The FEBS Journal

FEBS PRESS science publishing by scientists

REVIEW

Comparative insight into the regenerative mechanisms of the adult brain in zebrafish and mouse: highlighting the importance of the immune system and inflammation in successful regeneration

Jincan Chen[1], Hector Sanchez-Iranzo[1], Nicolas Diotel[2] and Sepand Rastegar[1]

1 Institute of Biological and Chemical Systems-Biological Information Processing (IBCS-BIP), Karlsruhe Institute of Technology (KIT), Germany
2 Université de La Réunion, INSERM, UMR 1188, Diabète Athérothrombose Thérapies Réunion Océan Indien (DéTROI), Saint-Pierre, La Réunion, France

Keywords
astrocytes; glial scar; immune system; inflammation; microglia; neural stem cells; radial glial cells; regeneration; zebrafish

Correspondence
S. Rastegar, Institute of Biological and Chemical Systems-Biological Information Processing (IBCS-BIP), Karlsruhe Institute of Technology, Karlsruhe 76344, Germany
Tel: +49 721 608 22507
E-mail: sepand.rastegar@kit.edu
and
N. Diotel, Université de La Réunion, INSERM, UMR 1188, Diabète Athérothrombose Thérapies Réunion Océan Indien (DéTROI), Saint-Pierre, La Réunion, France
Tel: +262 02 62 48 33 96
E-mail: nicolas.diotel@univ-reunion.fr

(Received 12 May 2024, revised 17 June 2024, accepted 18 July 2024)

doi:10.1111/febs.17231

Regeneration, the complex process of restoring damaged or absent cells, tissues, and organs, varies considerably between species. The zebrafish is a remarkable model organism for its impressive regenerative abilities, particularly in organs such as the heart, fin, retina, spinal cord, and brain. Unlike mammals, zebrafish can regenerate with limited or absent scarring, a phenomenon closely linked to the activation of stem cells and immune cells. This review examines the unique roles played by the immune response and inflammation in zebrafish and mouse during regeneration, highlighting the cellular and molecular mechanisms behind their divergent regenerative capacities. By focusing on zebrafish telencephalic regeneration and comparing it to that of the rodents, this review highlights the importance of a well-controlled, acute, and non-persistent immune response in zebrafish, which promotes an environment conducive to regeneration. The knowledge gained from understanding the mechanisms of zebrafish regeneration holds great promises for the treatment of human neurodegenerative diseases and brain damage (stroke and traumatic brain injuries), as well as for the advancement of regenerative medicine approaches.

Introduction

Regeneration is a widespread phenomenon in the animal kingdom, yet various organisms exhibit differing capacities for it. Zebrafish, in contrast to many mammals, display exceptional regenerative abilities [1]. For instance, in adult zebrafish, organs like the heart, fin, retina, spinal cord, and several brain regions can

Abbreviations
aIPC, adult intermediate progenitor cell; BBB, blood–brain barrier; BMP, bone morphogenetic protein; BrdU, bromodeoxyuridine; CNS, central nervous system; CSPGs, chondroitin sulfate proteoglycans; DAMPs, damage-associated molecular patterns; DCFH-DA, dichlorodihydrofluorescein diacetate; Dex, dexamethasone; dpl, days post-lesion; ECM, extracellular matrix; GFAP, glial fibrillary acidic protein; GLAST, glutamate aspartate transporter; GSH, glutathione; hpl, hours post-lesion; *id1*, *inhibitor of differentiation 1*; ILs, interleukins; LPO, lipid peroxidation; LTC4, leukotriene C4; NSCs, neural stem cells; OPCs, oligodendrocyte precursor cells; RGCs, radial glial cells; SOD, superoxide dismutase; TNF-α, tumor necrosis factor-α; V-SVZ, ventricular-subventricular zone; VZ, ventricular zone.

regenerate without scarring [2–6]. Many factors contribute to this enhanced regenerative capacity in zebrafish compared to mammals: (a) Activation of quiescent neural stem cells (NSCs) distributed within the central nervous system (CNS, such as brain, spinal cord, or retina), which generate new neurons to replace missing ones [3,5,7–12], (b) Ability to generate stem cells through dedifferentiation after injury, observed in fin and retina regeneration [13–16], (c) Activation of specific genes through *cis*-regulatory modules or differential chromatin accessibility, such as the *leptin* [17,18] or genes like *hif1ab*, *nrf1*, *tbx2b*, and *zbtb7a*, which are involved in regeneration through epigenomic regulators [19], (d) Positive contribution of the immune system to regeneration in zebrafish, unlike its potentially inhibitory role in mammals due to prolonged activation [20–23], (e) Capacity to regulate fibrosis processes, allowing damaged tissue to be replaced by new cells rather than scar formation [24].

Zebrafish has emerged as a prominent vertebrate model for studying regeneration due to its high regenerative capacity in both embryo and adult stages, its genetic resemblance to humans (> 70%) [25], and its amenability to genetic manipulation, including gene knockouts and CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9) genome editing. These features enable precise investigations into gene function, regulation, and cell fate dynamics during regeneration [1,4,25]. The similarities between the physiological and immune system cells, such as macrophages, neutrophils, and microglia, in zebrafish and humans make zebrafish a valuable model for drug discovery, toxicity studies, and high-throughput drug screening [26–28]. The transparency of zebrafish embryos and mutant lines like the *casper* strain allows real-time, non-invasive observation of organ development and regeneration [29–31].

