 3: Comparison of the main events of the inflammatory response in zebrafish and mammals after injury to the CNS.

Zebrafish	Mammals
Acute phase of inflammation	
Glial hypertrophy	
GFAP/vimentin upregulation	
Radial glia proliferation	Astrocytes proliferation
Microglia/leukocyte proliferation and infiltration in the lesion site	
Edema	
Chronic phase of inflammation	
No accumulation of glia and leukocytes in the lesion site	Accumulation of glia and leukocytes
No glial scar is observed	Ectopic ECM deposition leads to glial fibrotic scar
?	High expression of cytokines, chemokines and other inflammatory soluble factors such as INFγ, IL-1β, IL-6, TNFα

cells around the ependymal canal has been observed. Two to three weeks after injury radial glial cells assume a bipolar morphology and migrate to the injury site forming a scaffold called 'glial bridge' (Goldshmit et al., 2012). The formation of the glial bridge is a milestone in the neuro-regenerative process of the spinal cord because it has also been observed in other vertebrates, such as urodele amphibians or some reptiles (Rehermann et al., 2011; Pirrotte et al., 2016). The glial bridge could indeed represent a suitable microenvironment for both axonal regrowth and migration of newly generated neurons (Goldshmit et al., 2012). In the adult mammalian spinal cord, partial neurogenesis occurs in three cell typologies: oligodendrocyte progenitors (NG21/olig21, representing 80% of proliferating cells), astrocytes (GFAP1/Cx301/Sox91, representing <5% of proliferating cells), and ependymal cells (FoxJ11, representing <5%) (Duan et al., 2016).

After an injury, oligodendrocyte progenitor cells increase the dividing rate and produce a large amount of re-myelinated oligodendrocytes (Barnabé-Heider et al., 2010). Astrocytes proliferate and divide correspondingly, forming the border of glia scar without becoming stem cells (Barnabé-Heider et al., 2010; Lee-Liu et al., 2013; Burda and Sofroniew, 2014). Only the ependymal cells seem to be capable of division and self-renewal after a mechanical injury in rats, and generate a large number of astrocytes to participate in scar formation; meanwhile, they generate a small number of oligodendrocytes capable of myelinating axons (Burda and Sofroniew, 2014; Luo et al., 2015).

In the zebrafish spinal cord, a population of ependymal-radial glial cells, positive for markers such as OLIG2, HB9 and Islet-1/2, acts as NPCs specifically after injury and they are able to migrate and differentiate into mature neurons in the injury site (Reimer et al., 2008, 2009). In 6–8 weeks they mature in motor neurons that reach the peripheral muscles, as evidenced by the expression of ChAT and SV2 (Reimer et al., 2008). The site of the lesion is no longer visible from 5 to 6 weeks after the injury (Goldshmit et al., 2012), but already after a month the swimming ability is fully recovered (Hui et al., 2010). If neurogenesis is efficient, the axonal regrowth of the neurons from the encephalic nuclei is more limited. Not all types of descending axons from different encephalic nuclei are efficiently repaired, while ascending axons fail completely the regeneration (Becker et al., 1997, 1998; Grandel and Brand, 2013). In rats and mice ependymal cells seem to be regulated by both intracellular and extracellular factors, and thus have the neural stem cell properties, like stimulated by extrinsic remote signals to reflect nutrition, energy metabolism, oxygen content, hormonal status and other physiological alterations (Duan et al., 2016).

Despite that pro- and anti-inflammatory macrophages have been described in injury models of zebrafish, the polarization of microglia/macrophages after spinal cord injury has not been studied yet. Thus the study of environmental cues that potentially can activate, stimulate and maintain/activate the stem cell niches is still a hot field of research that surely will grow in the next years (Cullen et al., 2011).

Molecular basis of neuronal regeneration and axonal regrowth in zebrafish and mammals

Adult neurogenesis and neuronal regeneration are driven by the activation of specific molecular pathways including transcription factors, growth factors, neurotrophins and cytokines, expressed at the level of the neurogenic niche and eventually in the injured site. Only recently we have started to identify and understand their role in the regenerative response (Figure 4).

