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Review article

The role of neuro-epithelial-like and radial-glial stem and progenitor cells in development, plasticity, and repair

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ABSTRACT

Neural stem and progenitor cells (NSPCs) are the primary source of new neurons in the brain and serve critical roles in tissue homeostasis and plasticity throughout life. Within the vertebrate brain, NSPCs are located within distinct neurogenic niches differing in their location, cellular composition, and proliferative behaviour. Heterogeneity in the NSPC population is hypothesized to reflect varying capacities for neurogenesis, plasticity and repair between different neurogenic zones. Since the discovery of adult neurogenesis, studies have predominantly focused on the behaviour and biological significance of adult NSPCs (aNSPCs) in rodents. However, compared to rodents, who show lifelong neurogenesis in only two restricted neurogenic niches, zebrafish exhibit constitutive neurogenesis across multiple stem cell niches that provide new neurons to every major brain division. Accordingly, zebrafish are a powerful model to probe the unique cellular and molecular profiles of NSPCs and investigate how these profiles govern tissue homeostasis and regenerative plasticity within distinct stem cell populations over time. Amongst the NSPC populations residing in the zebrafish central nervous system (CNS), proliferating radial-glia, quiescent radial-glia and neuro-epithelial-like cells comprise the majority. Here, we provide insight into the extent to which these distinct NSPC populations function and mature during development, respond to experience, and contribute to successful CNS regeneration in teleost fish. Together, our review brings to light the dynamic biological roles of these individual NSPC populations and showcases their diverse regenerative modes to achieve vertebrate brain repair later in life.

1. Introduction

Once thought to be a structurally stable population of glia and neurons arising primarily during early development, the adult central nervous system (CNS) is now known to maintain the capacity to remodel throughout life. This occurs in part due to constitutive neurogenesis in neural micro-environments, commonly known as stem cell niches. Neurogenic plasticity within these niches is made possible by distinct classes of neural stem and progenitor cells (NSPCs), including radial-glial (RG), and neuro-epithelial-like (NE) cells, although the specific cellular composition of stem cell niches vary across brain divisions and vertebrate taxa (Lindsey and Tropepe, 2006; Kaslin et al., 2008, 2009; Lindsey et al., 2012; Grandel and Brand, 2013; Dambroise et al., 2017). For instance, NE cells are critical for building a rudimentary mammalian CNS during the earliest embryonic stages, but these cells typically acquire a RG phenotype later in development. In many regions of the CNS, these cells further transform into astrocyte-like cells in adulthood (Götz and Huttner, 2005; Kriegstein and Alvarez-Buylla, 2009). Unlike mammals, teleost fishes, such as zebrafish and medaka, retain separate NE and RG cells with NSPC properties in a

Abbreviations: aNSPCs, adult neural stem and progenitor cells; BrdU, 5-bromo-2'-deoxyuridine; CMZ, ciliary marginal zone; CNS, central nervous system; DAPI, 4′,6-Diamidino-2′-phenylindole dihydrochloride; dpf, days post fertilization; dpl, days post lesion; EdU, 5-ethynyl-2′-deoxyuridine; FGF, Fibroblast Growth Factor; GFAP, glial fibrillary acidic protein; GL, granule cell layer; hpf, hours post fertilization; INM, interkinetic nuclear migration; IP, intermediate progenitor cells; ML, molecular cell layer; NE, neuro-epithelial-like cells; NSPCs, neural stem and progenitor cells; PCNA, proliferating cell nuclear antigen; PGZ, periventricular grey zone; PI3K/PKB, Phosphoinositide-3-kinase–protein kinase B; PL, Purkinje cell layer; PML, peripheral mesencephalic lamina/peripheral midbrain layer; pRG, proliferating radial-glia; PV, parvalbumin; qRG, quiescent radial-glia; TMZ, tectal marginal zone; TMZe, tectal marginal zone external; TMZi, tectal marginal zone internal; wpf, weeks post fertilization

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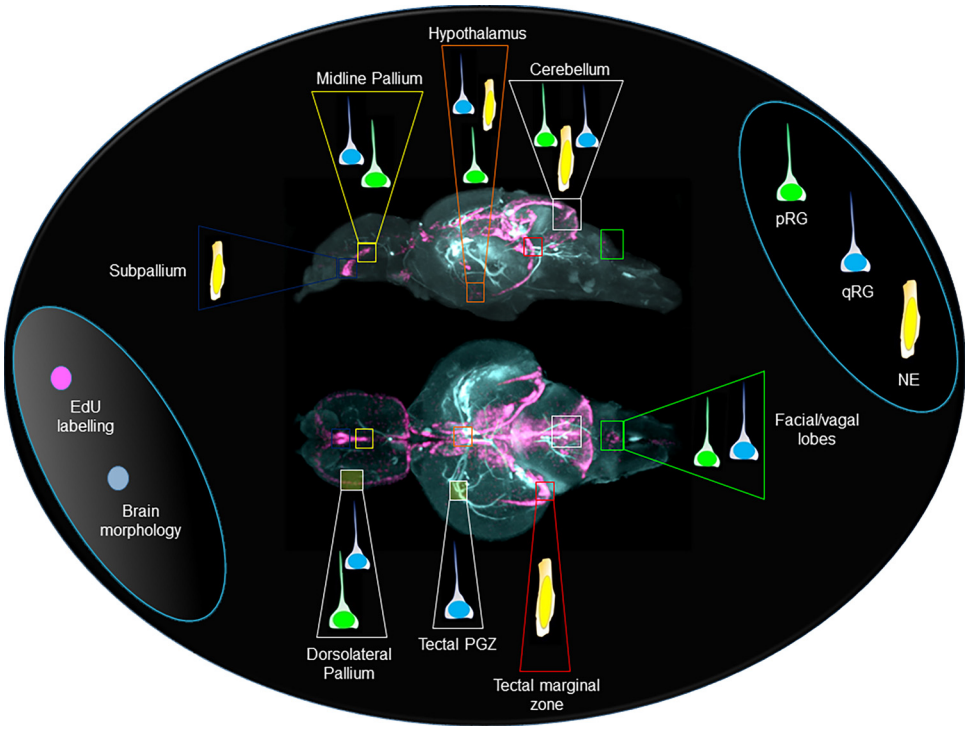

Fig. 1. Stem/progenitor cell populations composing adult stem cell niches along the brain-axis of the zebrafish. Lateral (top) and dorsal (bottom) images of a cleared whole brain showing brain morphology (light blue) and EdU labelling (pink) of actively proliferating stem cells in adult neurogenic compartments. Like colours denote the same niche shown in lateral and dorsal views. All stem cell niches are composed of one or more populations of proliferating radial-glia (pRG), quiescent radial-glia (pRG), and neuro-epithelial-like (NE) cells. EdU, 5-ethynyl-2′-deoxyuridine.

number of neurogenic zones from embryonic development into adulthood (Kaslin et al., 2009; Ito et al., 2010; Recher et al., 2013; Lindsey et al., 2014; Dambroise et al., 2017). The prevailing subtypes of NSPCs present in the mature CNS are a product of divergent developmental programs that, by adulthood, may confer different neurogenic and reparative potential. The heterogeneous nature of NSPCs can be considered at multiple levels, including their molecular signatures, cellular state (i.e. dormant, slow cycling, fast transit amplifying), their glionenic or neurogenic lineages, and finally the subtypes of glia and/or neurons they are capable of producing under physiological and pathophysiological conditions. The diversity of NSPC phenotypes across species, in addition to the heterogeneous nature of many stem cell niches themselves (Shen et al., 2006; Merkle et al., 2007; Lledo et al., 2008; Ganz et al., 2010; Marz et al., 2010), highlight the need to better comprehend these cells at the population level. Focusing at this level will undoubtedly elucidate the species- and niche-specific biological significance of NSPCs, along with their unique cellular and molecular profiles, and potential for tissue regeneration.

Since the inception of the field of adult neurogenesis (Altman and Das, 1965; Altman, 1969; Reynolds and Weiss, 1992), rodent models have played a central role in defining many properties of adult NSPCs (aNSPCs). Studies in the forebrain subependymal zone (also known as the subventricular zone) and hippocampal subgranular zone have been instrumental in uncovering the ultrastructural composition and cellular organization of these niches (Doetsch et al., 1997; 1999; Johansson et al., 1999; Seri et al., 2001, 2004; Mirzadeh et al., 2008; Tavazoie et al., 2008), stem cell lineage relationships (Alvarez-Buylla et al., 2001; Garcia-Verdugo et al., 2002; Ming and Song, 2011) and functional roles and plasticity (Mak and Weiss, 2010; Kempermann, 2011; Lazirini and Lledo, 2011; Frankland et al., 2013). Most recently, single-cell molecular profiling has further provided new information and classification schemes of forebrain stem cell lineages in the uninjured and injured brain (Llorens-Bobadilla et al., 2015; Shin et al., 2015; Luo et al., 2015). The extensive work in the mammalian system has also provided valuable insight into the limitations of CNS regeneration from these endogenous aNSPC populations (Fitch and Silver, 2008; Magnusson and Frisén, 2016). It is now clear that while neuro-trauma can elicit a proliferative response from aNSPCs within the niche (Bye et al., 2011), the resulting progenitors lack the potential to restore the full spectrum of lost cells (Liu et al., 2009; Magnusson et al., 2014). In addition, reactive proliferating astrocytes, oligodendrocyte progenitors, ependymal cells and pericytes result in glial scarring that severely limits repopulation of lost neuronal lineages (Fitch and Silver, 2008; Cregg et al., 2014; Sabelstrom et al., 2014). Despite recent studies showing that cues from the scar itself are needed to induce, in part, axonal repair (Anderson et al., 2016), taking advantage of resident aNSPCs in the mammalian brain remains a considerable hurdle in achieving complete functional neuroregeneration.

How aNSPCs behave outside of mainstream mammalian models continues to be a growing area of interest, providing fresh insight into the biological importance of these cells for tissue maintenance, cellular re-organization, and regeneration. Comparative studies of aNSPC activity between diverse models will build a greater depth of knowledge regarding the molecular regulation, neurogenic and regenerative plasticity, and cellular profiles of these cells to illuminate common themes in stem cell behaviour. More than any other non-mammalian model, the adult zebrafish delivers an exciting experimental system in which to study CNS tissue stem cells, plasticity, and repair. This model boasts an extensive number of life-long adult neurogenic zones in not only traditional forebrain niches (Adolf et al., 2006; Ganz et al., 2010; Marz et al., 2010; Lindsey et al., 2012; Kishimoto et al., 2011; Barbosa et al., 2015), but also in niches situated within primary sensory processing structures across the neuro-axis (Byrd and Brunjes, 1998, 2001; Ito et al., 2010; Kishimoto et al., 2011; Lindsey and Tropepe, 2014, Lindsey et al., 2014). These niches are formed distinctively by one or more combinations of constitutively proliferating radial-glia (pRG), quiescent radial-glia (qRG), and NE stem/progenitor cells, and their accompanying lineages (Fig. 1). Additionally, accumulating evidence positions the adult zebrafish as a champion of CNS regeneration to unlock new insight into the signals governing aNSPCs in tissue repair (Kaslin et al., 2008; Becker and Becker, 2008; Zupanc and Sirbulescu, 2011; Kizil et al., 2012b; Alunni and Bally-Cuif, 2016; Barbosa and Ninkovic, 2016). The locations of adult stem cell niches have been thoroughly mapped across the adult zebrafish brain and basic insight into some of the key aNSPC phenotypes have been gained (Zupanc et al., 2005; Grandel et al., 2006; Adolf et al., 2006). Nonetheless, we remain far

from understanding how aNSPC diversity arises during development and how stem cell niche heterogeneity contributes to tissue homeostasis, plasticity, and regeneration.