This review aims to elucidate the reasons behind the superior regenerative capacity of zebrafish in comparison to mammals. Emerging research indicates that the microglia/immune system plays a crucial role in successful regeneration of various tissues and this review will focus on this aspect. In particular, we will compare the contribution of immune cells and inflammation to telencephalic regeneration in zebrafish and mouse as mammalian models. Recent studies have revealed striking similarities in cellular mechanisms and signaling pathways involved in adult constitutive neurogenesis in the telencephalon of both zebrafish and mouse (Fig. 1). Consequently, the telencephalon serves as a suitable model to study and identify factors influencing regenerative capacity in zebrafish compared to mouse [3,32]. Understanding these mechanisms in zebrafish may hold significant implications for potential applications in treating human neurodegenerative diseases and discovering approaches to enhance regeneration in humans.

Immune response and brain repair following zebrafish telencephalon injury

In zebrafish following telencephalic injury, cell death occurs by apoptosis and necrosis, accompanied by edema formation [7–9,33]. This triggers the recruitment and activation of microglia, the resident macrophages of the CNS, and probably involves the recruitment of peripheral immune cells (macrophages, leukocytes, and neutrophils) [9,22,23,33]. The breakdown of the blood–brain barrier (BBB) allows these immune cells access to the injured area, initiating an acute local neuroinflammatory response [22]. In general, it is considered that inflammatory signals immediately increase vascular permeability, facilitating the arrival of various immune cells like leukocytes, macrophages, and microglia near the injury site. These cells aid in eliminating dying cells and infectious agents, participating in the control of the inflammatory processes and its gradual resolution in the days following injury as shown in mammals [34]. Furthermore, studies in zebrafish have demonstrated the critical role of the immune system and inflammation in activating the proliferation of radial glial cells (RGCs) that correspond to *bona fide* NSCs in the ventricular zone (VZ) of the injured hemisphere [22,23]. They generate newborn neurons that repopulate the lesion site through different mechanisms [7,8,11,35]. Additionally, there is an increase in oligodendrocyte precursor cells (OPCs), likely necessary for remyelinating damaged axons [9,36]. Importantly, unlike in mammals, neither chronic inflammation nor glial scarring is observed in zebrafish. Generally, damaged tissue is fully restored without any visible residual lesions after a few months [8,23,37,38] (Fig. 2).

Role of microglia in zebrafish telencephalon regeneration

One of the main challenges in zebrafish research is discerning the nature and role of CNS immune cells in regenerative processes, given the absence of unique and specific markers for each cell type. Typically, macrophages are identified as *mpeg1.1*$^{+}$/4C4^{-} and *mfap4*$^{+}$ cells, leukocytes/microglia as L-plastin^{+} cells, and microglia as *mpeg1.1*$^{+}$/4C4^{+} cells (Table 1) [22,39–41]. Generally, 4C4^{+} cells are widely recognized as microglia in the literature [40,42–44]. However, it is highly probable that there is some overlap between these