Morphogenetic factors

The fibroblast growth factors (FGF), a family of more than 22 proteins involved in proliferation and migration of NPCs and radial glia and axonal regrowth, are widely expressed during embryogenesis and in embryonic reactivation of proliferative programs (Gilbert, 2005; Goldshmit et al., 2012). In zebrafish reports have highlighted the importance of FGF signaling in the regulation of neurogenesis and neuro-regenerative process (Ganz et al., 2010; Kizil et al., 2011; Goldshmit et al., 2012). In the injured spinal cord FGF3, FGF8a and target genes such as *spry4, pea3* and *erm* are highly expressed by neural progenitors during neurogenesis (Goldshmit et al., 2012). FGF signaling is also involved in the regulation of the glial bridge formation. If this scaffold was inhibited, incorrect cell maturation of radial glia was observed (Goldshmit et al., 2012). Other studies report that in olfactory epithelium the HBCs give rise to *Mash*+ progenitors (neural fate), as well as epithelial supporting cells. These cells are particularly sensitive to FGF signalling pathways, like FGF2, but also to GDF11, Fst and bone morphogenetic protein 4 (BMP4) (Beites et al., 2005). In mice, FGF2 is over-expressed after ischemia and remains elevated for up to 2 weeks (Lin

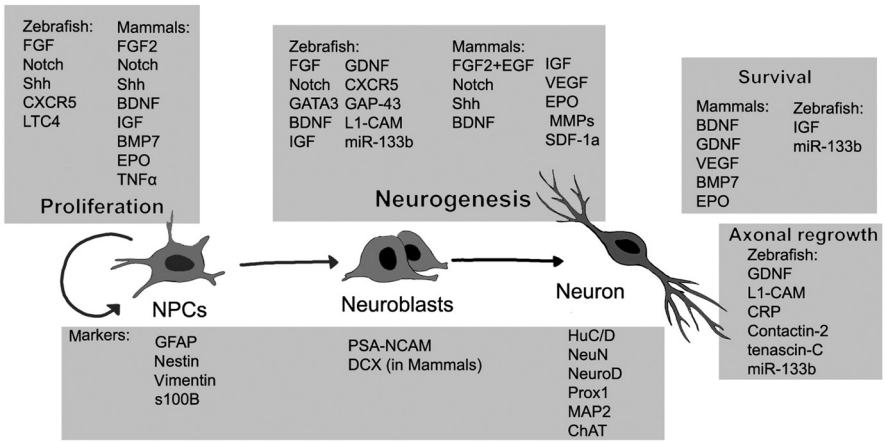

Figure 4: Key molecules involved and cell markers expressed during the neuronal regeneration and axonal regrowth in zebrafish and mammals.

et al., 1997), and it is enhanced during proliferation of NPCs in the SVZ and SGZ (Sun et al., 2009). Furthermore, it was reported that exogenous administration of FGF2 and endothelial growth factor (EGF) in rodents increases proliferation, neuronal differentiation and post-injury recovery (Nakatomi et al., 2002; Zheng et al., 2004; Türeyen et al., 2005; Oya et al., 2008).

Notch signaling (SNCH) plays pleiotropic roles in coordinating the differentiation of neuronal and glial cells both during embryonic neuronal development and in adult neurogenesis (Chambers et al., 2001; Park and Appel, 2003; Kim et al., 2008; Xiao et al., 2009; Chapouton et al., 2010). In zebrafish, NCH activity is associated with the control of the balance between proliferative and quiescent stage of radial glia. High levels of Notch expression are required for the maintenance of the quiescent state (Chapouton et al., 2010). The role of SNCH in neurogenesis and reparative therapy has been still unclear since the radial glia in proliferation expresses her4.1 and her4.5 under a high level of notch 1b signaling (Chapouton et al., 2010; Kroehne et al., 2011; Dias et al., 2012). Radial glial cells in zebrafish are subjected to a regulation by the SNCH. However, not all the cell populations respond in the same way; in some Notch seems to stimulate the proliferation, in other a quiescent state (Rothenaigner et al., 2011; Dias et al., 2012; Kishimoto et al., 2012). Probably, the different cellular response to SNCH reflected the presence of heterogeneity of Nch receptors and ligands, including the fluctuations in expression (Chapouton et al., 2010; Kizil et al., 2011). In mouse, the Nch1 receptors and their ligands Jagged1 and Delta1 are expressed in neurogenic regions of the adult CNS. Nch1 is expressed in SVZ and SGZ NPCs and in neuroblasts migrating along the RMS, and it seems to have a role in inhibition of their premature differentiation (Givogri et al., 2006). The ischemia process significantly increases Nch1 expression and its target genes such as HES1 in NPCs (Givogri et al., 2006; Wang et al., 2009; Xiao et al., 2009). During the post-ischemic neuronal differentiation of the neuroblasts, the expression of Nch1 and HES1 progressively decreases, coinciding with a significant increase in the number of newly generated neurons. Therefore, the SNCH reveals the ability to increase the pool of neural progenitors in the SVZ and regulates the differentiation of new neurons after ischemia (Givogri et al., 2006; Wang et al., 2009).

