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Regeneration of the central nervous system-principles from brain regeneration in adult zebrafish

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Abstract

Poor recovery of neuronal functions is one of the most common healthcare challenges for patients with different types of brain injuries and/or neurodegenerative diseases. Therapeutic interventions face two major challenges: (1) How to generate neurons *de novo* to replenish the neuronal loss caused by injuries or neurodegeneration (restorative neurogenesis) and (2) How to prevent or limit the secondary tissue damage caused by long-term accumulation of glial cells, including microglia, at injury site (glial scar). In contrast to mammals, zebrafish have extensive regenerative capacity in numerous vital organs, including the brain, thus making them a valuable model to improve the existing therapeutic approaches for human brain repair. In response to injuries to the central nervous system (CNS), zebrafish have developed specific mechanisms to promote the recovery of the lost tissue architecture and functionality of the damaged CNS. These mechanisms include the activation of a restorative neurogenic program in a specific set of glial cells (ependymoglia) and the resolution of both the glial scar and inflammation, thus enabling proper neuronal specification and survival. In this review, we discuss the cellular and molecular mechanisms underlying the regenerative ability in the adult zebrafish brain and conclude with the potential applicability of these mechanisms in repair of the mammalian CNS.

Key words: Zebrafish; Central nervous system; Brain injury; Glial scar; Regeneration; Restorative neurogenesis; Neural stem cells; Inflammation

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Core tip: Poor recovery of neuronal functions is one of the most common healthcare challenges for patients with different types of brain injuries. In contrast to mammals, zebrafish have developed specific mechanisms to activate a restorative neurogenic program in a specific set of glial cells (ependymoglia) and to resolve both the glial scar and inflammation, thus enabling proper neuronal specification and survival. In this

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review, we discuss these mechanisms and their potential applicability for the repair of the mammalian central nervous system.

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INTRODUCTION

In contrast to mammals, zebrafish can efficiently regenerate and recover lost tissue architecture and the function of vital organs including the spinal cord, retina, fin, heart and brain (Figure 1). Because traumatic brain injuries and neurodegenerative diseases pose a great burden to society, new therapeutic interventions must be developed. One possible approach is comparison between non-regenerative models (such as mammals, largely represented by mouse models) and regenerative models (often zebrafish or axolotl) to identify similarities and differences at the cellular and molecular levels that could be exploited to achieve regeneration in the human brain. One striking difference between these two models is the presence of numerous constitutively active neurogenic niches in the zebrafish adult central nervous system (CNS)^[1-3]. This feature has long been speculated to be the driving force underlying the endogenous regeneration observed in the adult zebrafish brain^[1,2,4]. However, neurogenic niches are also found in the mammalian CNS, albeit in lower numbers, thus suggesting the existence of additional cellular and molecular distinctions between mammals and zebrafish. To address these differences, endogenous regeneration in different areas of the zebrafish CNS has been extensively studied by using various injury paradigms^[5-17]. Numerous programs actively involved in the activation of neuronal progenitors in response to injury and contributing to restorative neurogenesis have been identified^[6,9,12-14,16,18]. Of note, these programs can be subdivided into specific categories: (1) Developmental programs that are reactivated in response to injury and that regenerate brain structures by mimicking developmental functions; (2) Injury-specific programs that are exclusively active in the context of regeneration and (3) Programs that are also active during development but have distinct functions in the context of regeneration^[6,9,12-14,16,18]. In addition to different models activating the generation of new neurons, zebrafish can synchronize the addition of neurons with the resolution of both glial scar and inflammation, thereby achieving proper specification and long-term survival of new neurons^[8,12-14]. These features have not been observed in mammals, in which neurons generated in response to injury do not survive, owing to the persistence of the glial scar. All these elements play a synergistic role in the endogenous regeneration of the adult zebrafish CNS. Therefore, we will focus on their comprehensive description after providing an introductory characterization of the cellular environment in different brain areas of the adult zebrafish brain under physiological conditions and the injury paradigms used to study regenerative responses in zebrafish.

Introduction and comparison of progenitor lineages in adult zebrafish and mouse brains

Similarly to the mammalian brain, the zebrafish brain contains several progenitor cell-types that generate distinct lineages. The most prominent feature of the adult zebrafish brain, in contrast to the mammalian brain, is the enrichment of neuronal progenitors within different neurogenic niches. These neuronal progenitors maintain a life-long capacity to produce new neurons^[1-3,19-22], although this feature decreases with age^[23], similarly to the mammalian adult neuronal progenitors^[24]. Interestingly, glial progenitors are present in both zebrafish and mammalian brains with similar abundance and cellular characteristics^[25-27]. These progenitors are scattered throughout the brain parenchyma and either self-renew or generate mature oligodendrocytes^[25].

Neurogenic niches and neuronal progenitor cells

The adult zebrafish brain contains various niches with proliferating progenitors, many of which can generate new neurons (neurogenic progenitors)^[1-3,19-22]. One of the best studied and characterized regions in the adult zebrafish brain is the telencephalon. This brain area contains a neurogenic niche lining in the ventricular

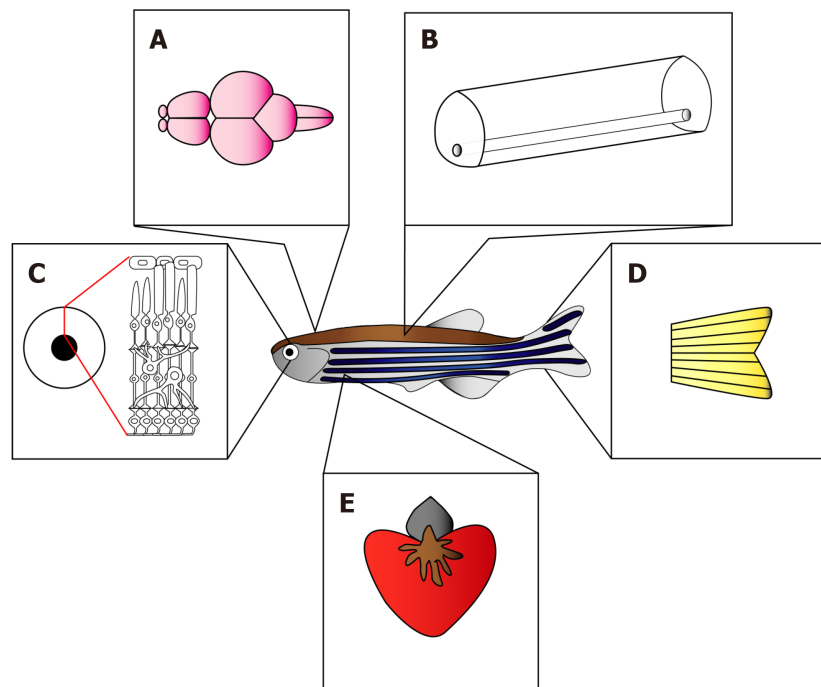


Figure 1 Regenerating organs in adult zebrafish. In contrast to mammals, adult zebrafish are able to efficiently regenerate the lost tissue architecture and retrieve the functions of brain (A), spinal cord (B), retina (C), fin (D) and heart (E).