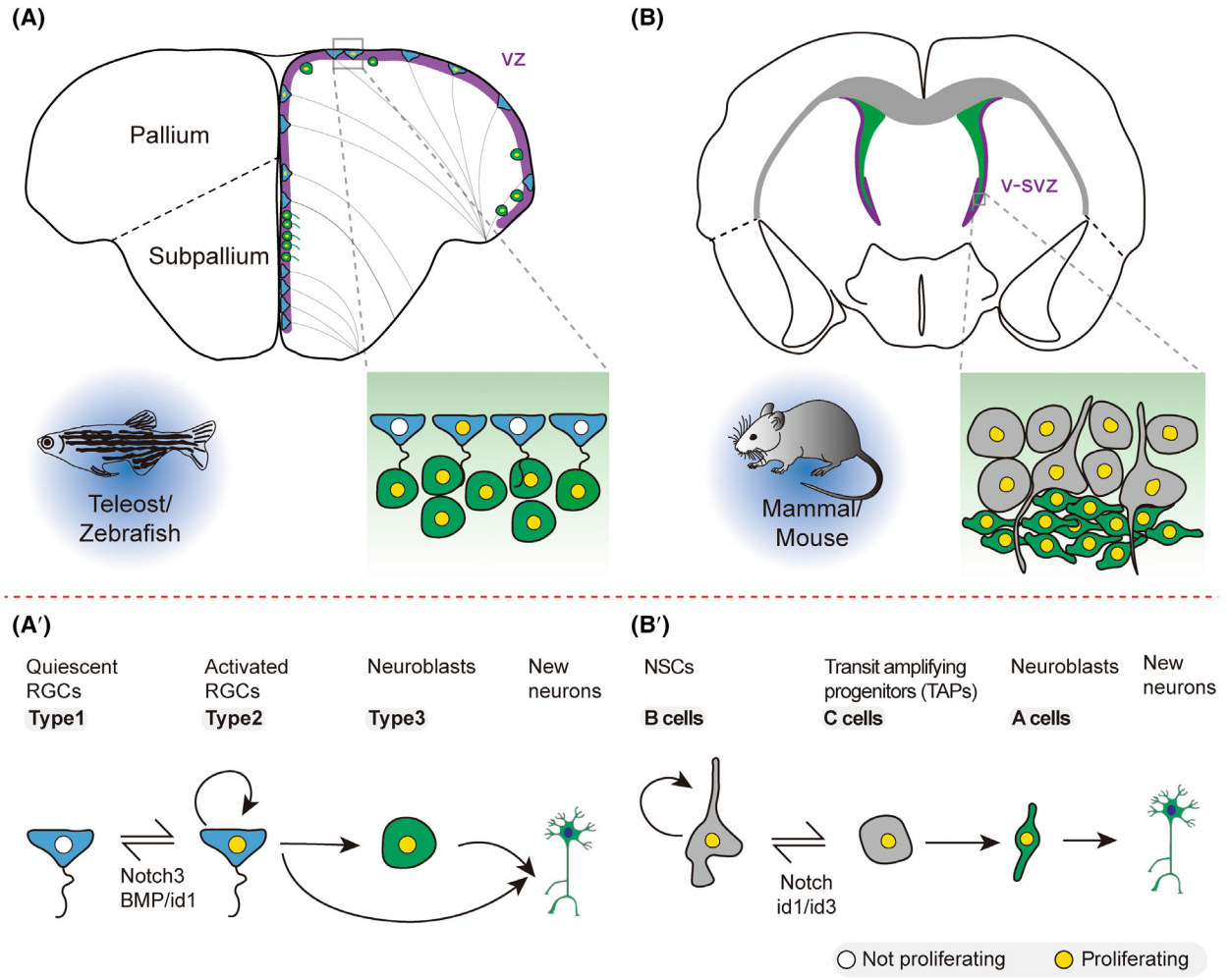

Fig. 1. Schematic representation of adult neurogenesis: A comparison of the neural stem cell niche in the telencephalic ventricular zone of zebrafish and mouse. (A) Transverse section through the telencephalon of an adult zebrafish illustrating the different cell types within this niche. (A′) This panel depicts the differentiation of radial glial cells (RGCs) into neurons and some signaling pathways controlling the activity of RGCs. In zebrafish, quiescent RGCs (type 1) are activated to become proliferative RGCs (type 2), which can generate proliferative neuroblasts (type 3), eventually differentiating into mature neurons. (B) Transverse section through the telencephalon of an adult mouse. (B′) This panel represents the various steps of neural generation starting from slow-dividing neural stem cells (NSCs) referred to as B cells. The B cells give rise to C cells, corresponding to highly proliferative progenitors also called transient amplifying progenitors (TAPs). The C cells differentiate into neuroblasts (A cells) that subsequently mature into neurons. Note that in the ventricular zone (VZ) of zebrafish telencephalon, RGCs correspond to NSCs. Also, the neurogenic niches are highlighted in red in mammals (ventricular-subventricular zone, V-SVZ) and zebrafish (VZ). Note that in mouse, the NSCs are astrocytes, while in zebrafish, the NSCs are RGCs. Although these two glial cell populations have different anatomies, they share very similar functions and genetic markers in the ventricular zone of the telencephalon.

markers, with certain "markers" being expressed by more than one cell type. Additionally, heterogeneity in the microglia population has also been observed in the zebrafish brain [33,40,45]. Therefore, in this review, we opt to refer to microglia/immune cells rather than specific markers for the sake of clarity and ease of comprehension, acknowledging the inherent challenges posed by the overlapping expression of markers and the observed heterogeneity within the microglia population in the zebrafish brain.

Upon injury, dying cells release endogenous molecules known as DAMPs (damage-associated molecular patterns) and various ILs (interleukins), which trigger the upregulation of pro-inflammatory cytokines and chemokines (Fig. 2). These molecules propagate the inflammatory response and facilitate the recruitment of microglia/immune cells (such as leukocytes, including neutrophils, macrophages, lymphocytes, and other white blood cells, Fig. 2) [21,48]. In adult zebrafish, the activation of these cells is swiftly observed within