Sonic Hedgehog signaling (Shh) plays an important role both in neurogenesis of the CNS and regeneration (Ingham and McMahon, 2001). In zebrafish, the uninjured spinal cord expression of the *shh* gene and transcription target factors such as *Olig2*, *nkx6.1* and *Pax6* are relatively very low. During the regenerative response *shh* is significantly increased in the glial-ependymal cells, acting as NPCs. It was reported that the Shh signaling pathway significantly decreases ventricular cell proliferation rate and the differentiation of new motor neurons (Reimer et al., 2009). In mice and rabbits, treatment with Shh after spinal cord injury promotes the proliferation of nestin+ ependymal NPCs. Post-ischemia treatment with Shh in rodents has neuro-protective effects and promotes behavioral recovery (Bambakidis et al., 2003, 2012). Shh is also involved in the regulation of the inflammatory response post-trauma (Bambakidis et al., 2012). Moreover, stimulating the proliferation of $Olig2^{+}$ cells, Shh induces glial hypertrophy and proliferation of oligodendrocytes and microglia (Amankulor et al., 2009).

Another molecular key player is represented by the brain-derived neurotrophic factor (BDNF) widely expressed both during embryonic development and in the adult brain of vertebrates. Its signalling supports

survival and hinders neurodegeneration post-ischemia through the TrkB PI3-K/MAPK/ERKs pathway and by the expression of anti-apoptotic genes such as *Bcl-2* (Schäbitz et al., 2000; Ferrer et al., 2001; Almeida et al., 2005; Donovan et al., 2008). In models of zebrafish for Huntington's disease, the reduced neuronal expression of BDNF causes death and aberrant neuronal development (Diekmann et al., 2009). Reports evidenced that in mammals the cerebral ischemia increases the expression of BDNF in endothelial cells and astrocytes (Duan et al., 2016). This neurotrophic factor is considered determinant to stimulate NPCs in differentiation, migration and integration, surviving of newborn neurons in the neural network of SVZ (Zigova et al., 1998). In BDNF knockout mice ischemic lesions are followed by limited neurogenesis and reduced neuronal survival (Schäbitz et al., 2000; Larsson et al., 2002).

The insulin-like growth factor (IGF) is a hormone peptide produced at the level of liver and brain under stimulation by the growth hormone. Reports showed that its neurotrophic activity is also exerted at the level of the injured brain (Liu et al., 2001), promoting the regenerative process by the proliferation of NPCs and their differentiation into neuroblasts (Kalluri and Dempsey, 2008). Evidence in rodents reported that IGF-1 can stimulate the NPC proliferation in the presence of FGF2, while it promotes neuroblast differentiation in the absence of it (Kalluri and Dempsey, 2008; Lanfranconi et al., 2011). In zebrafish, the IGF regulates the development of the notochord, retina, motoneurons, but it is also important to sustain neuronal survival. Indeed inhibition of the IGF-1 receptor (IGF1R) leads to neuronal apoptosis by caspase-3 activation (Schlueter et al., 2007; Zou et al., 2009).