zone (VZ), which is located at the outer brain surface, owing to the everted nature of this specific brain region (Figure 2A)^[28]. New-born neurons are deposited immediately below the proliferative zone, in the so-called periventricular zone^[19,20]. Progenitors residing in the VZ have a radial morphology similar to that of the mammalian neural stem cells (radial glia cells, RGCs) present during brain development. Their bodies are located at the ventricular surface, and their processes span throughout the parenchyma of the adult zebrafish telencephalon^[29]. Moreover, these cells are the functional orthologs of mammalian ependymal cells; therefore, we will refer to them as ependymoglia. Importantly, only a proportion of these cells generate neurons under physiological conditions, whereas most remain quiescent, a common feature shared by classical ependymal cells^[7,30,31]. However, numerous experimental manipulations such as changes in Notch signaling^[30] or injuries induce cell-cycle re-entry in many ependymoglia cells and/or generation of new neurons^[6-8,11-14,16,32,33]. Although almost all ependymoglia cells in the adult zebrafish telencephalon can generate neurons, there are at least two distinct neurogenic zones where ependymoglia cells are located: The dorsal and the medio-ventral neurogenic niches (Figure 2). These two zones differ in the proliferation rates of ependymoglia cells and their progenies, the size of the progenies that they produce and the type of newly generated neurons^[19,20,29,34]. As previously mentioned, under physiological conditions, only a small proportion of ependymoglia in the dorsal neurogenic niche are actively proliferating, whereas the majority remain quiescent^[7,30,31]. Ependymoglia cells express different markers including glial fibrillary acidic protein (Gfap), S100 calcium-binding protein B (S100 β), Nestin, brain lipid-binding protein (Blbp) and SRY-box 2 (Sox2)^[14,19,29,34-37], and can be further subdivided into non-dividing (type I) and dividing (type II) cells^[34]. According to previously developed live-imaging techniques, not only the proliferative state of ependymoglia but also the mode of division differs^[7,38]. Ependymoglia cells rarely divide symmetrically, thus giving rise to two new ependymoglia cells and thereby expanding the pool of adult neural stem cells (aNSCs). The largest fraction of activated ependymoglia cells divide asymmetrically, thus maintaining the stem cell pool and generating neuronal progeny^[7,38]. Moreover, a substantial proportion of ependymoglia lose their aNSC hallmarks and upregulate the neuronal marker HuC/D, thus suggesting that direct conversion of ependymoglia into neurons substantially contributes to the constitutive neurogenesis at the expense of the stem cell pool^[7]. Both direct conversion and generation of new neurons via intermediate progenitors in the dorsal neurogenic niche of the adult zebrafish telencephalon result in small neuronal clones (fewer than four cells)^[7,31]. In contrast to the low proliferation rate and small neuronal output of ependymoglia in the dorsal neurogenic niche, medio-ventral ependymoglia cells proliferate at higher rates and

produce larger neuronal progenies^[34]. Some progeny have migratory capacities and, similarly to those in the mammalian brain, migrate to the olfactory bulb through the rostral-migratory stream, whereas a proportion generate new neurons that are deposited periventricularly^[19]. Because live-imaging and clonal analysis techniques in the medial-ventral neurogenic niche are lacking, it remains to be investigated whether the same cell has the capacity to generate neurons fated to populate both the olfactory bulb and the periventricular zone. Therefore, new genomic approaches must be used to identify the transcriptomes of single ependymogial cells and address the existence of different sub-populations, identify specific markers to prospectively isolate these populations and subsequently decipher specific molecular pathways involved in region-specific generation of new neurons in the adult brain. The first steps toward the dissection of distinct molecular features of different progenitor cell types have enabled the identification of a population of Nestin-positive progenitor cells in the ventral nucleus of the ventral telencephalon, which weakly express canonical radial glial markers, display a typical neuroepithelial-like morphology and proliferate primarily with a short cell cycle duration (Figure 2B)^[29,34,39]. Proliferating oligodendrocyte transcription factor 2-positive (Olig2⁺) cells that are negative for typical oligodendrocyte markers, such as the SRY-related HMG-box 10 (Sox10) and myelin basic protein (Mbp), but are positive for polysialylated-neural cell adhesion molecule have also been found in the rostral migratory stream of the zebrafish telencephalon, together with a small population of Olig2-expressing cells positive for S100 β and displaying a typical radial glia-like morphology^[25]. However, the functions of these cells remain to be addressed.

Although the neurogenic niches and the mechanisms controlling neurogenesis in the adult zebrafish telencephalon are the most studied and best characterized, neurogenic niches are also present in other regions of the adult zebrafish brain, and they have specific features^[1,2,20-22,40]. Hence, differences and similarities between neurogenic niches of different brain areas should be considered with regard to region-specific restorative neurogenesis. In the optic tectum and cerebellum, for instance, aNSCs do not express typical glial markers and display a neuroepithelial-like phenotype. Radial glia-like cells exist, but in lower numbers, and are quiescent^[20,21,40-42]. In the junction between the mid- and hindbrain, hairy-related 5-positive cells exhibit some of the typical aNSC characteristics, including a slow cell cycle, self-renewal, and expression of Gfap, Blbp and Sox2, and they have the capacity to differentiate into neurons^[22].