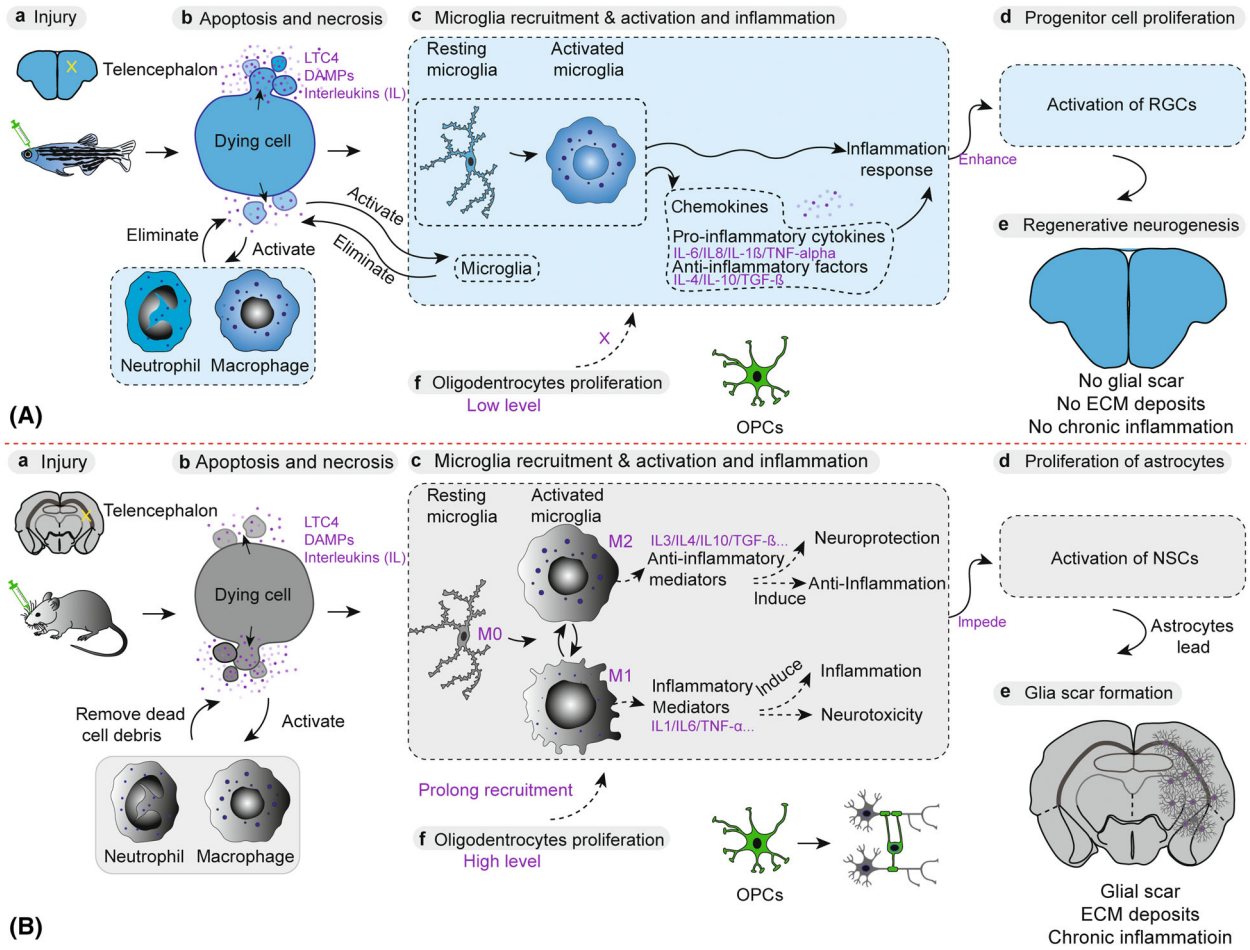

Fig. 2. Activation of cellular and molecular processes upon injury in the telencephalon of the zebrafish and mouse. In both zebrafish (A) and mouse (B), injury (Aa and Ba) leads to apoptosis and necrosis (Ab and Bb). As a consequence, inflammatory signals are activated, recruiting immune cells such as neutrophils, microglia, and macrophages to the injury site (Ac and Bc). In zebrafish, the activation of immune cells and inflammation is transient (Ac) and plays a positive role in activating RGCs (Ad), leading to neurogenesis without scar formation (Ae). However, in mouse, inflammation leads to astrocyte proliferation (Bd), and in most cases, astrocytes are involved in glial scar formation (Be). Additionally, extracellular matrix (ECM) deposition impedes neurogenesis and neurite plasticity, hindering successful regeneration, unlike in zebrafish. In both models, there is an observed increase in oligodendrocyte recruitment and/or proliferation (Af and Bf), but this recruitment/proliferation is much more pronounced in mice (Bf) than in zebrafish (Af). Note that direct experimental evidence about the recruitment of peripheral immune cells to the injury site of the adult zebrafish telencephalon are lacking, and the Fig. 2 data are based on speculation from data on larval stages.

Table 1. Key innate immune cells and their general markers in zebrafish telencephalon regeneration.

Cell types	Markers	References
Macrophages	*mpeg1.1*	[23,41]
	mfap4	[39]
Leukocytes	L-plastin	[8,22,46]
Microglia (resident macrophages)	L-plastin	[22]
	4C4	[23,40]
	mpeg1.1	[23,40]
	Apo-E	[9,47]

the first 2 h following injury in the lesioned hemisphere. Their recruitment through migratory and proliferative processes seems to peak between 2 and 3 days post-lesion (dpl) [22,23,33,49] (Fig. 2). However, the increase in the number of microglia and immune cells persists beyond 5 days in the injured hemisphere [8,9,22,23,33].