In this review, we focus on recent advances in our understanding of the roles NSPCs in the zebrafish CNS. With many excellent reviews already existing that discuss the detailed behaviour of zebrafish NSPCs under a single context, such as CNS regeneration (Kaslin et al., 2008; Alunni and Bally-Cuif, 2016; Barbosa and Ninkovic, 2016; Ghosh and Hui, 2016), it is not our intention here to repeat this work. Rather, the objective of this review is to evaluate stem cell behaviour through a comparative lens across CNS development and under different biological contexts. We commence this review by discussing the appearance and composition of neurogenic niches during embryonic development, including establishment of the three dominant NSPC phenotypes in the zebrafish (i.e. pRG, qRG, NE) that later comprise the majority of adult neurogenic zones throughout life (Chapter 1). Following the formation of neurogenic niches during embryonic development, neurogenesis continues to play an important role in postembryonic brain development and plasticity throughout life. One such role, explored here, is that neurogenesis enables the brain to adapt to ongoing changes in sensory experience. Chapter 2 begins by first discussing adaptive neuroplasticity during neuronal turnover in adulthood; a point at which neurogenesis rates are typically at their lowest. This section is then followed by new research highlighting the largely unknown importance of neurogenesis to postembryonic brain growth during sensitive and critical periods, when neurogenesis rates remain elevated prior to decreasing later in life. Finally, we discuss the importance of adult zebrafish neurogenic zones and individual aNSPC populations in the context of brain injury and regeneration (Chapter 3). Specifically, we review the unique regenerative contributions of niche-specific NSPC phenotypes in the zebrafish telencephalon, midbrain tectum, and cerebellum. This last section of our review, underscores the strength of zebrafish as a model system to study diverse regenerative contexts following neuro-trauma. Collectively, we showcase how knowledge of these NSPC phenotypes and their cell lineages under varying context can reveal mutual properties of stem cell function and regulation in the vertebrate brain. A common theme arising from our review is that across CNS neurogenic niches, the teleost retina and midbrain tectum are well suited systems to test many outstanding hypotheses concerning NSPC hierarchies, critical periods of sensory-dependent plasticity, and the regenerative potential of aNSPCs. Taking advantage of the rich diversity of lifelong stem cell niches and their NSPC heterogeneity in leading teleost models will progress our understanding of the distinct developmental, homeostatic, and regenerative capacity of stem and progenitor cells in the vertebrate brain.

2. Neuro-epithelial-like and radial-glial cells in brain development and homeostasis

Neural stem cells function as the basic building blocks of the CNS. Through diverse divisional modes, cell lineages, and subsets of inductive cues, NE cells and RG, orchestrate the growth of brain structures as they progress towards their adult form. Significant differences exist across vertebrate classes in terms of the phenotype of NSPCs that initiate brain development and those that persist in adult neurogenic compartments. Importantly, while NE and RG function to expand the CNS from embryonic development until birth in mammals, postnatally NE are altogether absent, while RG are found in a quiescent state (Kriegstein and Alvarez-Buylla, 2009). In the mature brain NSPCs in the form of B stem cells or astrocytes, both of which are derived from pRG are detected (*see* Fig. 2A). Conversely, in teleosts and amphibians, NE and RG phenotypes persist as NSPCs lifelong. As such, NE and RG phenotypes play a central role in early CNS development, and also drive constitutive neurogenesis in adulthood in addition to reactive neurogenesis following injury. Furthermore, it's important to note that parenchymal astrocytes are lacking in the CNS of teleost fish. In Chapter 1 of this review, we first discuss the fundamental role of NE cells during teleost CNS development and provide insight into cell lineages originating from NE cells. In particular, we argue that studying retinal and midbrain progenitor cell lineages will allow us to start to decode the hierarchical relationship of NSPCs in the teleost brain.

2.1. Prominence of neuro-epithelial-like cells in the teleost fish brain

Neuro-epithelial-like (NE) cells are very likely the most seminal stem cells of the nervous system. This population derive from embryonic stem cells during the earliest stages of neural development and give rise to many types of neurons, astrocytes and other glial cells. One hallmark of NE cells is that they are polarized along their apico-basal axis. A characteristic of the apical domain of NE cells is the presence of a primary cilium (Seeley and Nachury, 2010). NE cells form an epithelial barrier towards the lumen by establishing adherens junctions at the most apical end. These cells undergo two different forms of mitosis: expansionary symmetric divisions, and differentiating asymmetric divisions (Götz and Huttner, 2005). As shown in a number of cell phenotypes and model species, either the overexpression or the suppression of the proteins of the PAR complex (par3, par6 and aPKC) induce expansionary symmetric divisions to the detriment of neurogenic asymmetric divisions (Willardsen and Link, 2011).

Another characteristic of NE cells is that their nuclei perform apico-basal movements in synch with specific phases of the cell cycle, referred to as interkinetic nuclear migration (INM). As a result of INM the NE cell layer appears as a pseudostratified epithelium (Taverna and Huttner, 2010). Although this migration phenomenon was described for the first time more than 80 years ago, for a long time its functional importance was unknown. Only recently has it been revealed that this movement controls the cellular fate of progenitors by temporally exposing their nuclei to different signals (Taverna and Huttner, 2010). For example, Notch signaling, known to keep progenitors in a quiescent state, is mostly localized to the apical side of the neuro-epithelium. Notch regulates nuclear targets during the apical migration of nuclei of progenitors during retinal development in zebrafish (Del Bene et al., 2008).

In adulthood, at least three stem cell niches are home to NE populations that include one or more NE subtypes. One of the best described NE progenitor populations is located at the cerebellar recess. In this niche, the NE progenitors are polarized, and express *nestin, sox2, meis* and *musashi* stem cell markers, but not typical radial-glia (RG) markers (Kaslin et al., 2009). These NE cells give rise to intermediate progenitors that migrate to the granular cell layer where they differentiate into granular cells (Kaslin et al., 2013). Unlike the cerebellar niche, the composition of the subpallial niche of the telencephalon remains elusive due to the absence of specific molecular markers for different NSPC lineages. In addition to a small number of RG cells located in the dorsal portion of the subpallium (Lindsey et al., 2012), this neurogenic zone contains progenitors with NE characteristics. This population of NE are defined by apico-basal polarity, INM, an absence of RG-specific staining, but positive *nestin* expression (Ganz et al., 2010). Cell lineage experiments have demonstrated that a small cohort of NE cells are maintained from embryonic stages to adulthood in the subpallial domain. Moreover, these progenitors are further able to generate RG cells in the mature brain (Dirian et al., 2014). Lastly, recent work in the midbrain tectum has identified a well-defined NE lineage located in the caudal aspect of the adult tectum (Galant et al., 2016). This lineage hierarchy is characterized by a *Her5*-positive parent stem cell population that gives rise to slowly cycling labelling retaining cells, and finally amplifying progenitors that line the tectal marginal zone (TMZ). While the presence of NE cells at the TMZ has been known for some time (Ito et al., 2010), their place of birth has remained elusive. Moving forward, the recent isolation of NE specific markers that label patches of cells in the medaka pallium (Dambroise et al., 2017) will greatly assist in characterizing and contrasting NE stem/progenitor lineages more

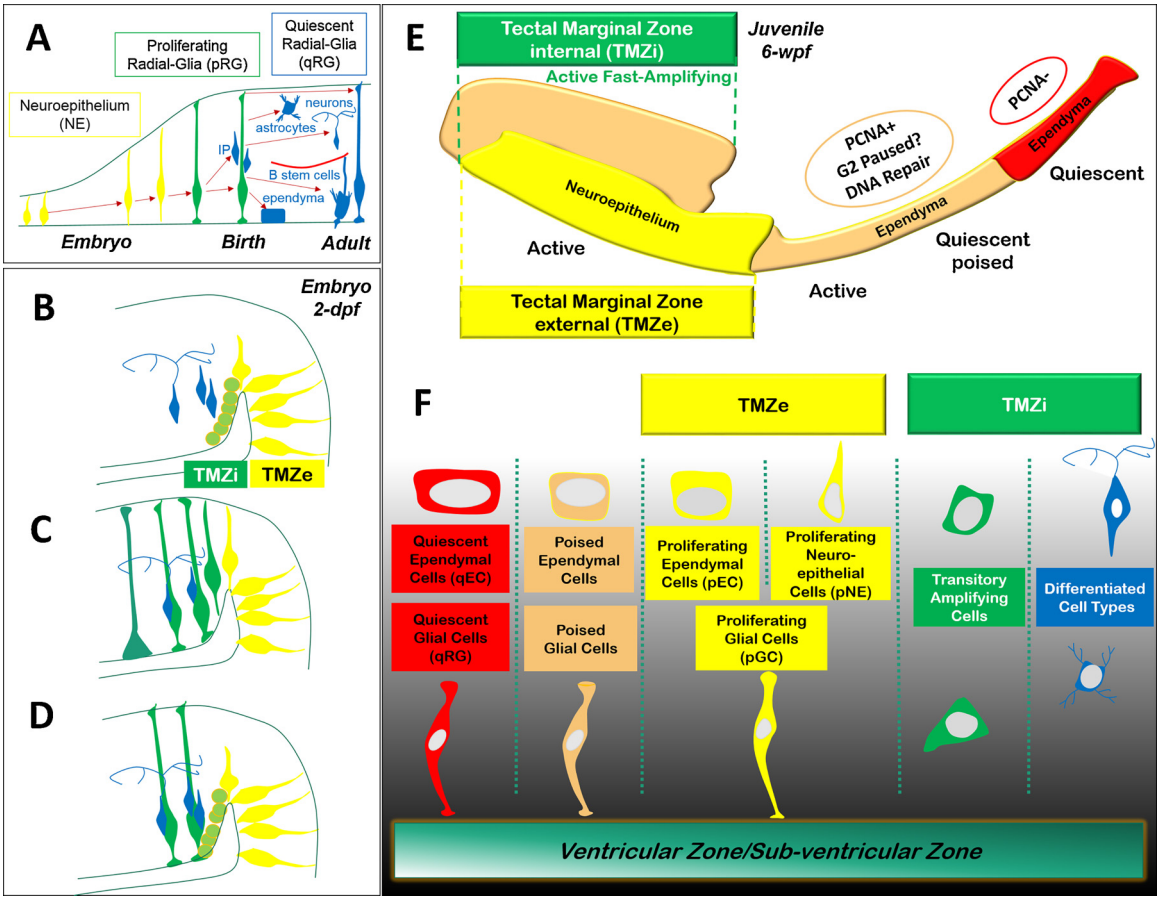

Fig. 2. Stem/progenitor cell populations in the zebrafish and medaka optic tectum. (A) Represents evolution of stem/progenitor cell types in the rodent brain from neuro-epithelial (NE) to radial-glial (RG) phenotypes (adapted from Kriegstein and Alvarez-Buylla, 2009). Drawing of the thickening of the rodent cortex with age indicated below. NE cells in early development divide symmetrically to generate more NE cells. Some NE cells likely generate early neurons. As the developing brain epithelium thickens, NE cells elongate and convert into RG cells. RG divide asymmetrically to generate neurons directly or indirectly through intermediate progenitor cells (IP). At the end of embryonic development, most RG begin to detach from the apical side and convert into astrocytes while IP production continues. A subpopulation of RG retains apical contact and continues to function as neural stem cells in the neonate (type B cell in the adult). Type B cells maintain an elongated NE organization with apical contact at the ventricle and basal endings in blood vessels, and continue to generate neurons and oligodendrocytes through IP. Some RG convert into ependymal cells.