Glial cell composition of the zebrafish brain parenchyma

Proliferation does not occur only in the dorsal and medio-ventral neurogenic niches, because proliferating cells are also found throughout the parenchyma of the adult zebrafish telencephalon, where oligodendroglial and microglial cells reside (Figure 2)^[25]. Cells belonging to the oligodendrocyte lineage express Olig2 and Sox10^[43]. In the adult mammalian cerebral cortex, oligodendrocyte progenitors generate primarily neuron-glia antigen 2-positive glia, maintaining them in constant numbers throughout life^[27], and to a lesser extent mature oligodendrocytes^[26]. Olig2 and Sox10 lineage-marker positive-cells have also been identified in the parenchyma of the adult zebrafish telencephalon^[25]. Additionally, a small proportion of these cells have been found to be positive for Mbp, a marker of mature oligodendrocytes^[25]. Under physiological conditions, only a few oligodendroglial cells have been identified as actively proliferating oligodendroglial precursor cells, on the basis of co-staining with proliferating cell nuclear antigen and the incorporation of the DNA base analog bromodeoxyuridine^[25]. Other studies in the adult zebrafish brain, and specifically in the cerebellum, have demonstrated the existence of a small proportion of Olig2-expressing cells positive for Sox10, which are located in the granule cell layer close to Purkinje cells, whereas most Olig2-expressing cells in this specific brain region display neuronal identity and are positive for the neuronal marker HuC/D^[44]. Another important population that displays some grades of proliferation and is involved in the maintenance of homeostasis in the adult zebrafish brain consists of microglial cells, the resident phagocytes in the brain. Under normal conditions, microglial cells display a branched and elongated morphology^[45]. However, under pathological conditions, microglial cells show a modified structure, acquiring an amoeboid-like morphology. In the mouse brain, "resting" microglia are not inactive and constantly use their processes to scan the CNS environment^[46]. Numerous studies performed in both the mammalian and zebrafish CNS have demonstrated that in addition to their major task as CNS guardians, microglial cells play an important role in the regulation and pruning of synapses^[47-50], apoptotic cell clearance^[51,52] and CNS angiogenesis^[53,54]. Interestingly, microglial cells located in the telencephalon, optic tectum and cerebellum of the adult zebrafish morphologically resemble those present in the mature mammalian CNS, and a large fraction of the microglial signature is also

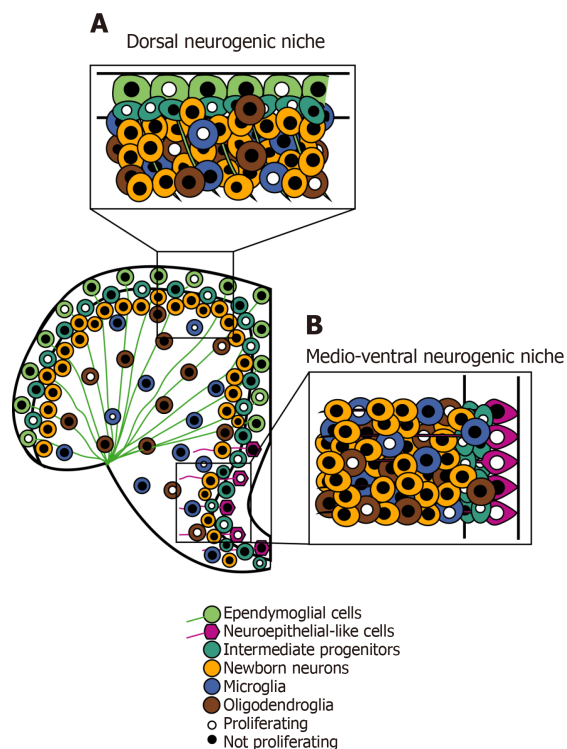


Figure 2 Schematic representation of the main cell types in the adult zebrafish telencephalon, with focus on two distinct neurogenic niches, the dorsal ventricular zone and the medio-ventricular zone. A: The dorsal ventricular zone hosts ependymoglia (light green), quiescent and slow-cycling adult neural stem cells, intermediate progenitor cells (light blue) and neurons (yellow); B: The medio-ventricular zone hosts neuroepithelial-like cells (magenta), characterized by faster cell cycle. Intermediate progenitor cells (light blue) are deposited in the subventricular layer and they can either differentiate into neurons (yellow) or migrate to the olfactory bulb. Microglial (blue) and oligodendroglial (brown) cells can be found in the subventricular zone and in the parenchyma of the adult zebrafish telencephalon.

conserved in zebrafish^[54,55]. Importantly, the adult zebrafish brain lacks the typical parenchymal, protoplasmic astrocytes, an abundant cell type that is present in the mammalian brain and has important functions under physiological conditions and after different types of injury or neurodegenerative diseases^[56]. Moreover, questions remain regarding which cell type takes over the function of protoplasmic astrocytes and whether their absence offers any beneficial effect toward successful brain regeneration.

Paradigms to study neurodegeneration and regeneration in the adult zebrafish brain

Zebrafish are a suitable animal model to reproduce typical phenotypes of neurodegenerative diseases or injuries affecting the CNS in humans (Figure 3)^[14,16,57-59]. However, these models very often replicate only a subset of phenotypes observed in degenerating or injured human brains, thus allowing useful but still restricted analysis of the regenerative responses. Therefore, understanding the limitations and specific features of each model system is crucial to allow proper cross-model comparison and to appreciate the applicability of these models to advance regenerative therapies in humans. Below, we summarize and compare most of the models used for brain regeneration studies in zebrafish.

To generate models for neurodegenerative diseases, methods have been largely based on alteration of specific gene expression, including transient downregulation by morpholinos^[60], targeted gene disruption through use of zinc finger nucleases^[61], transcription activator-like effector nucleases^[62] or clustered regularly interspaced short palindromic repeats^[63]. Most of the neurodegenerative models have been established in embryos or juvenile zebrafish. Indeed, these models have been valuable tools for understanding the etiology and the progression of specific diseases. Nonetheless, the programs activated at these stages are reminiscent of the endogenous programs active during development^[64], a characteristic that has also been observed in the postnatal mammalian brain^[65]. However, the mechanisms leading to endogenous regeneration in the adult zebrafish brain with signs of

