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REVIEW ARTICLE

Radial glia in the zebrafish brain: Functional, structural, and physiological comparison with the mammalian glia

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Abstract

The neuroscience community has witnessed a tremendous expansion of glia research. Glial cells are now on center stage with leading roles in the development, maturation, and physiology of brain circuits. Over the course of evolution, glia have highly diversified and include the radial glia, astroglia or astrocytes, microglia, oligodendrocytes, and ependymal cells, each having dedicated functions in the brain. The zebrafish, a small teleost fish, is no exception to this and recent evidences point to evolutionarily conserved roles for glia in the development and physiology of its nervous system. Due to its small size, transparency, and genetic amenability, the zebrafish has become an increasingly prominent animal model for brain research. It has enabled the study of neural circuits from individual cells to entire brains, with a precision unmatched in other vertebrate models. Moreover, its high neurogenic and regenerative potential has attracted a lot of attention from the research community focusing on neural stem cells and neurodegenerative diseases. Hence, studies using zebrafish have the potential to provide fundamental insights about brain development and function, and also elucidate neural and molecular mechanisms of neurological diseases. We will discuss here recent discoveries on the diverse roles of radial glia and astroglia in neurogenesis, in modulating neuronal activity and in regulating brain homeostasis at the brain barriers. By comparing insights made in various animal models, particularly mammals and zebrafish, our goal is to highlight the similarities and differences in glia biology among species, which could set new paradigms relevant to humans.

KEYWORDS

astrocytes, astroglia, blood–brain barrier, ependyma, glia, neurogenesis, zebrafish

1 | SETTING THE STAGE: DEVELOPMENT AND ANATOMY OF THE ZEBRAFISH BRAIN

A well-documented cascade of events takes place throughout the neural development of vertebrates, and zebrafish is not an exception to this (Kelsh & Raible, 2002; Raible et al., 1992; Schier, 1997; Schmitz, Papan, & Campos-Ortega, 1993). During gastrulation, the dorsomedial region of the ectoderm generates the neuroectoderm, and the convergent extension movements generate the neural tube (Appel, 2000; Bally-Cuif & Hammerschmidt, 2003; Chapouton & Godinho, 2010; Chitnis & Dawid, 1999; Driever et al., 1996; Eisen, 1991; Folgueira et al., 2012; Fulwiler & Gilbert, 1991; Granato & Nusslein-Volhard, 1996; Kimmel, Sepich, & Trevarrow, 1988; Kizil, Kaslin, Kroehne, & Brand, 2012; Schmidt, Strahle, & Scholpp, 2013; Strahle & Blader, 1994). The neural tube and the neuroepithelium then give rise to the entire central nervous system, which contains both neurons and glia (Lowery & Sive, 2009).

As in all vertebrates, the zebrafish brain is organized in four subdivisions: the telencephalon, diencephalon, mesencephalon and rhombencephalon (Mueller & Wullimann, 2016; Nieuwenhuys, 2011; Wullimann, Rupp, & Reichert, 1996), which have similar overarching cognitive, endocrine, homeostatic, and motor functions. Despite similarities in the function of these brain structures, some anatomical differences exist between teleost fishes, for example, zebrafish, and other vertebrates, due to the folding of the neural tube. First, in contrast to the mammalian neuroepithelium that folds around the ventricles, the zebrafish neuroepithelium reorganizes in a structure known as neural keel (Figure 1) (Lowery & Sive, 2004, 2005; Papan & Campos-Ortega, 1994). Next, the zebrafish telencephalon undergoes an eversion process, unlike the evagination occurring in mammals and non-teleost vertebrates (Figure 1) (Ganz et al., 2012; Nieuwenhuys, 2011; Wullimann, 2009). This eversion results in an inverted telencephalon, where the regions homologous to mammalian amygdala (Dm) and hippocampus (Dl) are located at the surface of the brain under a unique telencephalic ventricle in contrast to the two lateral ventricles of the mammalian telencephalon (Figures 1–3) (Fotowat, Lee, Jun, & Maler, 2019; Lal et al., 2018; Mueller, Dong, Berberoglu, & Guo, 2011; Mueller & Wullimann, 2009; Nieuwenhuys, 2009, 2011; Wullimann & Mueller, 2004; Wullimann et al., 1996). Importantly, general brain regionalization and cellular diversity of the zebrafish brain are not different from other vertebrates, including mammals, and contain diverse glial types (Cosacak et al., 2019; Raj et al., 2018), such as the radial glia also called astroglia (Than-Trong & Bally-Cuif, 2015), microglia (Casano & Peri, 2015), oligodendrocytes (Lyons & Talbot, 2014), and multiciliated ependymal cells (Ringers, Olstad, & Jurisch-Yaksi, 2020), each having a dedicated function in the brain.