GDNF signaling is involved in the development of spinal motor neurons and noradrenergic neurons and promotes the survival and differentiation of different types of neurons (Lanfranconi et al., 2011). In mice, post-ischemia expression of GDNF and its receptors is significantly increased in the damaged area and promotes both the proliferation and survival of newborn neurons (Wang et al., 1997). GDNF treatments in rats show increased proliferation of NPCs in neurogenic niches and reduction of the injured area, exerting a mitogenic and anti-apoptosis function (Kitagawa et al., 1998; Lanfranconi et al., 2011). In zebrafish, GDNF is expressed at the level of the telencephalon during development and adulthood (Lucini et al., 2008). It was reported that GDNF regulates the development of sensory and lateral line neurons, proliferation of NPCs, differentiation and survival of peripheral neurons and post-lesion axonal regrowth (Schuster et al., 2010).

BMPs are members of the transforming growth factor beta family (TGF-β). In the zebrafish, embryonic BMP signaling acts in the regulation of neuronal development, but their role in the adult CNS has not been further investigated (Holzschuh et al., 2005; Londin et al., 2005). In the mice olfactory epithelium, BMP4 is necessary to maintain the environment of the stem cell niche, whereas FGF8, BMP7, EGF, and TGF-α maintain the basal lamina compartment, and Fst, BMP7, BMP4, BMP2, and noggin regulate the lamina *propria* and the developing nasal bone (Beites et al., 2005).

In mice after CNS injury, BMP2, BMP4 and BMP6 are overexpressed and stimulate oligodendrocytes, Schwann cells and astrocyte differentiation, and, at the same time, they regulate the inflammatory response in the injury site (Sabo et al., 2009). BMP7 has been associated with promoting NPC proliferation in the post-injury neuro-regenerative response (Harvey et al., 2005). Indeed, treatments with BMP7 in mice lead to the reduction of the injury site, increasing cell proliferation in the SVZ and decreasing neuronal death by toxicity of oxygen radicals and glutamate (Harvey et al., 2005; Chou et al., 2006).

Vascular endothelial growth factor (VEGF) signaling is involved in the regulation of vascular permeability and angiogenesis (Gilbert, 2005). In zebrafish, the role of VEGF post-CNS trauma has not been studied yet, while its role in the repair of the damaged heart is known, probably in concert with Shh (Liang et al., 2001; Lavine et al., 2006; Lepilina et al., 2006). In rodents, the expression of VEGF and its receptors (VEGFR1/2) after ischemia is regulated by the hypoxia-induced transcription factor 1α (HIF-1α) (Marti et al., 2000; Zhang et al., 2002; Sun et al., 2003). It was reported that VEGF exerts a beneficial effect on NPC survival, and neuroblast differentiation and migration to the injury site (Jin et al., 2000; Matsuzaki et al., 2001; Svensson et al., 2002; Zhang et al., 2002; Sun et al., 2003; Thau-Zuchman et al., 2010). VEGF, through PI3-K, Akt, NF-kB and Bcl-2 pathways, regulates cell survival apoptosis of neuronal precursors and endothelial cells (Gerber et al., 1998; Nör et al., 1999; Jin et al., 2000; Thau-Zuchman et al., 2010). Furthermore, intra-cerebral infusions of VEGF reduce the size of the damaged region (Thau-Zuchman et al., 2010) and stimulate neurite regrowth of cortical neurons (Jin et al., 2006) and the expansion of SVZ (Gotts and Chesselet, 2005). The role of VGF in the olfactive epithelium is still unknown. Erythropoietin (EPO) has been described as a hematopoietic cytokine that promotes the proliferation, survival and differentiation of erythroid progenitors (Wang et al., 2004). In rats, EPO and its receptors are highly induced by HIF-1α in neuronal cells, NPCs, glial cells and endothelial cells in response

to traumatic brain injuries (Tsai et al., 2006; Xiong et al., 2011). EPO signaling mediates the pathways controlled by STAT, PI3-K/Akt, Ras/ERK, NF-kB, and promotes neuron survival (Sirén et al., 2001; Kadota et al., 2009). Moreover, EPO increases neurogenesis both *in vivo* and *in vitro* and regulates the migration of neuroblasts to the injury site (Wang et al., 2004; Tsai et al., 2006; Kadota et al., 2009). Interestingly, EPO showed the ability to promote spatial memory recovery after traumatic brain injuries in rodents (Lu et al., 2005).

Probably, EPO's permissive role in neuro-regeneration is linked to the stimulation of endothelial cells and astrocyte expression of VEGF and BDNF (Wang et al., 2004; Xiong et al., 2011), contributing therefore to the creation of the necessary micro-environment for an effective regenerative response (Wang et al., 2004; Xiong et al., 2011).