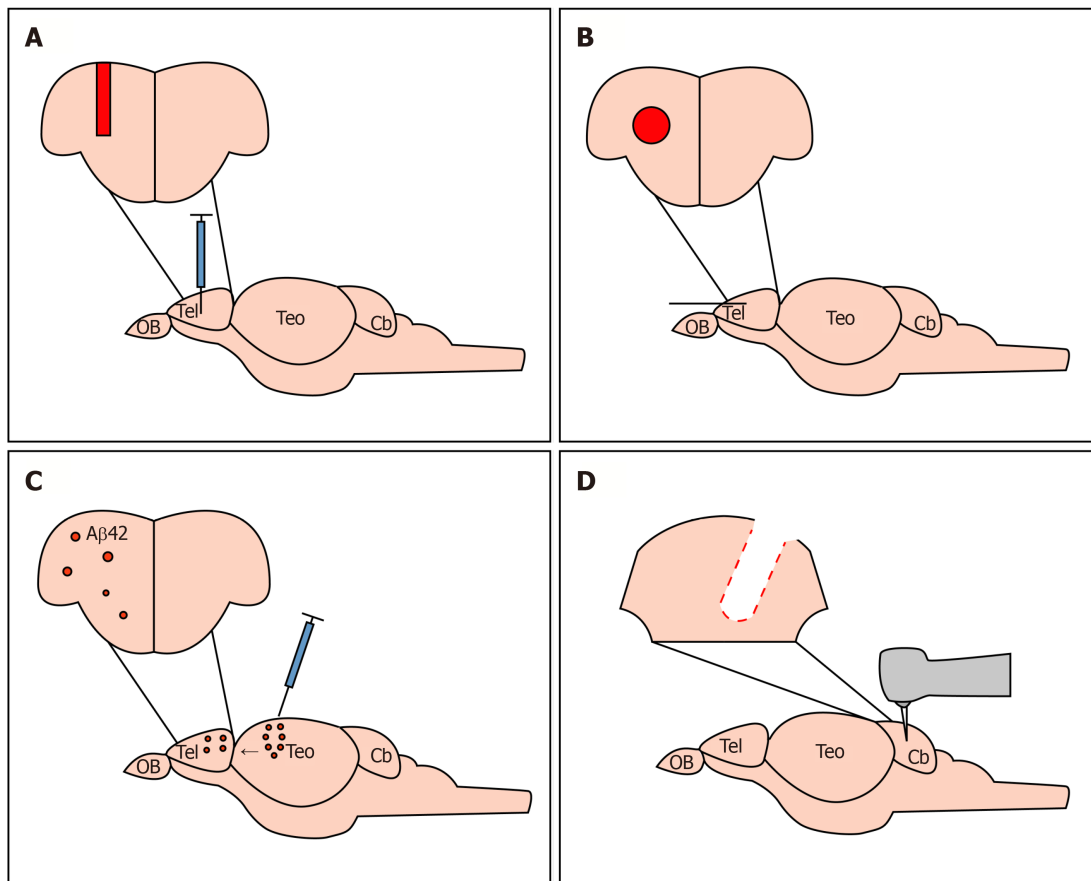


Figure 3 Established paradigms to study cellular and molecular mechanisms of regeneration in the telencephalon and cerebellum of adult zebrafish. A: Mechanical injury to lesion the adult zebrafish telencephalon, damaging the ventricular zone containing neural stem cells; B: Mechanical injury to lesion the adult zebrafish telencephalon, sparing the ventricular zone containing neural stem cells; C: Cerebroventricular microinjections of Aβ42 derivatives to study neurodegeneration in the adult zebrafish telencephalon; D: Mechanical injury of the adult zebrafish cerebellum.

neurodegenerative conditions such as Morbus Parkinson or Alzheimer's diseases still remain elusive. To address this question, a model for neurodegeneration in the adult zebrafish brain has been generated through cerebroventricular microinjection of Aβ42-derivates (Figure 3D)^[57]. Injection of Aβ42-derivates in the adult zebrafish brain, causing Alzheimer's disease-like phenotypes (apoptosis, microgliosis and neuronal loss), promotes activation of ependymoglia and enhances neurogenesis, typical responses observed during zebrafish brain regeneration in models of mechanical injuries^[6-8,11-14,16,32,33]. In this neurodegenerative model, the presence of Aβ42-derivates leads to interleukin 4 (IL4) upregulation in neurons and microglial cells. IL4 subsequently acts via signal transducer and activator of transcription 6 (Stat6) phosphorylation through the IL4 receptor present in aNSCs, thus leading to their activation^[57].

In addition to the development of neurodegenerative models, first attempts to model chronic brain injuries, such as small brain vessel diseases, have been achieved^[66]. To study the processes activated in response to rupture of microvessels and consequent microbleeds, a model of injury of blood vessel endothelial cells has been established by using a multi-photon laser^[67]. This injury model may be promising if optimized for the adult zebrafish brain, because it has been shown to recapitulate both cerebral hemorrhage and microbleeds^[67].

For traumatic brain injuries, numerous paradigms have been established to induce acute damage in different areas of the adult zebrafish CNS, to study the cellular and molecular mechanisms leading to endogenous regeneration^[5-17]. In particular, these mechanisms have been extensively analyzed in the context of regeneration in the adult zebrafish telencephalon. A wide range of injury paradigms, damaging different telencephalic structures, have been established and characterized (Figure 3)^[6-8,11-14,16,32,33]. In the current review, we refer to two different telencephalic injuries. In the first case, stab wound injury is performed through the skull into the medial region of the telencephalon. Owing to the everted structure of the adult zebrafish telencephalon, this injury damages the dorsal part of the VZ, containing

ependymoglia cells with stem cell properties, and the brain parenchyma, containing largely postmitotic neurons and glial progenitors (Figure 3A)^[11,12,32,33]. In the second case, the stab wound injury is performed through the zebrafish nostrils. This injury exclusively damages the parenchyma of the telencephalon, leaving the ependymoglia layer intact (Figure 3B)^[7,9,13,14,16]. The common features shared by these two different injury models are the activation of restorative programs in ependymoglia cells and the generation of new neurons. Therefore, the understanding of injury-mediated activation of cells with stem cell capacity in different injury models is also key to experimentally eliciting regeneration in species lacking endogenous restorative capacity. Moreover, because zebrafish have different cells with stem cell capacity spread throughout the adult brain^[19-21,29,34,42], one additional approach may be the comparison of regeneration in different brain areas in response to mechanical injuries. Indeed, some of these brain regions, including the optic tectum and cerebellum, have been analyzed to different extents in the context of regeneration. The optic tectum contains ependymoglia, but in the intact brain they have only transient and limited neurogenic capacity^[42,68]. However, in response to injury, ependymoglia cells enter cell cycle and generate new neurons engaged in regeneration^[69,70].