In this review, we will discuss the functions of radial glia and astroglia by comparing the knowledge from various animal models, particularly zebrafish and mammals. We aim to take a broad comparative approach and focus on the function of glial cells rather than their molecular markers and anatomical characteristics. Given the absence of star-shaped glial cells in zebrafish, there has been a long-standing idea that zebrafish do not have classical astroglia. We will here challenge this concept based on the evidence that in addition to its neurogenic ability, zebrafish radial glia plays homeostatic roles both at the level of neural circuits and brain barriers. We argue that, from a functional perspective, radial glia cells of zebrafish are in many aspects similar to mammalian astroglia. Thus, the zebrafish radial glia can be termed as astroglia, and should be considered as an ancestral homolog of mammalian radial glia and astroglia combined. In the following sections, we will present further evidences supporting these arguments.

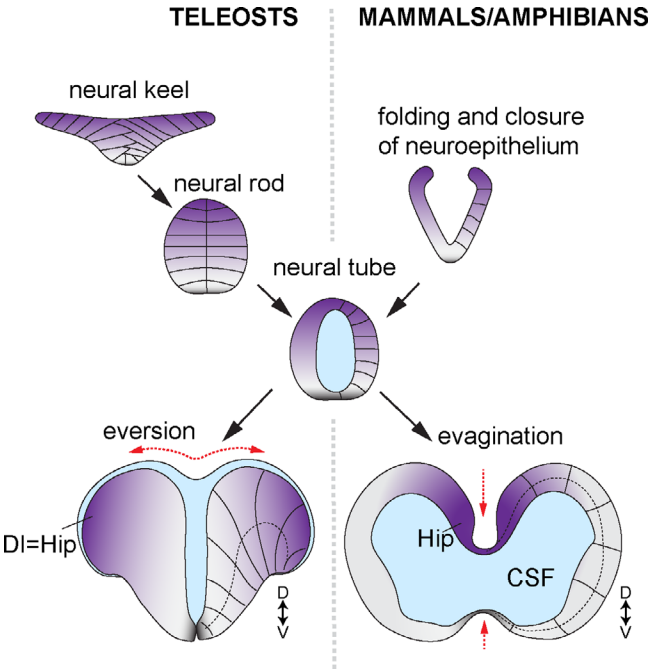

FIGURE 1 Folding of the neural tube in vertebrates. In teleost fish, including the zebrafish, the neuroepithelium organizes in structures known as the neural keel and the neural rode before inflating the ventricles and forming the neural tube. In contrast, the mammalian and amphibian neuroepithelium folds around the ventricles to form the neural tube. As a result, in both teleosts, amphibians and mammals, the neural tube surrounds the CSF-filled ventricles (cyan). Next, the zebrafish telencephalon undergoes an eversion process, unlike the evagination occurring in mammals and amphibians. The folding is indicated by the red arrows. The eversion results in an inverted telencephalon, with the homologous region to the mammalian hippocampus (Dl, Hip) located at the surface of the brain under a unique telencephalic ventricle. D: dorsal, V: ventral

2 | NEUROGENESIS AND NEURAL REGENERATION FROM GLIA

Zebrafish display high neurogenic and regenerative potential and thus has been an experimental model of choice for neural stem cells and neurodegenerative diseases. In the following sections, we will summarize the cellular and molecular aspects of the neurogenic potential of the zebrafish radial glia in comparison with the mammalian radial and astroglia.