Several other factors involved in the neuro-regenerative response have been recently identified in zebrafish and rodents. In the injured spinal cord of zebrafish, ependymal radial glial cells express high levels of the transcription factor SOX11b (Guo et al., 2011). Reports evidenced that SOX11b stimulates the proliferation of NPCs and migration to the injury site of the neuroblasts, and it regulates the expression of proneural genes such as *nestin* and *mash1a* (Guo et al., 2011).

The molecules that interact between neurons and ECM

Some key ions and molecules are cues of inducing both neurogenesis and reparative processes related to ECM. Calcium is, for example, a key regulator of axon degeneration caused by trauma and disease; its presence in the ECM is fundamental in activating the regeneration program of injured zebrafish neurons as revealed *in vitro* research (Vargas et al., 2015).

The neuronal adhesion molecules L1-CAM, L1.1 and L1.2 expressed after spinal injury in the zebrafish, seem to be correlated with regeneration of different types of neurons. L1.1 is overexpressed following lesions and its inhibition reduces axonal regrowth and decreases synapse formation with the result of a lack of recovery of motor function (Becker et al., 1998, 2004; Vajn et al., 2013). L1.2 is expressed at high levels by glial cells and it promotes the permissiveness of the environment, the differentiation of new neurons and correct axon regrowth (Becker et al., 1998). Contactin-2 is a neuronal adhesion protein, generally expressed by motoneurons and secreted into the cerebrospinal fluid. Experiments in which contactin-2 was downregulated have shown a reduction of motor function recovery and significant reduction of axonal regrowth (Lin et al., 2012). During the neuro-regenerative response the extracellular matrix is remodeled by metalloproteinases (MMPs) secreted by astrocytes. Although the degradation of the extracellular matrix can facilitate the breakdown of the blood-brain barrier, by increasing the edema and hemorrhage (Asahi et al., 2001), several experiments have shown a beneficial role of MMPs in neuroregenerative response in mammals (Lee et al., 2006). In mammals, MMP-9 showed the ability to degrade laminin and block the neuroblast migration (Lee et al., 2006; Wang et al., 2006; Kalluri and Dempsey, 2008). MMP-9 is involved in neuronal differentiation (Wang et al., 2006). Experiments of the knockdown of MMP-3 or MMP-9 in NSCs reported reduced neuronal differentiation in response to chemokines such as SDF-1α and VEGF (Barkho and Zhao, 2011). Therefore, the degradation of the extracellular matrix by MMPs has activated secondary mechanisms in collaboration with morphogenetic factors and chemokines that promote neuronal differentiation as well.

MicroRNAs

The miRs are small non-coding RNA molecules that regulate the translation and degradation of the mRNA target (Dharap et al., 2009). Both in all mammal models and in zebrafish, trauma to the CNS has been followed by the expression of several patterns of miRs responsible for the regulation of the inflammatory response, neurogenesis and axonal regrowth. The analysis and comparison of these patterns have shown that in mammals several miRs (e.g. miR-127, miR-133b, miR-181, miR-411, miR-99a, miR-34, miR-24, miR-331 and miR-384) are overexpressed (Dharap et al., 2009). Their targets are mainly anti-apoptotic genes such as *bcl-2* (miR-497), neuroprotection genes or proteins that regulate the inflammation. Again, energy and oxygen homeostasis genes are also regulated by miRs, for example, SOD2 (miR-145) and the transcriptional factor HIF-1α (Dharap et al., 2009; Yin et al., 2010). Reports showed that miR-9 and miR-139 are involved in the regulation of the Notch pathway (Liu et al., 2011). MicroRNAs take parts also in the inflammatory process. It is believed that the control of the intense gliosis and hypertrophy in astrocytes that leads to the formation of the glial scar is underwent from regulation of miR-21. In fact, in the injured spinal cord of mice, the expression of miR-21 is upregulated in reactive astrocytes around the site of the lesion (Bhalala et al., 2012). Unfortunately, only few studies have investigated the expression of miRs in post-injured zebrafish. In zebrafish, miR-133b, overexpressed