Similarly, numerous studies have focused on the identification of relevant programs involved in cerebellar wound healing and regeneration, with a special focus on cross-talk among apoptosis, inflammation, immune response, the cell cycle and cell adhesion (Figure 3C)^[15,17,71-73]. Interestingly, a recent study on regeneration in the adult zebrafish cerebellum has shed light on its limited restorative capacity to only specific cell lineages, in contrast to observations in the adult zebrafish telencephalon and optic tectum^[15].

Moreover, cerebellar regeneration is mainly supported by neuroepithelial-like cells, whereas RGCs (possibly sharing some hallmarks with telencephalic ependymoglia) appear to play a minor role^[15]. These results are in agreement with the observation that the RG cell pool is either quiescent or exhausted in the adult zebrafish cerebellum and that in response to injury, cell types derived from RGCs are not regenerated^[15]. These findings highlight the importance of dedifferentiation and reactivation of glial cells in response to injury and their capacity to reacquire neuronal stem cell characteristics, a feature achieved in mammals only *in vitro*^[74].

Beyond mechanical injuries, chemical compounds have been used to target specific or generic cell types in the adult zebrafish brain^[75-78] and subsequently study the restorative responses. Quinolinic acid-induced neurotoxicity in the adult zebrafish telencephalon promotes ependymoglia proliferation and activates neurogenic programs, thus enabling the long-distance generation and integration of new-born neurons^[77]. Paraquat intoxication results in altered redox levels and mitochondrial activity, thus partially mimicking the phenotypes of Parkinson's disease^[76]. Administration of cadmium chloride can induce brain damage because of its cytotoxic activity on glial cells^[75], and subchronic exposure to titanium (TiO₂) nanoparticles can induce neurotoxicity^[78]. Because these different injury models do not rely on mechanical injury and elicit rather limited inflammatory responses but still promote the activation of neurogenic programs, the analysis of these models may be relevant to identify core mechanisms of regeneration in the adult zebrafish CNS to experimentally activate them in the mammalian CNS.

Cellular and molecular mechanisms involved in regeneration and restorative neurogenesis in the adult zebrafish telencephalon

A fundamental feature of telencephalic injuries in the adult zebrafish is the capacity to restore the tissue architecture of the brain parenchyma, including the addition of new neurons. New neurons generated in response to injury (restorative neurogenesis) are positioned deep in the parenchyma (Figure 4D)^[7,14], an area that does not accommodate new neurons under physiological conditions^[19,20,31]. In fact, when neurons are generated in the intact telencephalon (constitutive neurogenesis), they are deposited in the layer underlying the VZ or in the olfactory bulb^[19,20,31]. Importantly, ependymoglia cells can generate neurons that contribute to both constitutive and restorative neurogenesis but may possibly rely on different cellular and molecular mechanisms^[4]. Importantly, endogenous neurogenesis supported by ependymoglia cells is not an absolute pre-requisite for successful regeneration. In fact, under physiological conditions, ependymoglia in the optic tectum are mostly quiescent. However, in response to injury, they become activated, generate new neurons and thus support the regeneration of this brain area. Specifically, the Wnt signaling pathway is activated in ependymoglia cells in response to injury and is a key regulator of ependymoglia proliferation and differentiation into neurons^[69]. A follow-up study has identified additional molecular pathways important for optic tectum regeneration. Sonic hedgehog is increased in ependymoglia in response to injury, and its activation increases the number of proliferating ependymoglia cells, thereby

limiting their differentiation into neurons. Notch activity is also regulated, and its levels are decreased after injury, thus inducing the same phenotype in ependymoglia cells as that observed with Sonic hedgehog^[70]. These results suggest that tight regulation of ependymoglia proliferation and differentiation is necessary to promote restorative neurogenesis in the adult zebrafish brain.

Although different injury paradigms vary in localization within the telencephalon and injury size, common cellular events in response to injury can be generalized (Figure 4). The first event occurring in response to traumatic brain injury is cell death, which is quickly followed by activation of an inflammatory response characterized by microglial cells' morphological modification and accumulation, together with leukocytes, at the injury site^[9,13,14,45]. The mobilization of microglial cells toward the injury site is controlled by long-range Ca²⁺ waves activating ATP signaling-dependent chemotaxis, through the purinergic P2Y12 receptor (Figure 4B)^[79,80]. Moreover, $\alpha 1$ receptors are responsible for "switching off" activated microglia, thus allowing these cells to abandon the injury site^[81]. Indeed, the inflammatory response is quickly resolved in the adult zebrafish telencephalon^[9,13]. The immune cell response is followed by increased proliferation of different cell types, both at the injury site (largely glial, Olig2-positive progenitors) and at the VZ (largely neuronal progenitors and ependymoglia) (Figure 4C)^[12-14,16]. Injuries in the adult zebrafish telencephalon not only increase proliferation of ependymoglia but also induce various injury-specific cellular behaviors. Continuous live-imaging of ependymoglia cells in the intact and injured zebrafish telencephalon has revealed symmetric non-gliogenic ependymoglia division in response to injury, a mode of division not previously observed in intact brains, which produces two intermediate neuronal progenitors and depletes the ependymoglia pool^[7]. Interestingly, this specific cellular behavior is complemented by direct conversion of ependymoglia to neurons, thus enlarging the neuronal output in regenerating brains. Importantly, direct conversion as a mode of neurogenesis is also present in the intact telencephalon^[7], thereby supporting the concept that successful regeneration in the adult zebrafish telencephalon depends both on mechanisms already present in uninjured conditions and on the activation of injury-specific pathways, including programs promoted by injury-induced inflammation^[6,8,9,11,39,82,83]. The proper coordination of these programs is key for successful regeneration in the adult zebrafish brain. Indeed, the aryl hydrocarbon receptor (AhR) has been identified as a key synchronizing pathway linking the direct conversion of ependymoglia to neurons with the inflammatory state in the brain parenchyma^[8]. AhR signaling is inactivated shortly after injury (period of high microglial activation) and subsequently promotes ependymoglia proliferation at the expense of neuronal differentiation (Figure 4E). This finding is also consistent with microglia-mediated activation of ependymoglia proliferation^[9]. Neuronal differentiation of ependymoglia through direct conversion is possible only when AhR signaling returns to basal levels (7 days after injury), coinciding with decreased microglial activation. Interestingly, interference with temporal regulation of AhR signaling after injury leads to aberrant restorative neurogenesis, because newly formed neurons fail to survive^[8]. In rodent models of stroke, ependymal cells have the potential to become activated and generate neuroblasts^[84,85]. In this case, however, a large proportion of neuroblasts do not survive, and no mature neurons are formed^[84,86]. These results lend strength to the concept that the activation of glial cells engaged in restorative neurogenesis by generating new neurons must be finely tuned and coordinated with the state of inflammation to enable proper neuronal survival and subsequent regeneration. After progenitor cells have been generated, they reuse developmental or constitutive neurogenic programs for neuronal differentiation. Prokineticin 2 (Prok2) and Sprouty-related EVH1 domain containing 2 (Spred2) are associated with migration and survival of neuronal progenitors to the injury site^[11,16,33]. Ectopic Prok2 expression has been observed in the zebrafish telencephalon in proximity to the injury site, and Prok2 has been proposed to first act as a chemoattractant to direct migration and later act as a neurotrophic factor^[16,33]. Similarly, young HuC/D-positive neurons use radial ependymoglia processes as a scaffold to migrate to their target sites in the injured brain^[33], as they do during development along the radial glia processes^[87]. These findings strengthen the hypothesis that the intrinsic capacity of regeneration in the adult zebrafish CNS may be supported by the ability to activate injury-specific programs and to enhance the restorative process by reactivating developmental programs and re-instructing the functions of genes normally present in the intact CNS. Therefore, we will further discuss the importance of these mechanisms in the context of regeneration.