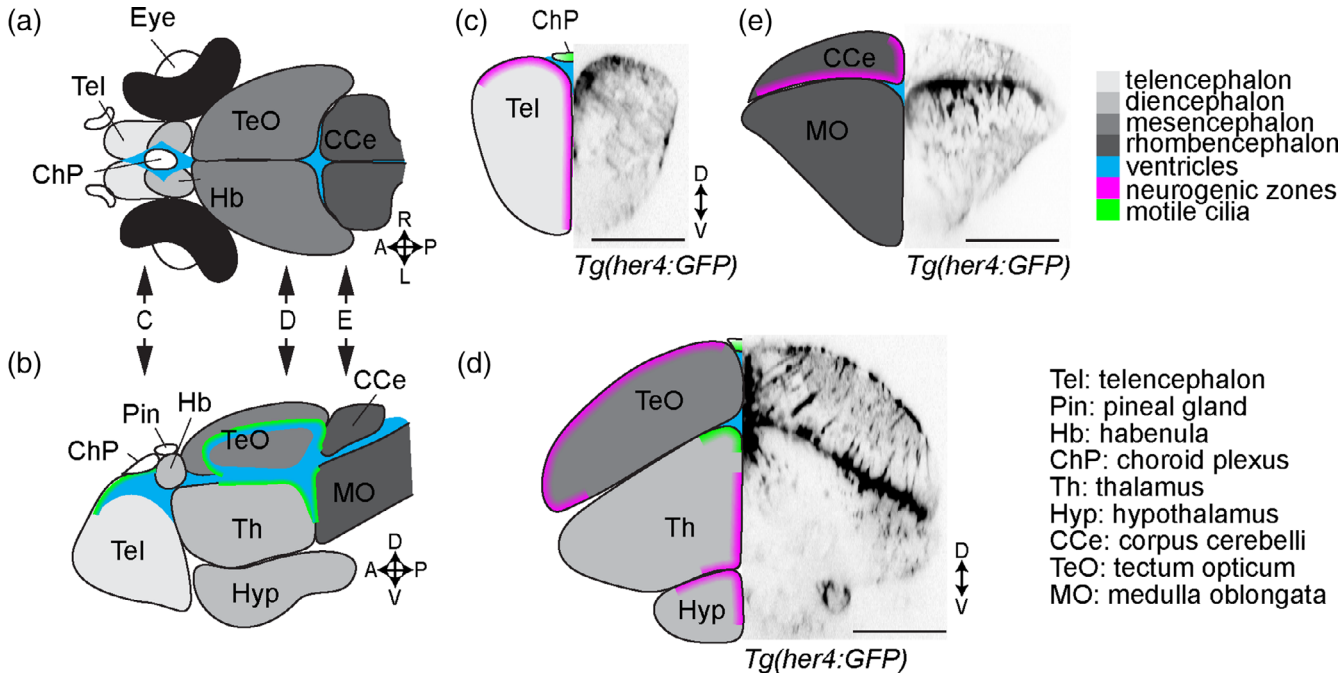

FIGURE 2 Anatomy of the larval zebrafish brain. Schematic representation of a 4–5-day-old larval zebrafish brain seen from dorsal (a), lateral (b), or transverse (c–e) views. Brain areas are represented in different shades of grey, ventricles in blue, neurogenic zones in magenta and motile cilia generating CSF flow in green. (c–e) Transverse sections through the telencephalon (c), di–/mesencephalon (d), and rhombencephalon (e) as indicated in panels (a) and (b) show the various brain regions and the distribution of *Tg(her4:GFP)* positive radial glia (Yeo, Kim, Kim, Huh, & Chitnis, 2007) obtained by confocal microscopy. Note the radial organization of radial glia with their nuclei located along the ventricles and processes reaching the pial surface. A: anterior, P: posterior, D: dorsal, V: ventral, R: right, L: left. Scale bar: 100 μm