The recruitment of microglia and peripheral immune cells is correlated with the induction of pro-inflammatory genes such as *il-1β*, *il-8*, and *tumor*

Table 2. Signaling pathways and chemical factors regulating inflammation during the regenerative process of the adult zebrafish telencephalon.

Signals	Possible roles in regeneration	References
Natural signals		
Upregulation of pro-inflammatory cytokines after injury: Interleukins IL-1β, IL-6, IL-8, and TNF-α	The propagation of the inflammatory response is correlated with microglia activation (ameboid change) and proliferation. The direct role of these cytokines in RGCs proliferation is uncertain	[22]
Upregulation of specific receptor involved in inflammation: Cysteinyl leukotriene receptor 1 (cysltr1)	Overexpressed in the injured hemisphere, specifically in RGCs. The use of Pranlukast (an antagonist of Cysltr1) inhibits regenerative neurogenesis after injury. Cysteinyl leukotriene signaling plays a direct role in injury-induced neurogenesis	[22]
Oxidative stress	Increased after brain injury, notably in microglia. Possible roles include involvement in microglial repair processes, phagocytosis, cell survival, and indirectly, neurogenesis	[33,50]
Pharmacological agents		
Dexamethasone (anti-inflammation)	Inhibits recruitment of microglia/leukocytes and expression of pro-inflammatory cytokines	[22]
Clodronate liposomes (microglia/marcrophage depletion)	Decreases RGCs and/or aIPC proliferation and subsequent neurogenesis	[23]

necrosis factor-α (*tnf*-α) from 6 h post-lesion (hpl) to 24 hpl [22] (Fig. 2A, Table 2). In zebrafish, the use of anti-inflammatory drugs or depletion of microglia during brain injury results in a significant reduction in the gene expression of pro-inflammatory cytokines [22,23] (Table 2). It suggests that microglia/immune cells are a crucial component of injury-induced neuroinflammation and are probably an important source of these pro-inflammatory cytokines.

Concurrently with microglia activation, oxidative stress is observed in the brain parenchyma indicated by increased lipid peroxidation (LPO), overexpression of genes involved in oxidative stress such as *nox2*, *gsr*, and *nrf2a*, enhanced superoxide dismutase (SOD) activity, and decreased glutathione (GSH) level [33,50]. Similarly, the use of DCFH-DA (dichlorodihydrofluorescein diacetate) probes, which fluoresce when oxidized, demonstrated the generation of oxidative stress as early as 30 min after injury and its persistence at 5 days, particularly in *mpeg1.1*$^{+}$ microglia/immune cells [33].

Overall, these findings clearly demonstrate that following brain injury, peripheral, and resident immune cells are recruited to the injury site, and are involved in inflammatory processes and oxidative stress.

The role of inflammation and immune cells during telencephalic injury in zebrafish

In mammals, persistent inflammation significantly impedes regeneration processes upon CNS injury [51,52] (Fig. 2B), often resulting in incomplete regeneration and enduring functional impairments, depending on the size and location of the lesion. However, contrary to the prevailing understanding in mammals, where inflammation is perceived as a regeneration inhibitor, it was initially surprising to find that inflammation and the immune response observed after traumatic brain injury are indispensable for initiating the regenerative process in zebrafish [22,23] (Tables 2 and 3). Work by Kyritsis *et al.* [22] demonstrated that acute inflammation is essential to kickstart telencephalic repair. In their study, sterile inflammation induced by intracerebroventricular injection of Zymosan yeast particles led to the recruitment of L-plastin^{+} cells, their transition to an amoeboid morphology, and an increase in the expression of pro-inflammatory cytokine genes [22]. This upregulation of pro-inflammatory cytokines and of immune cells then triggers the proliferation of RGCs, leading to regenerative neurogenesis [22]. In addition, depleting microglia using clodronate liposomes or drugs such as PLX3397 after brain injury resulted in limited neuroinflammation and decreased regenerative neurogenesis [23,53] [D. Fernezelian and N. Diotel, In press]. Similarly, the use of mutant fish devoid of microglia (i.e., *irf8*−/− and *csf1r*^{DM}) impaired telencephalic regeneration in zebrafish [23]. These data clearly demonstrate the role of inflammation/immune cells in brain regeneration.

Reactive gliosis and scar formation, a double-edged sword in the control of neurogenesis during injury

Following any form of brain injury in mammals, such as stroke or head trauma, microglia and astrocytes undergo activation, a process known as reactive gliosis [57]. This process involves the proliferation, migration,

Table 3. Factors and cellular pathways controlling zebrafish telencephalon regeneration.