(B-D) Representative parasagittal sections of 2-days post fertilization (dpf) zebrafish embryos (adapted from Recher et al., 2013). A pseudo-stratified neuro-epithelium previously called the posterior marginal layer (PML) is located externally around the two lobes of the optic tectum (external tectal marginal zone; TMZe). In the internal tectal marginal zone (TMZi), columns of cells are added in the optic tectum and in the torus semicircularis. After exiting the TMZi, RG become quiescent and form a ruffled ventricular cell layer that covers the entire floor of the OT (blue ependymoglial cells in (C). In (B), RG are proposed to originate from an amplification pool of round, fast-amplifying progenitors. Additionally, or alternatively in (C), they may be produced by a direct transition from elongated/radial NE to RG cells. In (D), glial cells are intermediate progenitors between the fast-amplifying cells of the TMZi and intermediate neuronal progenitors. (E) Transverse section of the lateral region of the tectum 6-weeks post fertilization (wpf) in juvenile medaka (adapted from Dambroise et al., 2017). Progenitor domains are similar to (B-D) with fast-amplifying progenitors in the internal tectal marginal zone (TMZi) and NE in the TMZe. Additionally, ependymal cells are found in the PML from larval stage, as a result of brain growth. In the centre of the PML (red), ependymal cells are quiescent (negative for PCNA and BrdU). In contrast, close to NE cells, ependymal PCNA positive cells (brown) express high levels of transcripts coding for DNA repair proteins. Some of them incorporate EdU, while some might be paused in G2. A model is proposed whereby ependymal cells produce NE cells, which in turn produce fast-amplifying progenitors. Therefore, parallel neurogenesis modes are illustrated in (F) between ependymal/neuro-epithelial progenitors present in the fish brain, and of glial progenitors found in the subventricular zone of the telencephalon. Refer to Recher et al. (2013) and Dambroise et al., (2017) for discussion of molecular makers.

Colors: yellow: NE: green; fast-amplifying intermediate progenitor: red; quiescent cells: blue; differentiated cells, IP: intermediate progenitor cell; NE, neuro-epithelial cells; nIPC, neurogenic intermediate progenitor cell; RG, radial-glia.

precisely across different adult neurogenic niches.

2.2. Many pathways from neuro-epithelial-like cells to radial-glia and neurons?

The cell lineages originating from NE along with the final differentiated glial or neuronal phenotype are to date poorly understood in the vertebrate CNS. Building on earlier work using rodent models, teleosts models can contribute novel insight towards understanding which cell types are derived from NE. In mice, NE cells start to differentiate into RG cells at embryonic stage E9/-E10 (Fig. 2A). The glial transformation phase is detected by the expression of glial-specific markers including the glutamate-aspartate transporter, β subunit of calcium binding protein, brain lipid binding protein, and the glutamine synthetase enzyme (Götz and Huttner, 2005; Pinto and Götz, 2007; Than-Trong and Bally-Cuif, 2015). During this phase, NE cells also express a variety of intermediate filament proteins such as vimentin and in some non-rodent species, glial fibrillary acidic protein (GFAP; Mori et al., 2005). The accumulation of cytoplasmic glycogen granules that can be detecting using electron microscopy, is a defining characteristic of the transformation of NE cells to a glial phenotype (Choi, 1981).

The above molecular changes mark the transition of NE to RG cells.

However, this transition is not abrupt. RG retain a number of NE cell attributes. In particular, these include expression of the nestin intermediate filament protein and antigens for RC1 and RC2 (RG cell marker-1 and -2), apico-basal polarity, the presence of adherens junctions, primary cilia at the apical surface, in addition to INM (Kriegstein and Alvarez-Buylla, 2009). Here however, the process of INM occurs somewhat differently in RG from that observed in the originating NE population. Unlike NE cells, the nucleus of RG does not migrate over the entire length of the apico-basal axis. Movement of the nucleus is confined to the portion of the cell between the apical surface and the basal boundary of the ventricular zone (Götz and Huttner, 2005). During this stage cells acquire radial morphology with their cell body located along the ventricular zone. Interestingly, both RG and NE cells may acquire an elongated radial morphology at this stage. This is particularly noticeable in ferrets and primates with an elaborate cortex where NE cells elongate as the cerebral vesicles enlarge and walls thicken (Morest and Silver, 2003). Furthermore, many of the NE cells span the extent of the ventricular wall and form a population of cells that have been proposed as “radial neuro-epithelial-like cells” (Morest and Silver, 2003). Presently, the mechanisms by which NE give rise to the RG cells in fish remain elusive. However, since these cell types are found in segregated domains within the teleost retina and midbrain tectum, these organs offer a particularly favourable context to study the shift from NE to a RG phenotype in real time or using clonal analyses.

The retina and optic tectum have similar growth pattern in teleost fish and are valuable experimental systems to investigate the transition of NE to RG during CNS development. Both structures expand via a so-called cellular conveyor belt mode (Devès and Bourrat, 2012; Joly et al., 2016). This mode of neurogenesis is defined by the addition of columns of cells at the periphery in a proliferative zone called the tectal marginal zone (TMZ; Joly et al., 2016). NE cells form an external layer (i.e. TMZe), while proliferating cells are found at the internal margin of the tectum (i.e. TMZi). NE tectal NSPCs are located within a thin epithelial layer that collectively serves as an interface between the optic tectum, torus semicircularis and cerebellum in fish. This complex laminar structure is known as the peripheral mesencephalic lamina/peripheral midbrain layer (PML; Grandel et al., 2006; Recher et al., 2013).

Several questions can be examined using the retina and tectum as experimental systems. For instance, do RG originate from an amplification pool of round, fast-amplifying progenitors (Fig. 2B), as suggested by Galant et al. (2016)? Alternatively, are glial cells produced by a direct transition from elongated/radial NE to RG cells (Fig. 2C), as previously described in the mammalian cortex? Another question that could be addressed by analysing tectal neurogenesis is whether neurons originate primarily from RG as described in Cooper and colleagues (2015), or from fast-amplifying progenitors at the TMZi (Fig. 2D)? These questions could be investigated from studies at larval stages of isolated fluorescent cells in real time, or from clonal analyses at later developmental ages of zebrafish. In addition, Cre-lox based lineage tracing experiments combined with 3-D imaging of clarified brains would provide considerable information at high cellular resolution on the structure of cell clones, as provided already in the retina (Centanin et al., 2011).

2.3. Diversity and hierarchy of progenitors in teleost fish

The heterogeneous nature of NSPCs that populate the teleost brain throughout life has led researchers to question the hierarchical relationship between these cell types from which arise *de novo* neurogenesis. The most intensely studied structure of the teleost brain continues to be the forebrain telencephalon. Within the dorsal telencephalon RG cells have been demonstrated to be a major constitutively active or inducible progenitor population (*see* Fig. 1*; pRG* vs. *qRG*). While it appears clear that within the pallium RG are responsible for driving the neurogenic lineage, the presence of upwards of 6 distinct ultrastructural morphologies composing this niche (Lindsey et al., 2012) has left the exact relationship between these cell types unresolved. In other regions of the teleost brain, including the cerebellum and tectum, NE cells appear to be the primary stem cell population positioned atop the neurogenic hierarchy despite the presence of RG stem/progenitor cells (Kaslin et al., 2009; Ito et al., 2010; Alunni et al., 2010; Lindsey et al., 2018a,b). Recent work in the caudal tectum has defined that the NE lineage is composed of at least three NSPC states characterized by marker expression and cell cycle kinetics (Galant et al., 2016).

An intriguing cell population that remains poorly understood in regards to its potential neurogenic contribution are the diverse cells in ependymal position (i.e. cells lining ventricles) that lack hallmarks of NE or RG cells. Some of these ependymal cells share morphological characteristics with the cuboidal, multiciliated ependymal cells detected in the forebrain of mammals. In particular, multiciliated, cuboidal, ependymal cells enclose the forebrain telencephalic ventricle of the zebrafish as a dorsal ependymal lining forming the ventricular epithelium (Broglio et al., 2005; Lindsey et al., 2012). These ependymal cells reflect the same morphology of the ependyma lining the lateral forebrain ventricles in mammals (Spassky and Meunier, 2017). This population therefore sits opposite the qRG and pRG that populate the stem cell niches of the dorsal and lateral pallium, separated by the cerebrospinal fluid of the telencephalic ventricle. However, an important difference between multiciliated ependyma of zebrafish and mammals is that in the zebrafish forebrain these ependymal cells do not directly neighbour NSPCs in the niche.

In contrast to ependymal cells with classic multiciliated, cuboidal features, in the zebrafish brain other ependymal cells display a flat or ovoid epithelial morphology and are uni-or bi-ciliated. For example, ultrastructural studies of the zebrafish forebrain have reported bi-ciliated cell morphologies in the dorsal zone of the subpallial niche as well as amongst the cells lining the diencephalic ventricle, although their specific identity is unclear (Lindsey et al., 2012). In alternative neurogenic compartments of the zebrafish brain, the position of ependymal cells adjacent the neuroepithelium have raised the question as to whether this population may be part of a more extension stem/progenitor lineage (*see* Fig. 2*E-F*). Recent findings suggest that ependyma in fish is diverse and in some brain regions may be even further upstream in the hierarchy of progenitors actively involved in neuro-epithelial-based neurogenesis (Galant et al., 2016; Dambroise et al., 2017). In contrast to studying the progeny derived from NE cells, studies of progenitors upstream of NE cells can be performed with accuracy in the retina and the tectum.

In the zebrafish retina, proliferative cells are negative for GFAP but positive for common stem cell markers (nestin, BLBP, sox2). This cycling population is also present in the ciliary marginal zone (CMZ), the interface between the retina and the ciliary epithelium (Raymond et al., 2006). In the medaka, a close relative of the zebrafish with similar biological characteristics, cell lineage analysis in the CMZ also shows that it contains multipotent non-glial NE stem cells capable of generating all neuronal types of the retina as well as the Müller glia (Centanin et al., 2011, 2014). Interestingly, these NE progenitors generate neurons without passing through a radial glial stage; a feature that has yet to be detected in the mammalian cortex (Kriegstein and Alvarez-Buylla, 2009).