Modifications of mechanisms present in the intact brain contributing to brain regeneration

The high correlation of restorative potential with the wide distribution of neurogenic

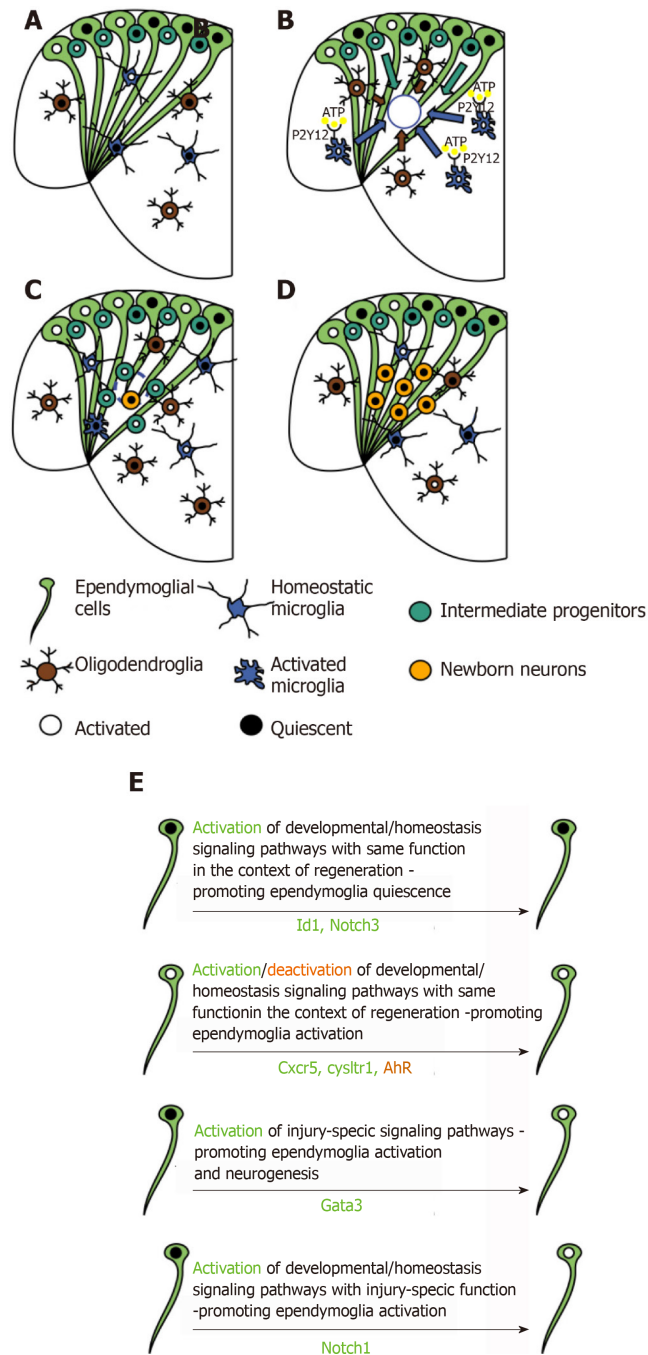


Figure 4 Glial cell reactivity and tissue restoration in the adult zebrafish telencephalon in response to stab wound injury. **A**: Representative scheme of cell composition in the intact telencephalon of adult zebrafish; **B-D**: Cellular response to mechanical injury in the adult zebrafish telencephalon; **B**: Injury-induced cell death stimulates the activation of inflammatory response. ATP is sensed by microglial cells (blue), through P2Y12 receptor, triggering their change in morphology and their migration, together with oligodendroglial precursor cells (OPCs, brown) at the injury site (blue circle); **C**: Microglial and oligodendroglial cell accumulation is resolved and intermediate progenitors (light blue), source of newly formed neurons (yellow), populate the injury site, where they start differentiating into neurons. Proliferation reaches its peak in the ventricular zone, where stem cells (ependymoglia cells, light green) reside. This cellular response seems to be required to increase the neuronal output and to re-populate the loss of progenitors in the subventricular zone, due to their migration to compensate the neuronal loss at the injury site; **D**: Regeneration is efficiently completed, stem cell activation returns to basal levels, surviving newborn neurons are found at the injury site and manage to survive, no signs of glial scar can be found; **E**: Scheme of genes specifically regulated in ependymoglia cells, relevant for their activation state and the promotion of restorative neurogenesis.