after spinal cord injury, is involved in the axonal regeneration of neurons of the medial longitudinal fasciculus nuclei and the superior and intermediate reticular formation (Yu et al., 2011b). Among the targets inhibited by miR-133b, there are both pro-apoptotic genes such as caspase-9 and calcineurin, both the effectors of the Rho pathway, and proteins associated with the inhibition of neuronal regeneration (Fournier et al., 2003; Yu et al., 2011b). It is interesting to underlie that in mice miR-133b is repressed for more than a week after spinal cord injury, while in zebrafish it remains active for all the process (Liu et al., 2009). This difference could be one of the causes of the failure of the neuro-regenerative response in the spinal cord of mammals. Interestingly, multipotent mesenchymal stromal cells of rats induced in the production of miR133b have stimulated the regeneration in neighbors neurons damaged (Xin et al., 2012).

Neuro-inflammation factors and chemokines

Among the regenerative mechanisms, recent evidence suggests that inflammation may be important in regeneration. Different events can be described following acute CNS injury in mammals and non-mammalian vertebrates. Recent studies indicated that acute inflammatory response that leads to the activation of the several molecules could be responsible for the reactive gliosis orchestration and activate neurogenesis.

Among the key molecules of neuroinflammation, leukotriene C4 (LTC4) signaling is required to activate proliferation and neurogenesis (Kroehne et al., 2011). In fact, the LTC4-CysLT1 pathway induces the expression of transcription factors such as GATA3, which promotes the NPC proliferation and their differentiation into neurons (Kizil et al., 2012). In injured telencephalon of zebrafish, CysTL1 has been detected in glial cells during inflammation (Kyritsis et al., 2012). The inflammatory response is suppressed in the first week post-injury without any chronic consequences in zebrafish (Kroehne et al., 2011; Goldshmit et al., 2012; Kishimoto et al., 2012), while in mouse and rabbit it prolonged for months (Lee-Liu et al., 2013). It is well known that mammals microglia, macrophages and oligodendrocytes release cytokines and toxic metabolites that induce a second event of neuronal death and inhibition of neuro-regeneration (Fawcett and Asher, 1999; Kim and De Vellis, 2005; Vajn et al., 2013).

Chemokines and cytokines have shown a plethora of roles and not only belong to inflammatory response (Jaerve and Muller, 2012; Kumar and Loane, 2012). Their beneficial or detrimental role for regeneration of the CNS is controversial (Kyritsis et al., 2014). Pro-inflammatory cytokines show negative effects on neuro-regenerations and NPC proliferation. IL-1β reduces the proliferation of NPCs both *in vivo* and *in vitro* (Wang et al., 2007), while TNFα promotes NPC differentiation into astrocytes and inhibits cell proliferation *in vivo* and *in vitro* (Ben-Hur et al., 2003; Iosif et al., 2008). Evidence suggests that interferon α (IFNα) and TGFβ inhibit neurogenesis (Buckwalter et al., 2006; Moriyama et al., 2011). The IFNγ shows opposite effects on neurogenesis. On the one hand, it stimulates neuronal differentiation and neurite regrowth in murine and human neuroblastoma (Wong et al., 2004; Song et al., 2005), while on the other hand, it is also able to inhibit the proliferation of NPCs in the SVZ *in vivo* (Martino et al., 2011; Yoneyama et al., 2011). Mice with chronic IL-6 expression show a significant reduction in hippocampal neurogenesis, while treatments with anti-IL-6 restore *in vitro* the rate of proliferation and neurogenesis to the control levels (Vallieres et al., 2002). Nevertheless, recently it has been demonstrated that IL-6 promotes neuroprotection, neurite outgrowth and synaptic formation (Yang et al., 2012; Leibinger et al., 2013) (Table 2). Moreover, the massive proliferation of astrocytes and extracellular matrix molecules contributes to the formation of the glial scar in mammals, considered the major obstacle to regeneration (Sofroniew, 2009). It has been proposed that the glial scar has positive effects in the acute phase of inflammation, in the chronic phase. It inhibits neuro-regeneration (Fawcett and Asher, 1999; Gris et al., 2004; Kroehne et al., 2011).