During tectal development at 2-days post fertilization (dpf), the cells at the prospective TMZ at the midbrain-hindbrain boundary constitute a pseudostratified epithelium of prismatic/bottle shaped cells. Major complex morphogenetic movements at the midbrain-hindbrain boundary are completed by 3-dpf. However, the PML, which serves as a link and a barrier located between two midbrain structures and the cerebellum, continues to grow after this later stage to parallel the growth of brain structures. The PML becomes continuously thinner as the brain approaches its adult form, with diverse cell morphologies observed in the PML, such as cuboidal or elongated cells (Jean-Michel

Hermel, unpublished). The cuboidal morphology is suggestive of classic ependymal cells.

As seen in transverse sections of the juvenile medaka (Fig. 2E), the lateral part of the PML is composed of a neuro-epithelium, which is bordered by PCNA-positive ependyma, and more distantly from the TMZi by a PCNA-negative quiescent ependyma (Fig. 2E; Dambroise et al., 2017). A few of the ependymal cells close to the neuroepithelium appear to be in mitosis as evidenced by phospho-histone 3 positive staining (Dambroise et al., 2017). Further studies are needed to determine if these ependymal cells could sit at the top of the hierarchy of progenitors involved in NE neurogenesis and to further define their individual molecular signatures (Recher et al., 2013; Dambroise et al., 2017; Fig. 2F). To understand the lineage relationship and detail how ependymal cells may give rise to other cell phenotypes additional tools such as NE/ependymal specific Cre lines are needed. Increasing our understanding of ependymal based neurogenesis (Fig. 2) may open new avenues for the reactivation of this cell type in mammals. Moreover, as we move forward in defining the diverse neurogenic lineages responsible for the production of newborn neurons in teleosts, it will be equally important to uncover how these lineages are perturbed under pathological conditions.

3. Experience-dependent neurogenesis from postembryonic development to adulthood

Traditionally, neurogenesis is considered an embryonic event, in which the majority of all neurons are generated during the initial formation of the nervous system. However, the discovery of adult neurogenesis challenged this assumption, demonstrating that neurogenesis continues postembryonically in the vertebrate brain. Contrasted with embryonic neurogenesis, in which high rates of cell proliferation and amplification produce a functional brain, adult neurogenesis is characterized by much lower rates of cell proliferation and neuronal incorporation. Adult neurogenesis is thought to play an important role in balancing persistent neuronal turnover in adulthood to modulate brain structure and function in response to cognitive or environmental challenges (Zhao et al., 2008). The shifting role of NSPC phenotypes from establishing a working CNS to maintaining the neuronal phenotypes required to respond to the surrounding world raises many questions. For instance, how do RG and NE NSPCs function to drive cell proliferation within neurogenic zones to fulfill the diverse requirements of early CNS development versus adulthood? Here, we compare adult and embryonic neurogenesis in the zebrafish in the context of well-studied mammalian models and explore previous work characterizing a known regulator of vertebrate adult neurogenesis, sensorimotor experience, in zebrafish. We also highlight recent work demonstrating that postembryonic neurogenesis, in part, mediates experience-dependent brain growth in early larval zebrafish. We argue that the genetic and experimental tractability of zebrafish can be harnessed to expand our understanding of how neurogenesis can adapt to a changing environment in early life stages to mediate brain growth.

Compared to embryonic neurogenesis, vertebrate adult neurogenesis is drastically restricted with fewer neural precursors producing a smaller proportion of post-mitotic cells exhibiting reduced neuronal differentiation (reviewed in Bernal and Peterson, 2004; Rao et al., 2005). In mammals, neurogenesis is considered a predominantly embryonic event and adult neurogenesis persists in only two widely accepted neurogenic niches. New neurons born in (1) the subependymal zone of the lateral ventricles that migrate along the rostral migratory stream to incorporate into the olfactory bulb and (2) the subgranular zone of the dentate gyrus that incorporate into the hippocampus (Ming and Song, 2005; see Feliciano et al., 2015 for a summary of non-canonical sites of postembryonic neurogenesis in mammals). Unlike mammals, neurogenesis in the zebrafish brain persists postembryonically in multiple ventricular and periventricular zones throughout the entire brain and that can be detected as early as 2-days post fertilization (dpf; Wulliman and Knipp, 2000). Most postembryonic neurogenic zones will continue to generate neurons into adulthood: characterizations of adult zebrafish neurogenesis report constitutive neurogenesis in upwards of 16 neurogenic zones distinguishable by location, morphology, or precursor lineage that collectively supply new neurons to all major brain divisions (Zupanc et al., 2005; Grandel et al., 2006; Adolf et al., 2006; Lindsey et al., 2012). The general pattern of adult neurogenesis in teleost fish appears to be a highly robust trait since a number of different species have shown similar organization of neurogenic zones to those reported in zebrafish (Ekström et al., 2001; Isoe et al., 2012; Tozzini et al., 2012; Olivera-Pasilio et al., 2017).

One important regulator of adult vertebrate neurogenesis is sensorimotor experience, including aerobic exercise, social interaction, and environmental enrichment (Kempermann et al., 1997; van Praag et al., 1999a, 1999b; Gheusi et al., 2009; Maruska et al., 2012, 2013). Interestingly, distinct neurogenic zones in the vertebrate brain exhibit some degree of independence in both the types of sensorimotor experience to which they respond and also the specific stage in the process of neurogenesis (i.e. proliferation, migration, differentiation, survival) that is altered in response to experience. While stage-specific regulation of adult neurogenesis has been well-documented in rodents (van Praag et al., 1999a; Rochefort et al., 2002; Stranahan et al., 2006; Mak et al., 2007; Leasure and Decker, 2009; Mak and Weiss, 2010), a small number of studies in zebrafish support the notion that distinct stem cell zones may similarly exhibit heterogeneous neurogenic responses to sensorimotor experience (von Krogh et al., 2010; Lindsey and Tropepe, 2014, Lindsey et al., 2014). Expanding our knowledge of how different neurogenic zones respond to changes in sensory experience by exploiting the widespread neurogenic capacity of the zebrafish brain offers a unique opportunity to identify different neurogenic response to sensory stimuli and the importance of new neuronal incorporation into different pre-existing neural circuits. In the first part of this section of the review, we will summarize previous work examining neurogenic responses to sensorimotor experience in the zebrafish brain. These studies will be discussed specifically in the context of similar work on mammalian models of adult neurogenesis. In this second part of this section of the review, we will shift our focus on earlier developmental stages, highlighting recent work demonstrating the power of zebrafish as a model to study the importance of sensory experience-dependent brain growth during postembryonic, not adult, development. Using visual experience-dependent neurogenic growth in the zebrafish larval optic tectum as a guide, we discuss how zebrafish could be useful in expanding our understanding of neurogenesis from embryogenesis to adulthood, and finally to the senescent brain of vertebrates.

3.1. Experience-dependent regulation of adult zebrafish neurogenesis

Across vertebrates, a strong research emphasis has been on factors that regulate the production, differentiation, and survival of new neurons in the adult brain. In part, this focus is driven by the potential to upregulate adult neurogenesis in hopes of replacing neurons lost following insults or neurodegeneration later in life (Boda et al., 2017). In mammals, aerobic exercise (van Praag et al., 1999a, 1999b), learning (Gould et al., 1999), and environmental enrichment (Kempermann et al., 1997; van Praag et al., 2000) are three of the most robust regulators of adult neurogenesis. Accordingly, hypotheses regarding the function of adult neurogenesis revolve around interactions with the environment and frame environmental changes as opportunities to incorporate new, or modulate old, information in pre-existing neural circuitry. Such functions include learning new information (Zhao et al., 2008; Moreno et al., 2009), forgetting old information (Frankland et al., 2013; Akers et al., 2014), and more generally enhancing cognitive flexibility (Kempermann, 2012; Aimone et al., 2014; Anacker and Hen, 2017). These modulatory functions of adult neurogenesis can be contrasted to those ascribed to embryonic neurogenesis, in which new neuron addition is considered critical to the development of a

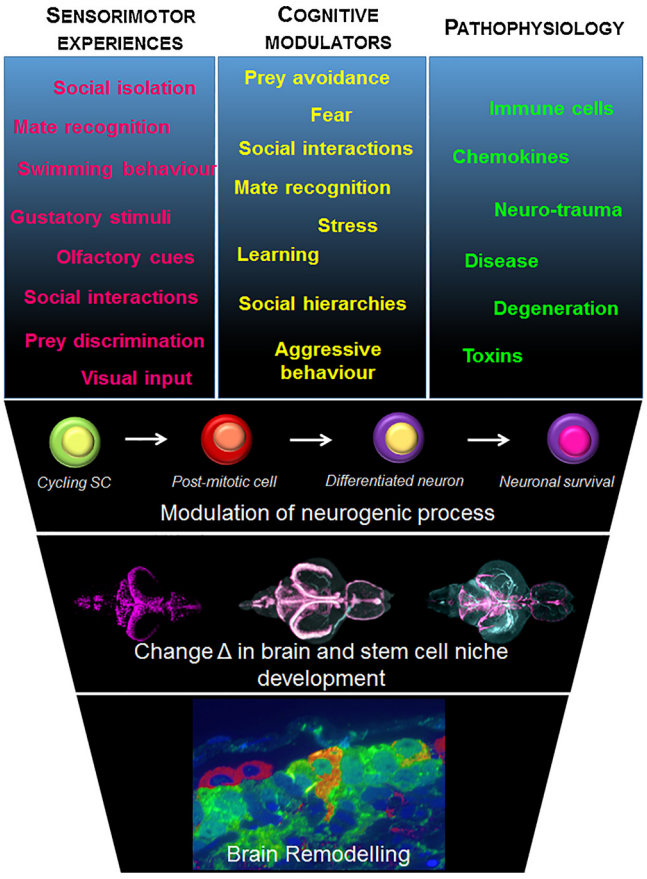

Fig. 3. Regulators of neurogenesis from postembryonic development to adulthood in zebrafish stem cell niches. It is predicted that sensorimotor experiences and cognitive modulators, alone or in combination can impinge on distinct stages of the neurogenic process leading to brain remodeling in teleost fishes. Similar brain remodeling can result as a consequence of pathophysiology. No specific relationships are implied based on this schematic. Classification based on this contextual organization of modulators can be used however, as a guide to test hypotheses concerning regulators capable of modulating neurogenesis in stem cell compartments of sensory processing structures or higher-order centers, respectively. Whole brain images stained with the proliferative, *S*-phase marker, EdU (pink), shown from left to right: larvae (5-days post fertilization), juvenile (~ 1-month), and adult (~ 6-months). EdU, 5-ethynyl-2′-deoxyuridine.

functional nervous system. Interestingly, sensory experiences have been reported to regulate adult neurogenesis in the mammalian subependymal (Rochefort et al., 2002) and subgranular (Brown et al., 2003) neurogenic niches independently of one another. This suggests that niche heterogeneity extends beyond the location of a neurogenic compartments in the brain and its cellular composition, to the neurogenic responses of different niches to distinct sensory experiences. Compared to work on mammalian models, few studies have investigated the possibility of experience-dependent neurogenesis in the adult zebrafish brain. However, with multiple distinct neurogenic niches continuing to produce newborn neurons throughout life, there is a greater capacity to investigate niche-specific modulation of neurogenesis by sensory input in zebrafish. Lifelong adult neurogenesis within primary sensory brain regions provide many exciting opportunities to test the mechanisms through which sensorimotor-dependent neurogenesis of pRG, qRG, or NE populations modulates brain structure and function (Fig. 3).