niches in the vertebrate brain supports the idea that at least some regulatory mechanisms that actively play a role in constitutive neurogenesis are re-used in the context of regeneration. Indeed, the Notch signaling regulates both constitutive and restorative neurogenesis. In the intact zebrafish brain, Notch signaling promotes ependymoglia quiescence^[30,88]. Importantly, two Notch receptors, Notch1 and Notch3,

are upregulated in the adult zebrafish telencephalon in response to injury (Figure 4E)^[6,11]. A correlation between Notch activation and neurogenesis has also been observed in the mouse brain^[84,89]. Striatal stroke decreases Notch signaling in ependymal cells, and Notch reduction promotes their differentiation along the neuronal lineage, without entry into the cell cycle^[84]. Forced activation of Notch1 in response to stroke prevents ependymal cell activation and the production of immature neurons. Moreover, Notch1 signaling is decreased in striatal astrocytes after stroke, thus promoting neurogenesis^[89]. In contrast, Notch1 activation after injury in the adult zebrafish telencephalon is instrumental for restorative neurogenesis, and its inhibition prevents the injury-induced proliferation of ependymoglia^[11]. These results suggest that Notch1 in zebrafish has an injury-specific function, promoting ependymoglia cell activation and proliferation, in contrast to its normal function under healthy conditions. Interestingly, blocking Notch3 upregulation after injury results in a significant increase in proliferating type II progenitors and a decrease in quiescent type I progenitors, thus suggesting that Notch3 signaling after injury has the same role as that observed in the intact brain: promoting ependymoglia cell quiescence^[6,30,88]. Similarly, inhibitor of DNA binding 1 (Id1) has been unexpectedly found to be upregulated in the injured zebrafish telencephalon (Figure 4E). Id1 is predominantly associated with quiescent progenitors (type I) and is expressed by only a small proportion of proliferating progenitors (type II)^[6,90]. The same pattern is maintained after injury, and increased numbers of Id1-positive cells as well as increased expression levels in individual cells promote their return to quiescence^[6]. The opposite regulation of the ependymoglia state in response to injury by Notch1 on one side and Notch3 and Id1 signaling pathways on the other side suggests an important concept for long term maintenance of restorative capacity that relies on the development of mechanisms that tightly regulate ependymoglia activation. These mechanisms are required to prevent stem cell pool depletion, possibly even by using the same ligands, as in Notch1 and Notch3 signaling. These results support the hypothesis that zebrafish CNS regeneration relies not only on re-activation of developmental programs but also on their modification by injury-specific signals.

Positive contribution of inflammation-related programs to restorative neurogenesis and tissue restoration

Inflammation has long been considered detrimental for neurogenesis^[91,92]. This concept has been challenged and revised to a model in which neurogenesis can be either promoted or impaired depending on the severity of the inflammatory stimulus and on the regenerative context^[93-99]. Moreover, inflammation, if tightly regulated, is a key element for regeneration in the context of different organs including the fin, heart and spinal cord^[100-106]. Indeed, the specific ablation of macrophages after adult zebrafish fin amputation affects wound healing, thus possibly impairing the proliferative capacity of the blastema^[103]. The same outcome has been obtained by treating adult zebrafish with dexamethasone, a drug that acts as an immunosuppressor reducing the activation of the inflammatory response. Interestingly, the restorative outgrowth of the caudal fin is significantly lower in treated animals than controls^[9]. These results confirm that inflammation is necessary to efficiently promote regeneration in many tissues, thus having a direct role in the regulation of numerous events, including cellular debris and fibrin clearance, angiogenesis and proliferation^[105-107]. Immunosuppression and decreased neuroinflammation also negatively affect restorative neurogenesis by decreasing ependymoglia cell proliferation and the generation of new-born neurons^[9,70]. In the adult zebrafish brain, various programs associated with inflammation and positive regulation of restorative neurogenesis have been identified. Among these, the chemokine receptor C-X-C chemokine receptor type 5 and cysteinyl leukotriene receptor 1 (Cysltr1) are upregulated in response to injury in the adult zebrafish telencephalon (Figure 4E)^[9,83]. Their active role in promoting ependymoglia proliferation and generation of new-born neurons, enhancing restorative neurogenesis in response to injury, has been convincingly assessed^[9,83]. Moreover, inflammation in the adult zebrafish regenerating brain not only regulates programs in the intact tissue but also promotes injury-specific programs, such as upregulation of GATA binding protein 3 (Gata3) (Figure 4E)^[82]. The zinc-finger transcription factor Gata3 is not expressed in either the embryonic or the intact adult zebrafish telencephalon^[82]. Gata3 upregulation in response to injury is required for neuronal regeneration, specifically promoting the proliferation of ependymoglia, neurogenesis and migration of new-born neurons^[9,82]. Interestingly, Gata3 is upregulated in the regenerating heart and fin, and its inhibition is sufficient to decrease regeneration^[82]. The effects of Gata3 on neurogenesis are strictly dependent on injury, because overexpression of Gata3 in uninjured conditions is not sufficient to increase neurogenesis^[9,82]. Additionally, injection of inflammatory molecules such as zymosan

A and leukotriene C4, a ligand for the Cys1r1, are sufficient to induce Gata3 expression^[82]. Together, these results suggest that tight temporal regulation of inflammation after injury is crucial for successful tissue restoration. This concept leads to key questions regarding the regulatory mechanisms defining the level of inflammation and the outcomes of restorative processes. In the zebrafish CNS, the initial acute inflammatory phase in response to injury is quickly resolved and is not followed by the prolonged activation typically observed in the mammalian brain^[9,13,108]. Different kinetics of resolution of the inflammatory response between zebrafish and mammals may be a key factor promoting regeneration in the adult zebrafish CNS. In fact, inflammation can chronically accumulate over time in some diffuse insults to the mammalian CNS and become chronically detrimental to brain regeneration^[109]. Moreover, zebrafish have also developed mechanisms to integrate neuroinflammation-induced programs with existing signaling governing neurogenesis in physiological conditions. For example, Gata3 expression after injury is dependent on the activity of the fibroblast growth factor (Fgf) signaling pathway, in both the regenerating brain and fin^[82]. Under physiological conditions in the adult zebrafish cerebellum and telencephalon, Fgf signaling is required for proliferation and homeostasis of aNSCs^[21,29]. In zebrafish larvae, similarly to the adult brain, the cerebellum can regenerate through repatterning of the anterior hindbrain, and this process is dependent on Fgf signaling^[110]. Moreover, Fgf signaling is involved in the regeneration of other zebrafish organs, including the spinal cord, fin and heart, where it promotes the formation of glial bridges, the recruitment of epicardial cells at the regenerating tissue, blastema formation and restorative outgrowth^[111-115]. These results convincingly show that regeneration relies not only on organ-specific programs but also on molecular mechanisms commonly activated in different tissues, thus strengthening the hypothesis that programs such as Fgf signaling, with important roles during development and adult brain homeostasis, may have a completely new function after they are integrated in the injury-induced context during regeneration. Interestingly, FGF is also increased in response to injury in the mouse brain^[116]. When blocked, neural progenitor/stem cell proliferation is significantly decreased, thus indicating that FGF has a crucial role in response to injury^[116]. However, despite FGF activation, the mouse CNS cannot regenerate, thereby highlighting the importance of synergistic activation of various programs, including the reactivation of developmental programs with distinct functions in the context of regeneration.