Factors	Cell types	Effects/Role	Signalings	References
Pro-inflammatory cytokines	Activated by microglia and likely within the ventricular niche	Increase number of RGCs and $Sox2^+$ cell proliferation	Stat3 signaling and Wnt/β-Catenin signaling	[23]
Pro-inflammatory cytokines	Microglia and probably other cells	Promotes RGC proliferation and subsequent neurogenesis	Cysteinyl leukotriene signaling	[22]
cxcr5	RGCs/Neurons	No impact on RGC proliferation but favors neurogenesis	Chemokine-mediated signaling pathway (Cxcl13/Cxcr5)	[54]
gata3	RGCs/Neurons	Required for proliferation of RGCs, reactive neurogenesis and migration of newborn neuroblast	Fgf/Fgfr1 pathway	[46]
Notch	RGCs and possibly neuroblasts	Involved in neural stem/progenitor cell proliferation during injury and the migration of newly generated neuroblasts to the injury site	Notch/Delta pathway	[12]
id1	Mainly in quiescent RGCs	Maintain/promote the quiescent state of RGCs	BMP/Id1 pathway	[38,55,56]
Vegf	Neurons and microglia	Promote the recruitment of microglia after injury, indirectly facilitating ventricular proliferation of RGCs	Vegf/Vegfr	[53]
Oxidative stress	Microglia and probably other cells	Might impact cell survival, and neurogenesis	H_2O_2, peroxidation, reactive oxygen species	[33,50]

and morphological changes of microglia and astrocytes, which become amoeboid and hypertrophic respectively [58–60]. Furthermore, reactive gliosis is also well characterized by the upregulation of specific cellular markers such as Iba1 in microglia and glial fibrillary acidic protein (GFAP) in astrocytes. In mammals, microglia are activated within minutes after brain injury [61] and participate in tissue clearance by phagocytosis [58]. They are a key component of the post-injury inflammatory response that facilitates brain recovery [62,63]. However, unlike zebrafish, inflammation may persists over a prolonged chronic phase, exacerbating brain damage [64,65]. Indeed, during this chronic phase (weeks to months after the initial injury), microglial activation (pro-inflammatory M1) is associated with pathological inflammation, neurodegeneration, and impaired neuroplasticity [58,66,67]. At the same time, astrocytes are also activated rapidly after brain injury (within 1–2 days). They migrate and delineate the boundaries of infarcted or damaged regions. This physiological process is a key event in the formation of the glial scar around the injured area [68–71]. The process of glial scarring initially has a fundamentally beneficial effect: it restricts cerebral edema and cell death, promotes the restoration of the BBB, and curtails excessive neuroinflammation that might propagate to other brain regions [72–74]. However, concurrently, it triggers the synthesis of numerous extracellular matrix (ECM) proteins, including collagen IV, tenascin C, and chondroitin sulfate proteoglycans (CSPGs) [75–77]. These ECM proteins, especially CSPGs, are widely recognized for their ability to inhibit axonal growth and restrict the migration of newborn neurons [76,77]. Moreover, the increased number of glial cells during gliosis has an impact on glial neuron and glial cell interactions, leading to axonal degeneration and neuronal death [78]. Additionally, astrocytes secrete various cytokines or proteoglycans that promote neurotoxicity and inhibit axon regeneration, respectively [79–82]. Recently Wehner and colleagues have identified another mechanisms in rat and human that leads to inhibition of axon regeneration in addition to previously known and chracterized scar components such as myelin-associated factors, basal lamina components, and CSPGs [83]. Using a cross-species comparative approach with mass spectrometry-based quantitative proteomics at different time points after spinal cord injury in zebrafish and rats, Kolb *et al.* [83] found that successful spinal cord regeneration in zebrafish is due more to the absence of axon growth-limiting factors in the injured ECM than to the presence of specific regenerative factors. Their comparative dataset revealed several small leucine-rich proteoglycans (SLRPs) to be exclusively enriched at the injury site in rat spinal cords but not in zebrafish. Similarly, in

injured human CNS tissue, elevated and abundant SLRPs were observed, akin to the rat injured spinal cord. Consistent with the supposed inhibitory role of SLRPs in CNS regeneration, genetic induction of these factors in zebrafish led to regeneration failure. Additionally, further experiments demonstrated that SLRPs modify the physical properties of the ECM, adversely affecting axon regrowth and regeneration in the spinal cord of rodent but not in zebrafish, where SLRPs are absent.

In conclusion, after brain injury in mammals, reactive gliosis gives rise to a glial scar that delineates the damaged area, initially limiting neuronal cell death. However, it subsequently impedes the regeneration process by restricting axogenesis, neuronal migration, and the functional integration of new neurons [73], thereby shifting the healing process away from regeneration.

In zebrafish, reactive gliosis also occurs after brain injury, exhibiting features similar to microgliosis and astrogliosis in mammals. However, it is noteworthy that adult fish brains lack astrocytes but possess astroglia-related RGCs [84–86]. It has been suggested that RGCs could perform some of the functions of astrocytes found in mammalian brain [3,7–9,11,87–90]. After injury, the astroglia-related RGCs display increased levels of GFAP and Vimentin, hypertrophy of glial processes, and a higher proliferation rate, typical of reactive gliosis (Fig. 3). However, unlike mammals, the adult zebrafish brain does not show chronic inflammation or persistent scarring after injury [8,22]. The absence of glial scarring is particularly intriguing because it seems to correlate with the remarkable ability of zebrafish to fully regenerate their brain [11]. Supporting this notion, in medaka (*Oryzias latipes*), a persistent glial scar is observed 14 days after injury to the optic tectum, in contrast to the absence of such scarring in zebrafish at the same neuroanatomical injury site [91]. In both species, these stab wounds activate radial glia proliferation and new cell generation. However, the number of new neurons detected 7 days after injury in the medaka brain is substantially lower than in zebrafish [91]. These data demonstrate that medaka and mouse, which form a persistent glial scar structure, are unable to fully regenerate their brain, unlike zebrafish. The absence of glial scarring as observed in zebrafish appears to be crucial for the success of the regeneration process and the activation of neurogenic programs. Interestingly, inhibition of microglia during brain injury results in a persistent lesion without visible scarring and CSPG deposition [23]. These results raise the question of why medaka produce ECM components that inhibit regeneration, while zebrafish do not. One possible explanation, based on observations of zebrafish during heart regeneration, is that ECM factors contributing to scar formation may initially be deposited in zebrafish as well. However, these factors are later resolved, preventing scar formation, as observed in heart regeneration (Fig. 3A‴) [92].