Often, many regulators known to affect adult neurogenesis include multimodal experiences hypothesized to mimic experiences animals face in the wild. One example of such stimuli is social interactions with conspecifics. In mammals, the removal of social experience by isolation impairs adult neurogenesis in both subgranular (reviewed in Holmes, 2016) and subependymal neurogenic niches (Monteiro et al., 2014). Lindsey and Tropepe (2014) sought to test whether adult zebrafish similarly exhibit a neurogenic response to social isolation and whether this experience affects distinct neurogenic zones differently. Fish raised among conspecifics and isolated for one week in adulthood exhibit reduced cell proliferation in NE populations within the caudal periventricular grey zone (PGZ) of the optic tectum, a midbrain structure involved in visual processing (Orger and Baier, 2005; Fleisch and Neuhauss, 2006; Nevin et al., 2010). Interestingly, the same proliferative response was observed in the vagal lobe, a brain stem structure involved in gustatory processing and containing an RG-dominant neurogenic niche (Morita et al., 1983; Lindsey et al., 2014; Yanez et al., 2017). Conversely, neurogenesis in both the dorsal pallium and ventral subpallium, two neurogenic domains within the zebrafish telencephalon composed of qRG and pRG, or NE cells, respectively, were unaffected by social isolation. The authors found a similar reduction in cell proliferation in the PGZ and vagal lobe when adult zebrafish were exposed to novel conspecifics for two weeks, again without associated changes in telencephalic neurogenesis. Thus, under these experimental conditions only NSPC populations located in primary sensory processing structures displayed changes in neurogenesis. These same cell types remained unaltered in forebrain niches indicating that they may be reserved for higher order cognitive functions. This study is one of the first to demonstrate independent regulation of adult neurogenesis between neurogenic niches in zebrafish. Niche-specific modulation of neurogenesis challenges the assumption that widespread neurogenesis throughout the teleost brain is simply an allometric mechanism to match brain growth to continued body growth throughout life in fish (Brandstätter and Kotrschal, 1990). Consistent with niche-specific neurogenic responses to social experience, the telencephalon, subpallium, septum, and preoptic area in adult zebrafish have been shown to exhibit region-specific changes in neuroplastic gene expression after either winning or losing a fight, or fighting a mirror image of one fish's self in comparison to non-socially-interacting fish (Teles et al., 2016). Specifically, the authors' found that *wnt3* and *neurod*, two genes associated with adult neurogenesis, were differentially regulated in the telencephalon of fish who won or lost a fight, whereas no such changes in these genes were recorded in the other regions tested, despite all regions incorporating new neurons throughout life. Together, these results highlight the value of adult zebrafish as a model towards understanding the mechanisms through which different neurogenic niches may independently modulate new neuronal production in response to sensory experiences.

A major limitation to manipulations including social experience is their multimodal nature. By providing multimodal stimuli, it is difficult to both isolate the specific sensory input driving neurogenic change and, by extension, evaluating the degree to which different neurogenic niches are affected by individual sensory experiences. A similar problem is faced in experiments using environmental enrichment, which often includes both the introduction of novel objects and sensations in the home cage of a lab animal. Environmental enrichment is associated with a robust increase in adult neurogenesis in mammals (Kempermann et al., 1997; van Praag et al., 2000) and, more recently, in the adult zebrafish (von Krogh et al., 2010). To address the multimodal limitation to this approach, Lindsey et al. (2014) exposed adult zebrafish to single-modality sensory experiences and tested whether changes in adult neurogenesis would only occur in neurogenic niches associated with the altered sensory input. Specifically, the authors' provided adult fish with one week of either novel chemosensory (i.e. olfactory and gustatory) experience or restrictive visual experience and sampled neurogenesis in olfactory, gustatory, and visual structures. Exposing adult fish to chemo-stimulation increased new neuron survival solely in the olfactory bulb and gustatory vagal lobe, but not the tectal PGZ involved in visual processing. Conversely, exposing fish to 7 days of either monochromatic green or low intensity light reduced the number of

proliferating cells in the PGZ and torus longitudinalis, involved in processing visual features and light intensity, respectively, without affecting neurogenesis in the gustatory vagal lobe. This study not only demonstrates the possibility of independent neurogenic regulation between distinct niches based on the sensory modality manipulated, but also demonstrates how distinct neurogenic niches individually modulate stages of the neurogenic process differentially. Whereas the olfactory bulb and vagal lobe contain predominantly RG populations as resident aNSPCs and respond to sensory enrichment with increases in neuronal survival, the PGZ and torus longitudinalis contain NE progenitors (Ito et al., 2010; Dambroise et al., 2017) and respond to visual experience with changes in proliferation (Lindsey et al., 2014). Understanding stem cell niche-specific neurogenesis is critical to pinpoint the cellular and molecular factors enabling specific niches to upregulate constitutive levels of neurogenesis in response to sensorimotor experiences. Such studies also provides a non-invasive approach to using sensory experiences as a means of harnessing adult neuroplasticity to targeted brain regions.

3.2. Postembryonic neurogenesis and visual experience-dependent zebrafish brain growth

Most research on zebrafish neurogenesis is focused on either the embryonic period or adulthood (Marcus et al., 1999; Schmidt et al., 2013), similar to work on mammalian neurogenesis (Kriegstein and Alvarez-Buylla, 2009; Urbán and Guillemot, 2014). This reflects the widely held view that following embryonic neurogenesis, postembryonic neurogenesis continues largely unchanged throughout development, only slowing with senescence (Kriegstein and Alvarez-Buylla, 2009; Götz et al., 2016). Recent work focusing on neurogenic brain growth during postembryonic development, defined here as the period of development between embryonic development and adulthood, has challenged this assumption. Accumulating evidence suggests postembryonic development includes unique neurogenic events, such as the production of neuronal populations not generated earlier or later in life. For example, the external granule layer of the mammalian cerebellum produces granule neurons exclusively during the first month to year of postnatal development, ceasing entirely before adulthood is reached (Ponti et al., 2008; Walton, 2012). In addition to unique patterns of neurogenic growth, neurons born during postembryonic development appear to also serve unique roles in brain function, producing lifelong changes in behavior. Suppressing rodent hippocampal neurogenesis specifically during adolescence using targeted genetic ablation of neural precursors produces permanent adult deficits in social behavior. However, no such deficits are found when neurogenic suppression is limited to adulthood (Wei et al., 2011; Kirshenbaum et al., 2014). This new insight prompts a refocusing on the importance of postembryonic neurogenic brain growth for healthy brain development. Here, we review evidence that postembryonic neurogenesis may represent a similarly unique development process in fish. Finally, we discuss a case of visual experience-dependent neurogenesis in the larval zebrafish. From this work, we propose that investigating postembryonic neurogenesis may reveal new functions of neuronal addition to the brain, such as the mediation of adaptive brain growth during sensitive and critical periods early in life.

Across teleost species, postembryonic brain development, encompassing larval and juvenile life stages, includes the highest rates of brain growth. In guppies, increases in neuronal number throughout the CNS are highest during postembryonic development and slow upon reaching adulthood (Birse et al., 1980). A similar pattern of brain growth was observed in four cyprinid species, in which postembryonic development included the fastest rates of brain growth and the emergence of species-specific enlargements in brain regions. These species-specific developmental differences are assumed to reflect sensory adaptations and are hypothesized to be driven by cell proliferation (Brandstätter and Kotrschal, 1990; Kotrschal et al., 2013). Though few studies have sought to characterize neurogenic processes unique to postembryonic development in zebrafish, in our own work we have documented a peak development of the predominantly GABAergic *dlx5/6*-expressing population, which integrate throughout the subpallium in the ventral telencephalon. Specifically, we found that the production of this population peaks by 3–4 dpf and is reduced to low, constitutive levels of production by 6 dpf (B. Souza, ZJH, VT; unpublished observations). Perturbing the development of this population by interfering with early dopaminergic signaling produces subsequent motor deficits (Souza et al., 2011), suggesting this short period of postembryonic development may be critical to normal motor development throughout life. As postembryonic development in zebrafish contains several critical changes in brain function, including the onset of visually-guided behavior (Portugues and Engert, 2009), learning (O'Neale et al., 2014), formation of kin memory (Gerlach et al., 2008), and development of swimming (Westphal and O'Malley, 2013), the contributions of ongoing, elevated neurogenic growth to this behavioral development is likely of critical importance.

In addition to being the period of highest brain growth, postembryonic development is also a distinct life stage as it encompasses a period of growth over which neural circuitry becomes sufficiently developed to process incoming sensory input to drive behaviors. The combination of neural circuit function and elevated neuroplasticity, including neurogenesis, makes postembryonic development the period of growth in which the brain is most sensitive to sensorimotor experience. This sensitivity is exemplified in the postembryonic preponderance of critical and sensitive periods, in which experiences drive irreversible or near irreversible changes in brain structure and function, respectively (Knudsen, 2004; Hensch, 2005). Traditionally, the neural substrates mediating these experience-dependent changes in brain development have been assumed to be limited to alterations in pre-existing cell projections and connectivity. For example, visual experience drives increased branching of geniculocortical afferents that underlies the development ocular dominance in mammals (Antonini and Stryker, 1996). With increasing work demonstrating the underestimated breadth of postembryonic neurogenesis, we argue that neurogenesis may also mediate experience-dependent brain growth. As an example, here we review recent evidence documenting visual experience-dependent neurogenic brain growth in the postembryonic zebrafish.

The optic tectum is a midbrain structure that processes predominantly visual input. The tectum receives visual input directly from retinal projections from the contralateral eye, which terminate within the dorsal tectal neuropil (Nevin et al., 2010). The midbrain tectum of teleosts exhibits lifelong neurogenesis and a net gain in neurons throughout life owing to neuronal production arising from the TMZ of the PGZ, where newborn neurons are added circumferentially to the upper neuronal layer of the PGZ (Raymond and Easter, 1983; Alunni et al., 2010; Ito et al., 2010; Cerveny et al., 2012). The resident source of new neurons in the teleost postembryonic tectal niche is a homogenous population of NE cells, which grow the tectum appositionally, with newer generations of neurons positioned atop older populations (Ito et al., 2010; Dambroise et al., 2017). Previous work suggests postembryonic tectal growth is sensitive to visual input in goldfish (Raymond and Easter, 1983; Raymond et al., 1983). Surgical removal of the input from one eye by 18 h post fertilization (hpf) results in an underdeveloped contralaterally innervated optic tectum in *Astyanax mexicanus* (Schmatolla, 1972). In *Xenopus* tadpoles, both dark rearing and exposure to visual stimulation modulates rates of cell proliferation in the tectum (Sharma and Cline, 2010), suggesting this visual experience-dependent development may be mediated by neurogenesis in anamniotes.