Similarly to models of traumatic brain injuries, a recent neurodegenerative model for Alzheimer's disease based on CMVI injection of A β 42 derivatives (see paragraph on experimental models) has enabled the discovery of another inflammation-induced pathway involved in aNSC plasticity and neurogenesis, IL4/Stat6 signaling^[57]. The accumulation of A β 42 in neurons leads to the activation of microglial cells/macrophages and the upregulation of IL4 in both neurons and microglial cells^[57]. The IL4 receptor is present in aNSCs, where IL4 promotes proliferation and neurogenesis via Stat6 phosphorylation^[57]. Interestingly, IL4 is not upregulated in response to mechanical injury, and A β 42 microinjection does not promote Gata3 upregulation^[57]. These results provide new insights into the association between aNSCs and immune cells and suggest that different mechanisms may be activated during regeneration in zebrafish, depending on the detrimental stimuli^[57]. These examples demonstrate that inflammation, if properly tuned, promotes organ regeneration and, in the specific context of the adult zebrafish brain, positively affects ependymoglia proliferation and restorative neurogenesis, inducing the activation of different programs necessary to elicit efficient tissue restoration. Therefore, a deeper knowledge of injury-induced neuroinflammation and its integration with signaling pathways operating under physiological conditions, and the comparison of these mechanisms in the context of different injury paradigms, appears to be necessary to open new avenues for the discovery of effective therapeutic approaches for both traumatic brain injuries and neurodegenerative diseases.

CONCLUSION

Traumatic brain injuries and neurodegenerative diseases in humans are major burdens for society that affect a large number of patients. The most immediate problems are the massive loss of neurons that cannot be replaced and the subsequent loss of vital neurological functions^[117,118]. Mouse models are indeed valuable tools to understand and characterize the cellular and molecular events following CNS injuries and diseases. However, similarly to humans, mouse models are characterized by poor regeneration and neuronal recovery in the CNS^[108,119]. For this reason, cross-comparison of non-regenerative species (mouse and human) with regenerative

species (zebrafish and axolotl) is important and may ideally deepen knowledge of the core mechanisms promoting endogenous regeneration in the adult zebrafish CNS. These core mechanisms may be prime targets to enhance regeneration in the mammalian CNS.

Zebrafish models appear to be valuable tools to complement the existing knowledge gained from studies in mammals, thus improving understanding of the limitations to CNS repair. However, like all animal models, zebrafish have limitations that should be considered for translational purposes. As already mentioned, most neurodegenerative and chronic injury models in zebrafish often only partially recapitulate the phenotypes observed in the human brain and are generally characterized in embryos or juvenile animals. For this reason, knowledge of disease progression and of programs activated to support regeneration during adulthood remains elusive. Another limitation, which in some cases can be a key feature coinciding with the better regenerative capacity observed in the adult zebrafish CNS, is the different cellular composition of the brain. A clear example is astrocytes, a glial population with important functions under physiological conditions in the mammalian brain that is also associated with the formation of the glial scar in response to injury^[120]. The glial scar is initially beneficial in limiting the injured tissue but is later detrimental, inducing a hostile environment for neuronal survival and integration^[120]. Astrocytes have not yet been identified in the adult zebrafish brain, and whether other cell types take over their functions remains unknown. This example suggests that other intrinsic differences between the mouse and zebrafish CNS might exist and should be identified to better characterize the cellular and molecular differences and similarities in the context of regeneration between regenerative and non-regenerative species. Finally, owing to the extensive genomic duplication in zebrafish, compensatory mechanisms may actually mask the real function of numerous genes that may be relevant for the regeneration of mammalian CNS^[121]. Nevertheless, gene duplication may also allow a higher degree of tuning of programs, thus promoting successful endogenous regeneration^[122]. Therefore, these mechanisms would be particularly interesting to study in the context of regeneration.

Despite their limitations, zebrafish models offer excellent and unique possibilities for studying neurogenesis and regeneration in the brain. The existence of various neurogenic niches enables the study of neurogenesis under physiological conditions in different brain areas in the same model^[3]. This comparison has enabled the identification of shared and unique cellular and molecular mechanisms promoting neurogenesis in different CNS areas that must be considered to better describe the role of restorative neurogenesis in CNS repair^[1-3,19-22]. Complementarily, numerous traumatic injury paradigms targeting different regions of the adult zebrafish CNS have been carefully characterized. From these comparisons, regeneration has been observed to be carried out by different cell types and molecular programs in specific brain areas^[5-17]. These results highlight the necessity to deeply understand the core mechanisms involved in the endogenous regeneration of the adult zebrafish brain, to target or introduce them in the mammalian CNS, with the aim of enhancing regeneration. Furthermore, because zebrafish do not display prolonged inflammation or persistence of glial scar at the injury site, they should be considered a valuable model for identifying key programs promoting the resolution of both inflammation and glial scar^[9,13]. Indeed, studies in the adult zebrafish brain have led to revision of the long-standing concept that inflammation is detrimental to CNS regeneration. This concept has now been challenged and replaced by a working model in which inflammation can be detrimental, if it persists chronically, but also beneficial at early phases by promoting the activation of restorative neurogenesis programs^[9]. Therefore, a detailed understanding of cellular and molecular processes in response to insult in the adult zebrafish brain may cause a paradigm shift in understanding regeneration in the CNS.

In this review, we have provided a detailed description of the main cell types in the adult zebrafish brain, a broad overview of relevant zebrafish models for neurodegeneration and traumatic brain injuries and basic principles unifying currently known mechanisms relevant for CNS repair. Thus, the stage is now set to better understand the cellular and molecular mechanisms that promote endogenous regeneration of several brain areas in the adult zebrafish CNS. These concepts provide further opportunities for deeper understanding of CNS repair in zebrafish and for integration of these findings with the data obtained from mammalian studies.

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