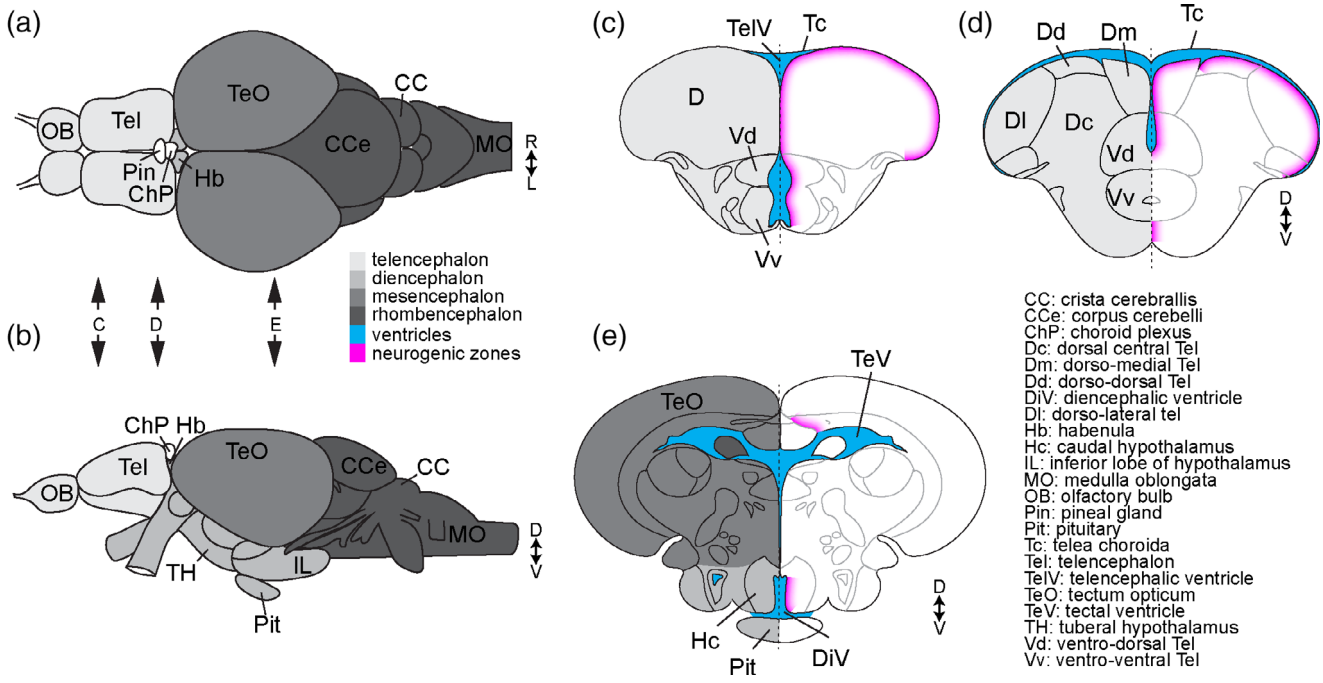

FIGURE 3 Anatomy of the adult zebrafish brain. Schematic representation of the adult zebrafish brain seen from dorsal (a), lateral (b), or transverse (c–e) views. Brain areas are represented in different shades of grey, ventricles in blue, and neurogenic zones in magenta. (c–e) Transverse sections through the anterior (c) and posterior (d) telencephalon and di-/mesencephalon (e) as indicated in panels (a) and (b). Note the wide distribution of neurogenic zones along the telencephalic ventricle. R: right, L: left, D: dorsal, V: ventral

2.1 | Contribution of glia to embryonic and adult neurogenesis

During vertebrate neural development, the neuroepithelium differentiates into glia as the ventricles appear (Pacary, Martynoga, & Guillemot, 2012; Stagaard & Mollgard, 1989). The earliest form of glia is the radial glia, which as its name suggests, spans from the apical ventricular end to the basal layer, often containing blood vessels. Radial glia acts as both neural stem cells, giving rise to neurons and intermediate progenitors, and scaffold cells for the new neurons to migrate over (Götz, 2012) and form cortical layers (Hansen, Lui, Parker, & Kriegstein, 2010; Kriegstein & Alvarez-Buylla, 2009; Lui, Hansen, & Kriegstein, 2011; Molyneaux, Arlotta, Menezes, & Macklis, 2007). Thus, malfunction of radial glia leads to neurodevelopmental disorders, indicating that the glial function is of utmost importance to the development of the brain.