Precise control of inflammation, astrogliosis, and neurogenesis is the key to a successful regeneration process

In the telencephalon of adult zebrafish, as mentioned earlier, inflammation is precisely controlled and only transiently activated during the regenerative process. Similarly, lesion-induced neurogenesis is tightly regulated in the telencephalic region of adult zebrafish. Studies have revealed that after injury, there is an initial phase of intense neurogenesis [8,9,12,22,35,46], followed by an increase in the expression of *id1* (*inhibitor of differentiation 1*), a member of HLH (helix loop helix) family of transcriptional regulator, in RGCs in the VZ, typically around 5 dpl [38,56]. This gene, a direct target of the bone morphogenetic protein (BMP) signaling pathway, is required to limit the proliferation of RGCs in order to limit excessive neurogenesis that could lead to a massive depletion in the number of NSCs [38,55]. Consistent with this finding, zebrafish mutants lacking the *id1* gene are unable to regenerate their brains properly after consecutive telencephalic lesions [55]. Furthermore, overexpression of the *id1* gene induces NSC quiescence, while knockdown of the *id1* gene using morpholinos increases the number of proliferating RGCs and promotes neurogenesis [56]. These gain- and loss-of-function studies highlight the importance of *id1* in maintaining the balance between dividing and quiescent NSCs by promoting RGCs quiescence [38,55,56]. It is interesting to note that in mouse, the *Bmp* and *Id* genes are also activated after injury, but their role seems to be modified, since they are involved in gliosis and the formation of glial scars. It has been reported that following traumatic brain injury and vascular rupture in mouse, fibrinogen coagulation factor is released in the subventricular zone (SVZ), where it activates BMP signaling and increases the expression of its direct downstream mediator, Id3 [93]. In contrast to zebrafish, BMP-induced Id3 upregulation in the SVZ promotes astrogenesis over neurogenesis by upregulating the expression of astrocyte-specific genes such as GFAP and glutamate aspartate transporter (GLAST) [94]. Thus, the combined activity of acute inflammation and signaling pathways such as BMP and their downstream target genes in zebrafish are