The CXCR5 chemokine seems to play a central role in regulating the telencephalon neuro-regenerative response. CXCR5 is highly expressed by radial glial cells in proliferation and cooperates in the activation of neuroblasts differentiation (Kizil et al., 2012).

In mice, following ischemia, endothelial cells and reactive astrocytes overexpress the stromal derived factor SDF-1α and angiopoietin 1 (ANG-1) regulating the differentiation and migration of NPCs and neuroblasts, which express the respective ligands CXCR4 and TIE-2 (Imitola et al., 2004; Ohab et al., 2006; Robin et al., 2006). In fact, the SDF-1α/CXCR4 interaction activates pathways involved in migration and neuronal survival (Imitola et al., 2004; Peng et al., 2004; Robin et al., 2006). In zebrafish, the interaction SDF-1α/CXCR4 drives axogenesis during embryonic development, but their role in adult neurogenesis has not been investigated yet (Li et al., 2005; Miyasaka et al., 2007).

Over the past decades, intensive research efforts have focused on the discovery of novel targets of which manipulation could enable regeneration after CNS/axonal trauma (Figure 4). Modulation of the acute inflammatory

response has been proposed as a promising strategy to induce axonal regeneration (Bollaerts et al., 2017).

The role of inflammation during axonal regeneration was studied after optic nerve injury in rodents treated by zymosan, a pro-inflammatory glucan molecule derived from the yeast cell wall. It was reported that zymosan can induce RGC axon growth, by the Toll-like receptor 2 (TLR2) pathway, as well as by the activation of smaller molecule Pam3Cys (Fischer et al., 2000; Hauk et al., 2010; Fischer and Leibinger, 2012). Instead, oncomodulin (Ocm), an inflammatory mediator, directly acts on RGCs by the JAK/STAT3 and mTOR pathways (Fawcett and Asher, 1999; Bollaerts et al., 2017). Moreover, inflammatory stimulation elicits the secretion of IL-6 family cytokines from reactive astrocytes (Bollaerts et al., 2017). In rat after spinal cord injury, microglia activated, and neutrophils and blood-borne macrophages recruited to the lesion site (Schwartz and Yoles, 2006). Microglia/macrophages mostly show the proinflammatory phenotype, secreting pro-inflammatory cytokines such as TNF-α and IL-1β, while anti-inflammatory microglia/macrophages, which produce anti-inflammatory cytokines including IL-4 and IL-10, are present only in a small percentage. The reason of this observation can be a cue of further research in future.

Comparative analysis of gene expression in mammals has allowed the identification of the molecules responsible, expressed in the glial scar (Fawcett and Asher, 1999; Vajn et al., 2013). The chondroitin sulfate proteoglycans (CSPGs), myelin-associated glycoprotein (MAG) and the tenascin-R (Fawcett and Asher, 1999; Vajn et al., 2013) are considered molecular cues involved in axonal regeneration. In rodents, it has been demonstrated that CSPGs inhibit axonal regrowth both *in vivo* and *in vitro* (Dou and Levine, 1994; Hynds and Snow, 1999; Bradbury et al., 2002; Yiu and He, 2006; Shen et al., 2009; Gardner and Habecker, 2013). In zebrafish, CSPGs drive the regeneration by preventing aberrant connections of nerve axons (Fawcett and Asher, 1999; Becker and Becker, 2002; Vajn et al., 2013). Tenascin-C results are overexpressed by oligodendrocytes following trauma. In rodents, tenascin-C and -R inhibit axonal regrowth (Becker et al., 2000; Tang et al., 2003), while in zebrafish, tenascin-R and -C are permissive toward regeneration. Tenascin-R takes part in the process of regeneration of the optic nerve and tenascin-C promotes locomotor recovery after spinal cord injury (Becker and Becker, 2002; Yu et al., 2011a).