To test whether visual experience-dependent tectal growth may be mediated by postembryonic neurogenesis, we reared zebrafish larvae from 5 to 16 dpf in either control or low intensity light conditions (Hall and Tropepe, 2018). By using environmental light manipulations, we avoided the possibility of activating degenerative and regenerative

mechanisms, which may be associated with destructive removal of visual input. Additionally, we maintained circadian rhythmicity with a day:night cycle not possible under strict dark rearing, and we exposed larvae to light intensities characteristic of the variety of aquatic habitats zebrafish inhabit in the wild (Engeszer et al., 2007). By 5 dpf, the visual system in zebrafish is functional (Fleisch and Neuhauss, 2006) and exhibits visual experience-dependent changes in tectal activity (Avitan et al., 2017). We found that rearing larvae in low intensity light reduced the survival of 5 dpf-born neurons from NE stem cells by 16 dpf. However, this decrease in neuronal survival only occured in larvae that were reared in low intensity light for the first 5 days post neuron generation. Interestingly, the qRG stem cells were not affected by this treatment. We further found that low intensity light rearing resulted in a significantly underdeveloped tectum by 16 dpf and that the effects of low intensity light on tectal neuron survival appear to be mediated by retinotectal glutmatergic input regulating BDNF expression in the tectum (Hall and Tropepe, 2018). As the total volume of retinotectal afferents within the tectum was not affected by light rearing environment, the anatomical consequences of low intensity light rearing on the tectum appear to be mediated primarily by changes in neuronal survival. A recent study found that following the destructive removal of retinal inputs, new tectal neurons fail to coordinate their neural activity with those of neighbouring mature neurons (Boulanger-Weill et al., 2017). Presumably, this coordination of neuronal activity requires sufficient visual input. Our work on the impacts of low intensity light rearing in zebrafish shows that restricting visual experience has developmental consequences for neurogenesis, with fewer new neurons surviving in the growing tectum. In conjunction with work demonstrating that visual deprivation negatively impacts visually-guided behaviours critical to early survival (i.e. prey capture; Avitan et al., 2017), this work demonstrates how experience-dependent brain growth during postembryonic development could be mediated by the modulation of specific neurogenic niches and types of NSPCs throughout the zebrafish brain.

4. Radial-glia and neuro-epithelial-like cells in brain regeneration

Tissue regeneration in the vertebrate CNS is a key priority for uncovering new therapeutic strategies to aid patients with neurodegenerative disease or trauma (Li and Chen, 2016). Unveiling the regenerative potential of NSPCs along with their molecular control holds promise for therapeutical intervention, while at the same time revealing the unique biology of the CNS of diverse vertebrate species. Striking differences exist between mammalian and non-mammalian models in their regenerative capacity. In mammals, limited tissue repair is a result of lack of obvious NSPCs, a general non-permissive tissue environment for neurogenesis as well as glial/fibrotic scarring and chronic inflammation (Fitch and Silver, 2008; Buffo et al., 2010; Göritz et al., 2011; Cregg et al., 2014; Raposo and Schwartz, 2014; Shimazaki, 2016; Magnusson and Frisén, 2016). Interestingly, mammalian astrocytes, oligodendrocyte progenitors and ependymal cells can be converted into progenitors that can produce glia and neurons suggesting that they may have a latent capacity for neural repair (Buffo et al., 2005, 2008; Magnusson and Frisén, 2016; Brulet et al., 2017; recently reviewed in Gascón et al., 2017). For example, is has been illustrated that non-reactive astrocytes under physiological conditions can be converted to neurons *in vitro* and *in vivo*, by tuning Notch signalling levels or forced expression proneural factors such as NEUROD1, and thus could serve as source of neural repair following acute brain injury (Buffo et al., 2008; Magnusson et al., 2014; Magnusson and Frisén, 2016; Brulet et al., 2017; Gascón et al., 2017). Furthermore, ependymal cell populations in the adult mammalian forebrain and spinal cord have been shown to also possess regenerative potential to give rise to neurons Carlén et al., 2009; Li et al., 2016; Gascón et al., 2017). In contrast to mammalian models, the zebrafish has become the vertebrate model of choice to expand our understanding of the cellular and molecular programs required for successful CNS regeneration. In the adult zebrafish, neuroregeneration in the brain and spinal cord is driven by a variety of NSPCs, including, but not limited to pRG, qRG, and NE (Becker and Becker, 2008; Kizil et al., 2012a; Alunni and Bally-Cuif, 2016). However, the full reparative potential of these different cell types, the complement of neuronal lineages they can produce, and their intrinsic regulation across different stem cell niches is still largely unclear.

Reviews over the last 10-years have brought to light the value of using the zebrafish model to identify mechanisms underlying functional vertebrate CNS regeneration (Becker and Becker, 2008; Kaslin et al., 2008; Zupanc and Sirbulescu, 2011; Kizil et al., 2012a; Alunni and Bally-Cuif, 2016; Barbosa and Ninkovic, 2016; Ghosh and Hui, 2016). In close association, the zebrafish model is also becoming extensively used to study the effects of brain neurodegeneration as a result of disease or exposure to heavy metals/toxins (Alfaro et al., 2011; Yu and Li, 2013; Bhattarai et al., 2016; Monaco et al., 2017; Vijayanathan et al., 2017; Maheras et al., 2018). Particularly attractive is the diversity of stem cell compartments positioned along the zebrafish brain axis (Zupanc et al., 2005; Adolf et al., 2006; Grandel et al., 2006; Lindsey and Tropepe, 2006; Chapouton et al., 2007; Kaslin et al., 2009; Ito et al., 2010; Lindsey et al., 2012, 2014; Lindsey et al., 2014). This allows the opportunity to dissect how niches composed of varying combinations of NSPCs respond in an injury context.

Early misconceptions and simplified models have resulted in the thinking that most aNSPCs within the adult CNS retain the genetic blueprint, or multipotency, to give rise to all adult cell lineages of the mature brain following injury. Likewise, from only a handful of initial studies in the adult forebrain where successful glial-driven regeneration has been reported (Baumgart et al., 2012; Kroehne et al., 2011; Marz et al., 2011; Skaggs et al., 2014), the notion that tissue repair is championed uniquely by RG cells has evolved. The heterogeneous nature of aNSPC populations in the dorsal telencephalon (Ganz et al., 2010; Marz et al., 2010; Lindsey et al., 2012), midbrain tectum (Chapouton et al., 2007; Recher et al., 2013; Duncan et al., 2016; Dambroise et al., 2017; Galant et al., 2016; Lindsey et al., 2018a,b), and of the hindbrain cerebellar and vagal niches (Kaslin et al., 2009, 2013; Lindsey et al., 2014), raises the question of which cell type sits atop the lineage hierarchy and whether the regenerative capacity of related aNSPCs is conserved across different stem cell domains (Fig. 4). From research investigating the regenerative potential of aNSPC populations

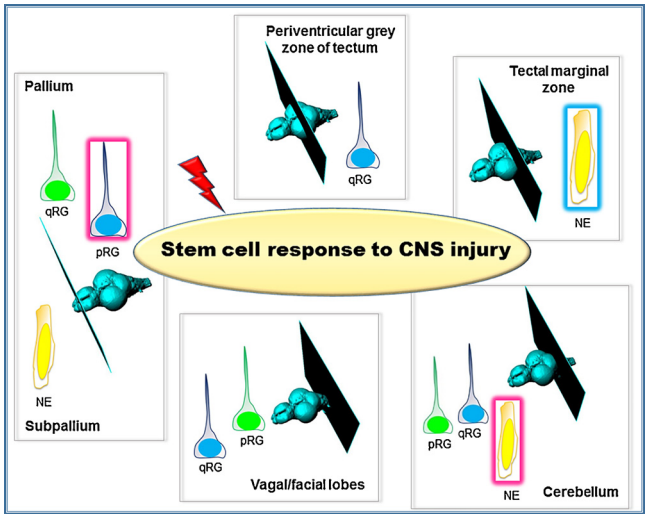

Fig. 4. Adult neural stem cell response to CNS injury across major stem cell niches of the zebrafish brain. Only in the forebrain dorsal pallium and cerebellum have the stem/progenitor cells responsible for replenishing lost neuronal lineages following damage been conclusively identified (pink borders; candidate cells shown with blue borders). pRG, proliferating radial-glia; qRG, quiescent radial-glia; NE, neuro-epithelial-like cell.

in neurogenic zones external to the adult forebrain (Ramachandran et al., 2011; Wu et al., 2014; Wan et al., 2014; Kaslin et al., 2017) it is increasingly evident that individual aNSPC subtypes are endowed with varying regenerative capacities and molecular control. Whether these properties are a consequence of cell-specific reparative programs, or the permissiveness of the stem cell micro-environment upon lesion, is still poorly understood.

Activating and recruiting NSPCs is critical for replenishing lost tissue. A key feature of the regenerative ability of the zebrafish CNS is the ability to engage and mobilise diverse subtypes of NSPCs. In particular, activation of quiescent NSPCs is a trademark of neural regeneration in zebrafish. Mechanistically, the ability to enhance the production of new cells upon injury can be controlled at the level of the stem cell or at the level of progenitors. The most common strategy to quickly replenish lost cells is to increase the size of the pool of amplifying progenitors. Utilisation of amplifying progenitors is a hallmark for rapid growth and expansion of large brain areas such as the cortex or cerebellum during development but also a key feature of adult subependymal/subventricular zone neurogenesis in rodents (Goldman, 2003; Kriegstein and Alvarez-Buylla, 2009).

Interestingly, amplification is less pronounced during neural development or in adult vertebrates displaying indeterminate growth (Kaslin et al., 2008). For example, cerebellar growth in the embryo or adult zebrafish is chiefly regulated at the primary NSPC level (Kaslin et al., 2009, 2013; Chaplin et al., 2010; Butts et al., 2014). In contrast, cerebellar expansion in mammals takes place postnatally and is largely controlled at the level of amplifying granule cell progenitors (Altaba et al., 2002; Sotelo, 2004). In the zebrafish retina, Müller glia are thought to repopulate lost retinal lineages post-injury by undergoing dedifferentiation (i.e. by changing morphology and marker expression) and subsequently producing a lineage of rapidly proliferating multipotent progenitors that can replenish lost cell lineages of the neural retina (Bernardos et al., 2007). In contrast, no indication of dedifferentiation of RG or the appearance of fast cycling progenitors are seen after telencephalic lesion (Kroehne et al., 2011; Barbosa et al., 2015). Similarly, no evidence for dedifferentiation or significant amplification of progenitors is seen following tectal, cerebellar or spinal cord injury (Reimer et al., 2008; Becker and Becker, 2008; Kaslin et al., 2017; Lindsey et al., 2018b; Shimizu et al., 2018).

In this last section of our review, we bring together the various regenerative modes used by different subsets of NE, pRG, and qRG cells of the zebrafish to achieve successful tissue repair throughout life. Here, we focus our attention on three adult stem cell compartments that are currently best characterized, including the forebrain telencephalon, midbrain tectum, and hindbrain cerebellum.

4.1. Activation of radial-glia regulate telencephalic regeneration

The adult zebrafish telencephalon remains best understood under physiological and pathological conditions compared with all other stem cell niches in this model. Anatomically, telencephalic niches are typically divided into dorsal pallial and ventral subpallial domains, characterized by RG dominant or NE dominant stem cell compartments, respectively (Ganz et al., 2010; Lindsey et al., 2012). A number of reports have performed detailed investigation of the response of RG cells to injury in the periventricular zone surrounding the dorsal forebrain ventricles using a variety of lesion and imaging techniques (Kroehne et al., 2011; Marz et al., 2011; Kyritsis et al., 2012; Kizil et al., 2012b; Baumgart et al., 2012; Kishimoto et al., 2012; Skaggs et al., 2014; Barbosa et al., 2015). Much less is known about the ventral stem cell niche where NE populations reside.