In late embryonic and early post-natal periods of mammals, radial glia detaches from the ventricular region and retracts its processes to generate a stellate structure in the parenchyma. These cells are called astrocytes or astroglia, and the process is named as astrogliogenesis (Alvarez-Buylla, Seri, & Doetsch, 2002; Doetsch, 2003a; Laywell, Rakic, Kukekov, Holland, & Steindler, 2000; Raponi et al., 2007). The neurogenic capacity of glia cells decreases as they progress from radial glia to astrocytes (Doetsch, 2003a; Kriegstein & Alvarez-Buylla, 2009).

During the post-natal stages in mammals, the majority of the astroglia are non-neurogenic although they divide, expand and populate almost the entire central nervous system (Burns, Murphy, Danzer, & Kuan, 2009; Gotz, Sirko, Beckers, & Irmler, 2015; Heins et al., 2002). Yet, some astrocytes are set aside in specific regions of the brain and continue to be neurogenic progenitors throughout life (Doetsch, Garcia-Verdugo, & Alvarez-Buylla, 1997; Goldman & Nottebohm, 1983; Kempermann, van Praag, & Gage, 2000; Steiner, Tata, & Frisen, 2019). Two such regions that are highly studied are located in the forebrain (telencephalon) and are called neural stem cell niches of the subventricular zone (SVZ) of the lateral ventricle and in the dentate gyrus of the hippocampus (Doetsch, 2003a, 2003b; Doetsch, Caille, Lim, Garcia-Verdugo, & Alvarez-Buylla, 1999; Doetsch & Scharff, 2001; Morrens, Van Den Broeck, & Kempermann, 2012; Urban & Guillemot, 2014). In humans, adult neurogenesis is still controversial but many studies are in favor of the presence of newborn neurons in adult human brains (Arellano, Harding, & Thomas, 2018; Boldrini et al., 2018; Ernst et al., 2014; Kempermann et al., 2018; Moreno-Jimenez et al., 2019; Sorrells et al., 2018). These neural stem cell niches generate lineage-restricted neurons, but are not sufficient to generate enough cells to replenish the original network functionality in disease conditions (Eisch et al., 2008; Haughey, Liu, Nath, Borchard, & Mattson, 2002; Kempermann, Krebs, & Fabel, 2008; Phillips, Michell, & Barker, 2006; Rodriguez & Verkhratsky, 2011; Tincer, Mashkaryan, Bhattarai, & Kizil, 2016). In fact, neural stem cells and neural progenitors even reduce their proliferative and neurogenic ability in many brain diseases (Demars, Hu, Gadadhar, & Lazarov, 2010; Mu & Gage, 2011; Rodriguez & Verkhratsky, 2011; Tincer et al., 2016; Waldau & Shetty, 2008; Q. Wang et al., 2006). This might be the reason why mammalian brains are poorly regenerating, and activating the neuroregenerative abilities of neural stem cells are emerging as potential ways to tackle various neurological diseases (Choi & Tanzi, 2019; Gage & Temple, 2013; Im et al., 2010; Kizil, 2018; Kizil & Bhattarai, 2018; Lindvall & Kokaia, 2006; Nato et al., 2015).

The progression of neuroepithelium into astroglia and oligodendrocytes also prevails in zebrafish. However, the degree of astrogliogenesis is lower and glia retains its radial glia identity throughout life (Alunni & Bally-Cuif, 2016; Chapouton & Godinho, 2010; Chapouton, Jagasia, & Bally-Cuif, 2007; Grandel, Kaslin, Ganz, Wenzel, & Brand, 2006; Kizil, Kaslin, et al., 2012). This keeps a larger pool of radial glial cells and neuroepithelium in adult stages, and may explain why the neurogenic ability is more widespread in zebrafish compared with mammals. Zebrafish contains neural stem cell niches that are distributed throughout the whole rostrocaudal axis, which is delineated by the ventricles (Figures 2 and 3; Lam, Marz, & Strahle, 2009; Mueller & Wullimann, 2009; Zupanc, 2008). In many of these brain structures, the newly born neurons are sequentially deposited in layers as described in the telencephalon (Furlan et al., 2017), habenula, and spinal cord (McLean & Fetcho, 2009).