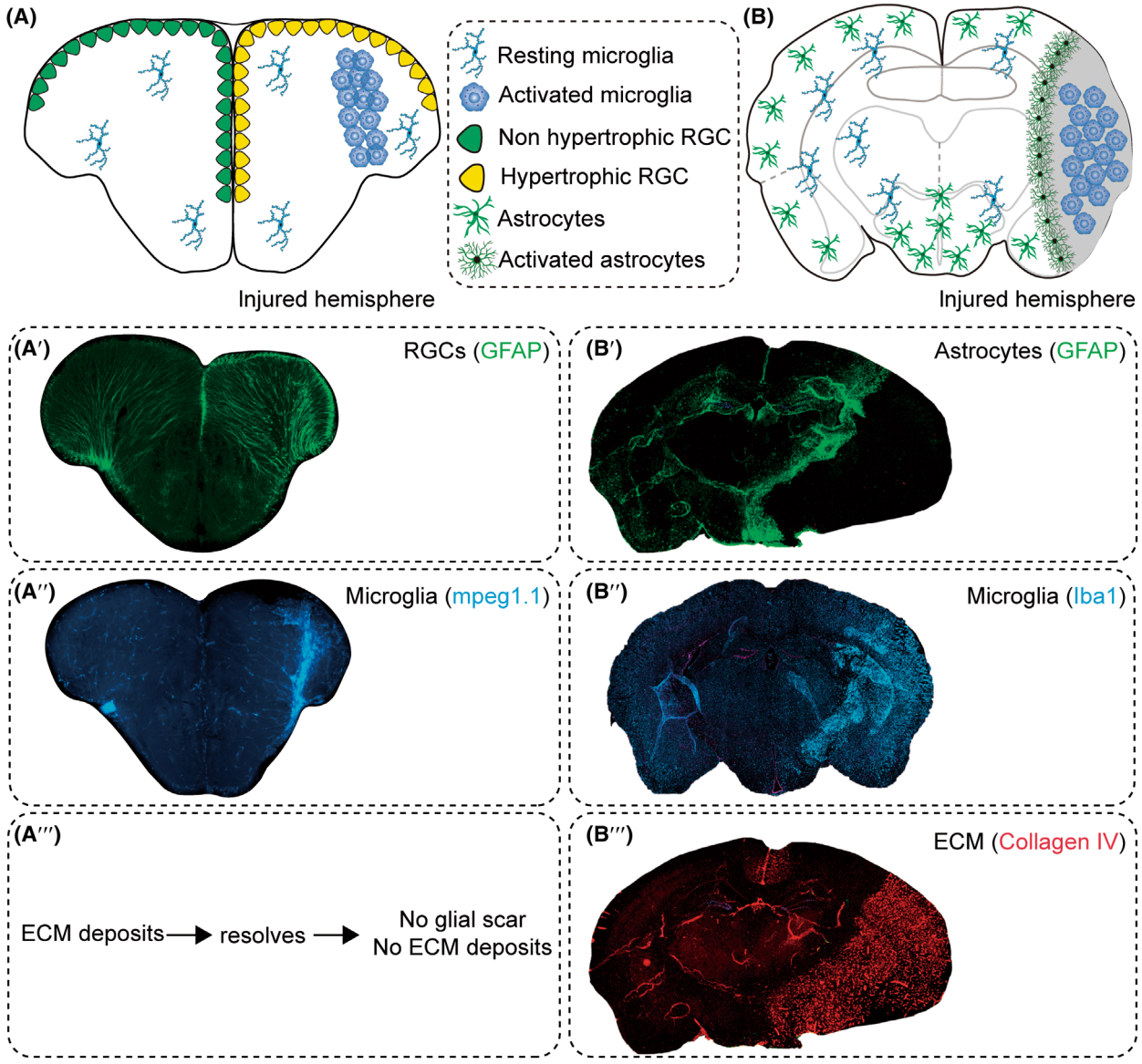

Fig. 3. Comparison of reactive gliosis and scar formation in zebrafish and mouse. In zebrafish, injury leads to gliosis and activation of microglia (A–A″). GFAP is overexpressed in neural stem cells in zebrafish (A′), while in mammals, such overexpression occurs in astrocytes (B′). In both species, microglia (mpeg1.1 in zebrafish and Iba1 in mammals) are recruited within and around the damaged area (A″ and B″). Extracellular matrix (ECM) proteins, such as collagen IV, Tenascin, and CSPGs, are detected in the damaged tissue of mammals but not in zebrafish. Initially, there is deposition of ECM in zebrafish, but this resolves over time, resulting in no ECM deposits and no scar formation at the end (A‴). In mice, inflammation and gliosis coincide with ECM deposition (B–B‴), resulting in scar formation, which subsequently impedes regenerative neurogenesis. Note that immunostainings were performed in the DéTROI laboratories (N. Diotel, unpublished data).

among the mechanisms that positively control regenerative neurogenesis in the zebrafish telencephalon and facilitate a successful regeneration process.

Future lines of research

Similar to observations in zebrafish, studies in mouse have shown that brain damage can trigger NSCs proliferation in key neurogenic areas such as the SVZ and the dentate gyrus (DG) [95–101]. However, despite this proliferative response, the survival and integration of the newborn neurons remain limited within the existing neural circuitry of the mouse brain. This limitation is primarily due to challenges in their migration to the damaged area, attributed to the dense presence of astrocytes and the repulsive properties of ECM.

Given this evidence and previous findings, it seems sensible to suggest that strategies aimed at controlling inflammation, enhancing neurogenesis, addressing fibrosis, and improving the survival of neuroblasts could be beneficial. Specifically, inhibiting the expression of certain ECM factors such as CSPGs and SLRPs, which are produced as a consequence of injury and can negatively influence regeneration, could be crucial. Inspired by the remarkable brain regeneration observed in zebrafish, these strategies hold promise for developing drugs or approaches that could facilitate effective regeneration in rodents and other mammals. These advancements would not only enhance brain plasticity but also foster the formation of new connections among surviving neurons following brain injuries such as stroke or traumatic brain injury. Moreover, such strategies might support the seamless integration of newly generated neurons, potentially paving the way for successful brain regeneration in mammals.

Acknowledgements

The research in Sepand Rastegar laboratory is supported by the Helmholtz Association BioInterfaces in Technology and Medicine and Natural, Artificial, and Cognitive Information Processing (NACIP) Programs and by project grants of the German Research Foundation (the Deutsche Forschungsgemeinschaft), RA 3469/5-1. JC is supported by a fellowship from the China Scholarship Council (CSC), Grant Number: 202106310017. This work was supported by European Regional Development Funds (FEDER) RE0022527 ZEBRATOX (EU-Région Réunion-French State national counterpart. We thank Julien Clain and Danielle Fernezelian for sharing immunostaining pictures on zebrafish and mouse telencephalon. We also gratefully acknowledge the support of the KIT Publication Fund at the Karlsruhe Institute of Technology. Open Access funding was made possible and organized by Projekt DEAL.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

JC, HS-I, ND, and SR wrote the review. SR and ND conceived the idea for this review manuscript and coordinated its preparation and writing. All authors contributed to the article and approved the submitted version.

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