The MAGs, glycoproteins of the immunoglobulin-like lectin family, are expressed by oligodendrocytes and microglia in the lesion site and interacted with specific receptors of the Nogo family (neurite outgrowth inhibitor). Their receptors, NgR1, NgR2 and gangliosides GT1a and GT1b, are overexpressed by myelinated axon fragments and at the same time, connected to the transduction pathways that inhibit axonal growth. In zebrafish, MAGs have a different role from those of mouse, first of all, the non-inhibitory action (Fawcett and Asher, 1999; Yiu and He, 2006; Vajn et al., 2013). Nogo-A protein is involved in the regulation of synaptic plasticity and in the protection from oxygen radical (Yiu and He, 2006). It is overexpressed by oligodendrocytes and neurons following injury. In mouse, Nogo-A has a C-terminal domain, and Nogo-66 and Nogo-A-delta 20 have an N-terminal domain. It is reported that both domains show activity toward neuro-regeneration (Oertle et al., 2003). Nogo-66 activates the pathway mediated by RhoA and its effectors, such as Rho-associated kinase, driving the growth cone collapse and/or the inhibition of neurite growth (Fournier et al., 2003; Yiu and He, 2006). In zebrafish, Nogo-A lacks the N-terminal inhibitory domain (Fawcett and Asher, 1999; Abdesselem et al., 2009; Vajn et al., 2013).

In mouse and rat, ephrin and semaphorin prevent the regeneration process. Ephrins and their receptors are a family of molecules involved in the regulation of axonal growth during development, but they are also present in the adult CNS. Following injury, in rodents several ephrins and their receptors are overexpressed by neurons/astrocytes and activate signal transduction pathways that provoke the collapse of axonal growth cone and consequent neural death (Willson et al., 2002; Mann et al., 2003; Goldshmit et al., 2004, 2011; Fabes et al., 2006; Arocho et al., 2011; Thundyil et al., 2013). Semaphorins are a large family of membrane and/or secreted proteins involved in axonal growth during development. Sema-3A, for example, has been overexpressed after trauma. Its role has been associated with the inhibition of axon regrowth (De Winter et al., 2002). In zebrafish, spinal cord glial cells in proliferation creates a scaffold the used by growing axons and neuroblasts to migrate toward the injury site (Kroehne et al., 2011; Goldshmit et al., 2012). These studies have evidenced the importance of interaction among matrix, glial cells and neurons to regenerate the spinal cord (Kroehne et al., 2011; Goldshmit et al., 2012; Lee-Liu et al., 2013). Moreover, an important point emerging from the studies of neural stem cells is that many of the pro-inflammatory and inflammatory molecules expressed within the stem cell microenvironment during the injury repair are also important and common in the other regenerative systems. Thus, the possibility of manipulating the process by a sequence of morphogenic factors opens the possibility of repairing not only the nervous system but also a panel of multiple tissues.

Conclusions

The success of the neuro-regenerative response requires a series of coordinated cellular processes: proliferation and migration of NPCs, neuronal differentiation, cell survival and integration of new neurons generated in the existing neural network. A current strategy is therefore intended to promote the migration and neuronal differentiation of NPCs and their survival at the injury site through the manipulation of the neuroinflammmation process that involved chemokines, growth factors, signaling molecules, which alter the neurogenic niche environment (Sieger and Peri, 2013; Kyritsis et al., 2014). However, thanks to the translational model like the zebrafish, it has been possible to explore the control of gene expressions by multiple pathways, activated by the environmental molecules (Fernàdez-Hernàndez and Rhiner, 2015) or cellular intrinsic factors (Russo et al., 2017). The effects on the CNS of some morphogenic factors such as EPO and VEGF are still under-investigated in zebrafish and their effects could be linked to the inflammatory process. The comparison and analysis of the different patterns of gene expression and miRNAs in neurogenic regions would identify the intrinsic factors that allow the efficient regeneration of the zebrafish neural tissue. The elucidation of these cellular and molecular processes associated with the success of the repair of the CNS might therefore lead us to understand how we can efficiently proceed to form new neurons and glial cells, or stimulate the latter one to the myelination process (William, 2014). Moreover, understanding similarities with other neurogenic regions should provide us with insight into a common regulatory network that defines the neural stem cell state, and will provide us with important knowledge for facilitating neurogenesis in regions of the adult nervous system where regeneration is limited or absent. Again, the emergent studies in *ex vivo*, by using tissue pre-engineered neural constructs growing in three-dimensional culture or by neurosphere culture or by biohybridized neural-electrical of microsystems, has taken advantage to the information of neuroanatomical and functional characteristics in order to obtain in future the control of neuroregeneration (Cullen et al., 2011; Onhishi et al., 2013).

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