Different injury paradigms have been used to specifically probe the behaviour of telencephalic stem cell populations and their potential for neuroregeneration. These include stab lesions along the long-axis of the forebrain (Kroehne et al., 2011; Kyritsis et al., 2012; Baumgart et al., 2012), stab lesions dorsolaterally through the neurocranium (Marz et al., 2011; Kishimoto et al., 2012), and injections of neurotoxins (Skaggs et al., 2014; Bhattarai et al., 2016). These injury methods produce an increase in RG proliferation, similar to the observed increase in subependymal RG-like cell proliferation following injury in proximity to the lateral ventricles in the rodent brain (Liu et al., 2009; Bye et al., 2011; Magnusson et al., 2014). For example, stab lesions through the central parenchyma of the zebrafish telencephalon identified RG progenitor cells as the main neurogenic population reacting and producing cells after injury (Kroehne et al., 2011). Moreover, these RG are the primary source of newly generated parenchymal neurons of multiple cell lineages.

It is increasingly clear that qRG rather than constitutively pRG are chiefly responsible for reactive neurogenesis post-injury. Under homeostatic conditions, most RG cells reside in a quiescent, non-cycling state. Analysis of cell division modes and clonal analysis aimed at understanding the divisional mode of RG cells under homeostasis has shown that qRG progenitors are both self-renewing and capable of generating various cell phenotypes via asymmetric divisions (i.e. one non-glial daughter and one glial cell; Ganz et al., 2010; Rothenaigner et al., 2011). Following injury, asymmetric division of RG cells appears to be most prevalent (Kroehne et al., 2011; Barbosa et al., 2015). Interestingly, live imaging of RG post-injury in the adult dorsal telencephalon has demonstrated that in very rare instances, RG shift their mode of cell division from asymmetrical to symmetrical division. This shift towards exhaustive symmetrical division serves to generate two neural precursors and more rapidly expand the neuronal population on the behalf of exhausting the NSPC population (Barbosa et al., 2015; Barbosa and Ninkovic, 2016).

One of the earliest cues that initiate the regenerative response and activation of RG is inflammation (Kyritsis et al., 2014; Kizil et al., 2015). Inducing sterile inflammation by injecting immunogenic particles activates qRG in the dorsal telencephalon and enhances neurogenesis. Conversely, immunosuppression blocks RG activation and regenerative neurogenesis after injury (Kyritsis et al., 2012). Furthermore, three-dimensional imaging of the whole brain after injury shows systemic activation of NSPCs and immune cells that temporally correlate across the brain axis (Lindsey and Kaslin, 2017; Lindsey et al., 2018a). Leukotriene signalling is one of the early inflammatory signals that modulate activation of RG after injury (Kyritsis et al., 2012). Other signals related to inflammation or immune cells such as the chemokine receptor *cxcr5* and the transcription factor *gata3* are necessary for reactive proliferation and regenerative neurogenesis following brain trauma (Kizil et al., 2012a, 2012b). Likewise, *gata3* has been shown to further rely on Fibroblast Growth Factor (FGF) signalling to promote the proliferative response proceeding CNS damage (Kizil et al., 2012b).

Notch signalling is one of the key contributors responsible for controlling the quiescent state of RG in zebrafish. High expression of the direct Notch target gene *her4.1* (mammalian hes1/5 orthologue) is a hallmark of RG in the zebrafish brain (Ganz et al., 2010; Kroehne et al., 2011; Dong et al., 2012). Chemical of genetic blockade of Notch shifts qRG to re-enter the cell cycle in the telencephalon by increasing their degree of symmetric gliogenic division (Chapouton et al., 2010; Kroehne et al., 2011; Rothenaigner et al., 2011; Alunni et al., 2013; de Oliveira-Carlos et al., 2013). Mild traumatic brain injury in adult zebrafish has shown differential expression of genes, such as *notch1* between 3-days post-lesion (dpl) and 21-dpl, which appears to correlate with RG cells (Maheras et al., 2018). Still unknown is whether Notch levels in pallial qRG are diminished post-lesion, and whether such levels are discernible alongside Notch expression in pRG under a regenerative state. Evidence in the aging zebrafish brain has additionally shown that a greater number of qRG exist in the dorsal stem cell niche and that fewer of these cells are responsive to injury (Edelmann et al., 2013). This implies that the capacity of qRG cells to re-enter the cell cycle appears to decline over time or that the pool of cells is gradually depleted as previously suggested (Kaslin et al., 2013; Barbosa et al., 2015; Kaslin et al., 2017). Curiously, elevated Notch signalling has also

been reported to correlate with increased cell proliferation of RG in the pallium and NE cells in the subpallium of the adult zebrafish (Kroehne et al., 2011; Kishimoto et al., 2012). This demonstrates the possibility of opposing roles of the Notch pathway in regulating different NSPC subtypes in the teleost CNS. Indeed, the level of notch signalling controls the cellular response and output after injury in the adult rodent CNS (Carlén et al., 2009; Magnusson et al., 2014; Traiffort and Ferent, 2015; Kato et al., 2018), suggesting that Notch signalling is pivotal in mediating proliferative activity of glial and ependymal cell lineages and fate specification of these cells.

Within the pallial niche, the *id1* gene, encoding a negative regulator of E class basic helix-loop-helix proteins, has recently been mapped to qRG (Diotel et al., 2015; Viales et al., 2015). Under homeostasis, these cells promote stem cell quiescence, but display enhanced expression of *idl* with injury. As such, it has been proposed that this gene may be implicated in preserving the stem cell pool and counteracting injury-induced neurogenic signals (Viales et al., 2015). This mechanism would ultimately serve to reduce a subpopulation of quiescent cells that re-enter the cell cycle with injury, setting them aside for later use and avoiding complete exhaustion of the quiescent NSPC population.

4.2. The role of quiescent radial-glia and neuro-epithelial-like cells in tectal midbrain regeneration

The clear separation of distinct NSPC niches of the midbrain tectum provide a good experimental model system to study lineage relationships between NE and RG cells and their respective roles in repair. In particular, the roof of the tectal ventricle harbours an extensive and uniform population of largely, if not entirely, quiescent RG. Under homeostasis, these RG show no evidence of cell division (Venegas et al., 1974; Nguyen et al., 1999; Grandel et al., 2006; Ito et al., 2010; Alunni et al., 2010; Recher et al., 2013; Dambroise et al., 2017; Lindsey et al., 2018b). Although the hierarchical lineage relationship is not entirely understood of the TMZ “conveyor belt” model (*see* section 2.2), cells with epithelial and NE-like characteristics serve as progenitor cells for tectal RG. A recent lineage tracing study suggests it is possible that tectal RG can transiently act as neural progenitors in the TMZ during transition from an epithelial/NE state to RG (Galant et al., 2016). Outside the TMZ the tectal RG morphologically and molecularly resemble the qRG of the dorsal telencephalon (Ganz et al., 2010; Ito et al., 2010),

A fundamental question is whether the qRG population of the tectum can be activated and contribute to tissue regeneration after injury. Stab lesion assays through the centre of the optic tectum demonstrate that a relatively small proportion of the qRG population in proximity to injury is capable of entering the cell cycle (Lindsey et al., 2018b; Shimizu et al., 2018). The relative activation of qRG is modest and local in comparison to the response detected after telencephalic lesion (Kroehne et al., 2011; Marz et al., 2011; Kishimoto et al., 2012). Furthermore, the tectal qRG response results in little or no neuronal regeneration at the lesion site (Shimizu et al., 2018; Lindsey et al., 2018b). A few newborn neurons have been reported at the lesion canal within the first 7-dpl in one study (Shimizu et al., 2018). However, our own work has shown no evidence of *de novo* neurogenesis arising from the activated qRG population near the lesion site using short (7-dpl) and long (2-, 4-, 6-, and 8-weeks post-injury) EdU pulse-chase experiments and co-labelling with the neuronal marker HuC/D (Lindsey et al., 2018b). Nevertheless, we detected newly produced and long-term maintained RG at the lesion site suggesting that the tectal RG can give rise to their own lineage (Lindsey et al., 2018b). These findings implicate the qRG population as serving a more structural role in maintaining the epithelial barrier and supporting the tectal circuitry. Interestingly, the NE progenitors at the TMZ respond to tectal injury and increase proliferation and neurogenic output suggesting that compensatory regenerative neurogenesis takes place (Lindsey et al., 2018). This regenerative neurogenesis seems to be aimed at overall recovering neurons of the tectum but not specifically at the injury site and could thus be proposed as compensatory.

The molecular regulation of midbrain qRG during the regenerative process has only begun to be interrogated. Wnt/β-catenin signalling is crucial for early midbrain-hindbrain boundary patterning of the CNS (Rhinn and Brand, 2001; Lekven et al., 2003; Buckles et al., 2004; Hüsken and Carl, 2013; Recher et al., 2013) and tissue-wide regeneration in the zebrafish (Stoick-Cooper et al., 2007; Ramachandran et al., 2011; Azevedo et al., 2011; Meyers et al., 2012; Wan et al., 2014; Wehner et al., 2014; Stewart et al., 2014; Duncan et al., 2015; Briona et al., 2016). As such, Wnt/β-catenin signalling has been a candidate pathway most recently examined in the injury context. In the uninjured adult retina, inhibition of glycogen synthase kinase-3β is sufficient to stimulate Müller glia to re-enter the cell cycle and give rise to progenitors capable of producing all major retinal cell types (Ramachandran et al., 2011). While physiological levels of Wnt/β-catenin are detected in qRG cells of the midbrain tectum (Lindsey et al., 2018b), this pathway does not appear to be necessary or sufficient for the proliferative response of these cells following neuro-trauma at 3-dpl. Nevertheless, transient upregulation of GFP reporter expression 2-days following tectal lesion in the qRG layer, along with differential temporal expression of *ascl1a* and *dkk1b* over the first 24- hrs post-injury has been reported (Shimizu et al., 2018). Furthermore, the compensatory neurogenic response from the NE appears to occur independently of Wnt/β-catenin signalling (Lindsey et al., 2018b). Together these findings may suggest high temporal control of the qRG population post-injury by Wnt/β-catenin signalling. As previously described (*see* section 4.1), high levels of Notch signalling in the mature dorsal telencephalon maintain RG in a quiescent state, and attenuation of Notch shifts cells to newly re-enter the cell cycle (Chapouton et al., 2010; Alunni et al., 2013). Uncovering the combined role of both Wnt/β-catenin and Notch signalling in the midbrain following injury will be a significant next step to compare how this population of qRG are controlled in relation to those of the forebrain.

4.3. The adult cerebellar niche of the zebrafish illustrates that neuro-epithelial-like cells play a central role in CNS tissue regeneration

Studies in the adult cerebellar niche have been instrumental in demonstrating that RG cells are not the only candidate stem cell population implicated in the regenerative process. NE cells are the predominating NSPC population that are maintained throughout life in the zebrafish cerebellum (Kaslin et al., 2009, 2013; Kaslin et al., 2017). The simple three layered architecture, relatively few and distinguishable cell types, well known neural development and highly conserved composition makes the cerebellar system well suited for cellular and molecular studies (Kaslin and Brand, 2012; Kaslin et al., 2013).