While several regions of the adult zebrafish brain were studied for neurogenic ability (Alunni & Bally-Cuif, 2016; Ito, Tanaka, Okamoto, & Ohshima, 2010; Kizil, Kaslin, et al., 2012; Lam et al., 2009), neural stem cells in the dorsal telencephalon of adult zebrafish brain are the most widely investigated (Adolf et al., 2006; Barbosa et al., 2015; Baumgart, Barbosa, Bally-Cuif, Gotz, & Ninkovic, 2012; Bhattarai et al., 2016, 2020; Coolen, Thieffry, Drivenes, Becker, & Bally-Cuif, 2012; Cosacak et al., 2019; Diotel, Beil, Strahle, & Rastegar, 2015; Dray et al., 2015; Katz et al., 2016; Kizil et al., 2012; Kyritsis et al., 2012; Marz et al., 2010; Marz, Schmidt, Rastegar, & Strahle, 2012; Rodriguez Viales et al., 2015; Than-Trong et al., 2020; Zupanc, 2008). They consist of radial glia, which express the cell proliferation markers proliferating cell nuclear antigen (PCNA) and Mcm5 upon division (Cosacak et al., 2019; Marz et al., 2010). This proliferation of radial glia is called constitutive proliferation, as it Alzheimer's disease continues throughout the life of the organisms albeit reducing in magnitude with aging, and leads to a homeostatic mode of neurogenesis(Alunni & Bally-Cuif, 2016; Kizil, Kaslin, et al., 2012; Than-Trong & Bally-Cuif, 2015; Zupanc, 2008). Notch signaling and associated molecular cascades are among the major determinants of neurogenesis by regulating the balance between quiescence and proliferation (Alunni et al., 2013; Berberoglu et al., 2014; Jiao et al., 2011; Kishimoto, Shimizu, & Sawamoto, 2012; T. Shimizu & Hibi, 2009; Than-Trong et al., 2018) (Coolen et al., 2012; Coolen, Katz, & Bally-Cuif, 2013; Katz et al., 2016). In addition to Notch, hyperglycemic conditions and hormonal signaling through estrogen were also shown to keep radial glial stem cell pool quiescent (Diotel et al., 2013, 2018; Dorsemans, Lefebvre et al., 2017; Dorsemans, Soule et al., 2017; Rastegar et al., 2019). Altogether, it appears that maintaining the

quiescence in adult zebrafish brain is an important way for maintaining the life-long proliferative ability of neural stem cells, as shown also for mouse brains (Costa, Gotz, & Berninger, 2010; Kalamakis et al., 2019; Llorens-Bobadilla et al., 2015; Mizrak et al., 2019; Petrik et al., 2018; Robel, Berninger, & Gotz, 2011; Silva-Vargas, Crouch, & Doetsch, 2013; Silva-Vargas, Maldonado-Soto, Mizrak, Codega, & Doetsch, 2016; Urban et al., 2016).

2.2 | Glial plasticity in response to disease and injury

One fascinating aspect of zebrafish glia is its plasticity response after disease or injuries (Barbosa et al., 2015; Baumgart et al., 2012; Becker et al., 1998; Bhattarai et al., 2020; Cosacak et al., 2017; Cosacak, Papadimitriou, & Kizil, 2015; Fleisch, Fraser, & Allison, 2010; Kizil et al., 2012; Kizil, Kyritsis et al., 2012; Kyritsis, Kizil, & Brand, 2014; Kyritsis et al., 2012; Marz et al., 2012; Mokalled et al., 2016; Y. Shimizu, Ueda, & Ohshima, 2018; Tincer et al., 2016; Zupanc, 2008). Neural stem cells in adult zebrafish brain can also change their mode of division from asymmetric to symmetric after injury (Barbosa et al., 2015). In essence, the tight regulation of quiescence and proliferation balance is a determining factor for regenerative output in adult zebrafish brain and contributes to the maintenance of an effective pools of stem cells that are ready to react to the loss of neurons by neuro-regeneration.