In the zebrafish cerebellum the stem cell niche and its composition plays a critical role in regulating homeostatic growth and neural regeneration after injury (Kaslin et al., 2009, 2013; 2017). The zebrafish cerebellum proportionally grows more than other brain structures during juvenile stages. In particular, the main body of the cerebellum that contain granule cells expands significantly throughout life. However, the growth is selective and mainly granule cells are added while other core components of the cerebellar circuitry such as the Purkinje cells cease to be produced during the late phase of juvenile development (Kaslin et al., 2009, 2013). Importantly, the growth is controlled at the level of neural stem and progenitor cells. The cerebellar stem and progenitor cells arise early during embryonic development from a common domain of progenitors in the rhombic lip and form two distinct populations inhabited by NE and RG stem and progenitor cells. Remarkably, only the NE cell pool persists in the adult and the ventricular RG stem cells gradually become quiescent, or alternatively exhausted, during juvenile stages (Kaslin et al., 2009, 2013). Genetic lineage tracing showed that the loss of active RG progenitors temporally overlap with the ceased production of neuronal subtypes such as the Purkinje

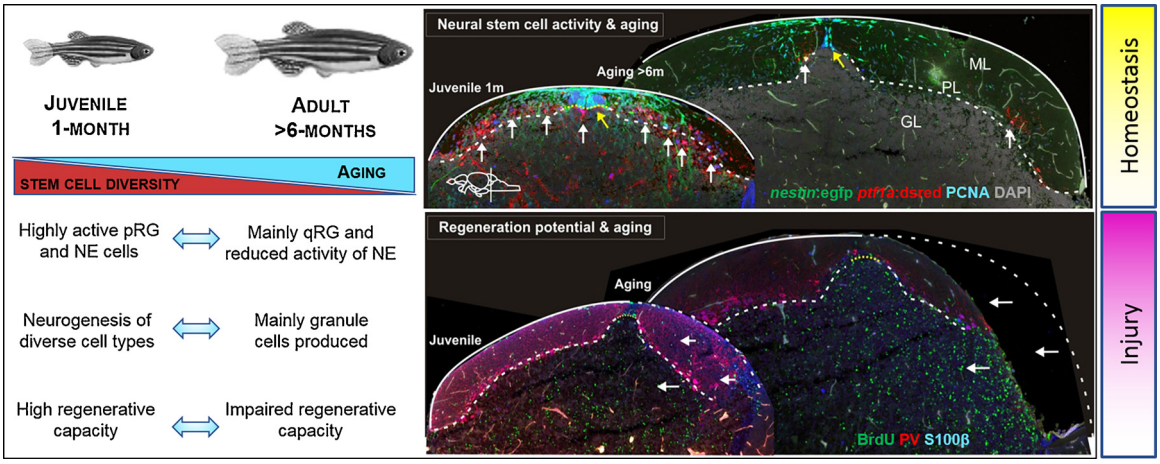

Fig. 5. The diversity of stem cells is lost in the cerebellum during the transition from juvenile to adult and has an impact for homeostatic and regenerative neurogenesis. The juvenile zebrafish maintains pRG and NE stem and progenitor cells (labelled by red and green) and can produce all major cell types during homeostasis and after injury (BrdU labelling of cells in GL, PL and ML). The site of injury is labelled with white arrows in bottom panel. In the adult cerebellum, the pRG become quiescent, whereas NE cells are maintained and continuously contribute to granule cell production (BrdU labelling in GL). The adult cerebellum does not produce all cell lineages and is not able to produce all cell types after injury (No recovery of PL or ML, but BrdU labelled cells present in GL). pRG, proliferating radial-glia; NE, neuro-epithelial-like cell; BrdU, bromo-deoxyuridine; GL, granule cell layer; ML, molecular cell layer; PL, Purkinje cell layer; PCNA, proliferating cell nuclear antigen; PV, parvalbumin; DAPI, 4′,6-Diamidino-2-phenylindole dihydrochloride. Figure adapted from Kaslin et al., 2013; 2017.

cells. Furthermore, the quiescence of the ventricular RG correlates with a transformation from radial morphology to flat epithelia similar to the transformation of RG to astrocytes observed in mammals (Kaslin et al., 2009, 2013).

Both NE and RG stem and progenitor cells are significantly activated after unilateral ablation of tissue in one of the cerebellar hemispheres (Kaslin et al., 2017). Activation of the NE cells results in widespread replenishment of granule cells and re-growth of lost cerebellar tissue. Activation of the ventricular RG results in very modest recovery of selected inhibitory inter-neurons. Early produced neuronal cell lineages such as the Purkinje and Eurydendroid cells don't regenerate. Intriguingly, the juvenile zebrafish cerebellum that harbours active RG and NE can regenerate all major cell types including the Purkinje cells (Fig. 5 Kaslin et al., 2017). Taken together, only the cell types that are produced during homeostatic growth regenerate after injury in the cerebellum demonstrating the irreplaceable role of particular NSPCs such as the NE in growth and repair. At present, evidence suggests that RG cells play a minor role in adult cerebellar neurogenesis and in recovery after injury. Furthermore, the data suggests that RG stem and progenitor cells over time may lose their potential in producing diverse cell lineages. From a comparative standpoint, the regenerative capacity of adult cerebellar RG along with that of telencephalic and tectal RG, implies that this cell type is distinguished by diverse niche-specific regenerative potential that is likely governed by a combination of local cues in the niche and unique molecular programs.

Specialised cerebellar glia, the Bergmann glia that are located in the cerebellar parenchyma are largely if not completely quiescent in the adult zebrafish cerebellum (Kaslin et al., 2009). Bergmann glia are produced at a very low rate in the juvenile and adult zebrafish from the lateral margin of the cerebellar stem cells niche (Kaslin et al., 2013). Bergmann glia are able to enter cell cycle after injury and to some extent regenerate after injury but the source of the regenerated cells is unclear (Kaslin et al., 2017). However, it is possible that they may be able to produce their own lineage and thus share many similarities with the developmentally closely related qRG in the tectum.

Little is known about the signals that specifically control the cerebellar stem cell niche. However, there is a significant body of work that have examined the establishment of the midbrain and hindbrain territories during development (Buckles et al., 2004; Kaslin and Brand, 2012; Duncan et al., 2015). In particular, FGF and Wnt/β-catenin signalling is important in defining and maintaining NSPCs of the midbrain and hindbrain (Rhinn and Brand, 2001; Lekven et al., 2003; Köster and Fraser, 2006; Kaslin and Brand, 2012). SHH signalling plays a pivotal role in amplifying granule progenitors during post-embryonic cerebellar development in birds and mammals (Altaba et al., 2002). In contrast, SHH signalling is not involved in granule cell production or cerebellar development in anamniotes such as zebrafish (McFarland et al., 2008; Kaslin et al., 2009; Chaplin et al., 2010; Hibi and Shimizu, 2012). In the adult zebrafish brain, NE progenitor cells of the cerebellar and ventral forebrain pallial niche require FGF signalling for proliferation and maintenance (Kaslin et al., 2009; Ganz et al., 2010). Decreased signalling is coupled with a reduction in progenitor and granular cell proliferation in the cerebellar niche (Kaslin et al., 2009). FGF signals, targets, and receptors indeed appear to be widespread throughout several adult stem cell niches in the zebrafish, commonly correlating with the behavioural state of ventricular RG (Topp et al., 2008). Under homeostasis, the FGF signalling pathway is essential for constitutive proliferation in the subpallial NE population of the adult telencephalon and NE cells of the cerebellar niche (Kaslin et al., 2009; Ganz et al., 2010). Interestingly, Fgf3/8 and 17 are expressed within domains where NE cells are found in the telencephalon, tectum and cerebellum (Topp et al., 2008; Kaslin et al., 2009; Ganz et al., 2010), suggesting that the NE cells may produce FGFs and may also be regulated by FGFs in an autocrine fashion.

One study aimed at uncovering differentially expressed genes in the whole zebrafish cerebellum after stab injury has provided additional insight towards the molecular programs regulating cerebellar regeneration (Wu et al., 2014). Specifically, upregulation of pathways related to cell cycle and DNA replication, PI3K/PKB pathway, and cytokine signalling, amongst others, were identified. Of interest, the chemokine receptors 3, 4, and 7 (CXCR3, CXCR4, CCR7) were upregulated and associated with the initiation of the inflammatory response following wounding of the cerebellum. This is in general agreement with studies of the injured telencephalon, where chemokine signalling modulates regenerative proliferation and neurogenesis of pallial RG cells (Kizil et al., 2012a, 2012b). Furthermore, Wu et al. (2014) also identified components of the FGF signalling pathway that may be important not only for stem cell niche maintenance, but additionally for tissue repair.

5. Conclusion

The focus of the present review has been to discuss the contribution of radial-glia (pRG, qRG) and neuro-epithelial-like (NE) NSPCs to the zebrafish brain at different developmental stages and under varying conditions. A key aim has been to bring to light the current state of knowledge of these cell populations within distinct postembryonic and adult stem cell niches; common themes that may govern these cells under different circumstances, and the many unanswered questions concerning the regulatory control and neurogenic potential of pRG, qRG, and NE cell populations. Of particular note, we show that both stem cell phenotypes are driven towards the common goal of building, and subsequently, preserving, the structure and function of the CNS. However, RG and NE populations orchestrate these using different sets of cellular and molecular commands. How these cellular and molecular instructions dictate neuronal production at consecutive stages of CNS development, with experience-dependent plasticity, or during neuroregeneration remains the next fascinating set of questions to resolve.

NE and RG stem/progenitor cells together play a fundamental role in constructing a functional CNS during embryonic development, fine-tuning and growing the postembryonic CNS, balancing neuronal turnover into adulthood, and replacing lost neurons during CNS repair. The multifaceted, life-long commitment of these cells to CNS modelling, remodelling, and regeneration showcases the importance of these cells and their progeny to allow teleost models, such as the zebrafish and medaka, to thrive, respond, and adapt to their environment. Only in the last decade have we begun to appreciate how integral RG and NE stem/progenitor cells are at progressive stages of CNS development, emphasizing the need to characterize RG and NE cells in greater detail to unveil their dynamic cellular and molecular regulation in health and with injury. Additionally, studies targeting these stem/progenitor populations in niches responsible for encoding diverse stimuli using specific sensory and behavioural paradigms will move us closer to uncovering the biological significance of these cells in experience-dependent plasticity. The contrasting nature of diverse teleost neurogenic niches allow further in depth analysis using recent technological advances. For instance, single cell sequencing and ATAC sequencing will address many of the unresolved questions surrounding the lineage relationship and molecular differences between NE and RG. The ever-growing toolkit available in the zebrafish and medaka, from live imaging of cells during early development, stem cell lineage methods, advanced tissue engineering, correlative electron microscopy, as well as newer 3-dimensional imaging approaches in adults (Lindsey and Kaslin, 2017; Dambroise et al., 2017; Lindsey et al., 2018a), promises a bright future to study lifelong stem cell populations and their gliogenic and neurogenic properties.

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