Radial glial cells in the adult zebrafish brain also react to neuronal loss by increasing neural stem cell proliferation and neurogenesis (Bhattarai et al., 2020; Bhattarai, Thomas, Cosacak et al., 2017; Bhattarai, Thomas, Papadimitriou, et al., 2016; Bhattarai, Thomas, Zhang, & Kizil, 2017; Cosacak et al., 2017; Cosacak, Bhattarai, & Kizil, 2020; Cosacak et al., 2019; Kizil, 2018; Kizil & Bhattarai, 2018). In an induced Alzheimer's disease model of adult zebrafish, injection of human amyloid-beta42 into the cerebrospinal fluid (CSF) was shown to form beta-sheet aggregates and lead to inflammation, synaptic degeneration, neuronal death, and cognitive decline (Bhattarai et al., 2017; Bhattarai, Thomas, Papadimitriou, et al., 2016). Interestingly, the zebrafish radial glia responds by inducing the proliferative and neurogenic ability, which is contrary to the mammalian glia in Alzheimer's disease. New neurons are formed and integrated into the circuitry despite the prevalent amyloid toxicity. This regenerative ability is enabled by the neuronal expression of interleukin-4 (IL4), an anti-inflammatory factor, which directly activates a sub-population of radial glial cells through its receptor il4r and intracellular STAT6 signaling (Bhattarai, Thomas, Papadimitriou, et al., 2016) or indirectly through a network of serotonergic neurons, brain-derived neurotrophic factor (BDNF)-producing periventricular neurons, and nerve growth factor receptor (NGFR)-positive neural stem cells (Bhattarai et al., 2020). The neurogenic response after amyloid-beta42 is persistent but reduces in magnitude with aging (Bhattarai, Thomas, Zhang, & Kizil, 2017). These mechanisms indicate a fine balance between homeostatic proliferation and pathology-induced neurogenesis in adult zebrafish brain.

2.3 | Heterogeneity of stem cell pools and radial glia

Stem cell pools in vertebrates were long believed to be a homogenous mass of cells that give rise to diverse cell types within that tissue (Goss, 1991). In the last two decades, several studies from zebrafish and axolotl showed that stem cell pools might be heterogeneous and contain progenitors for specific cell types (Antos & Tanaka, 2010; Kragl et al., 2009; Poss, Keating, & Nechiporuk, 2003; Tanaka & Ferretti, 2009). In the mammalian central nervous system, neural stem cells are heterogenous (Alvarez-Buylla et al., 2002; Codega et al., 2014; Doetsch, 2003a, 2003b; Doetsch et al., 1997; Doetsch, Caille, et al., 1999; Doetsch, Garcia-Verdugo, & Alvarez-Buylla, 1999; Doetsch & Scharff, 2001; Florio et al., 2015; Kalamakis et al., 2019; Llorens-Bobadilla et al., 2015; Mizrak et al., 2019; Pollen et al., 2015; Silva-Vargas et al., 2013). In zebrafish nervous system, few markers were used to label radial glial cells or astroglia (e.g., *GFAP*, *S100b*, *her4.1*, *nestin*). The neurogenic capacity was inferred based on the proliferative status (marked by PCNA or Mcm5) or the prevalent Notch signaling (Baumgart et al., 2012; Bhattarai et al., 2020; Bhattarai, Thomas, Papadimitriou, et al., 2016; Cosacak et al., 2019; Diotel et al., 2015; Grupp, Wolburg, & Mack, 2010; Ito et al., 2010; Kizil, Kyritsis et al., 2012; Lam et al., 2009; Marz et al., 2010; Rodriguez Viales et al., 2015; Topp et al., 2008).

The advance of technology, particularly single-cell transcriptomics, has now brought a novel way to study the heterogeneity of radial glia cells. This approach identified different types of neural progenitor cells after sorting her4.1-positive glial progenitors (Cosacak et al., 2019; Lange et al., 2020). Pre- and proliferating neuroblasts, two of the neural progenitor types identified, contain profoundly different molecular programs suggesting that neuroblasts might significantly change their molecular profiles toward the cell lineage they will differentiate. Indeed, some neuroblast markers can be seen in early neuronal types that indicate a continuum between particular neuroblasts and their lineages (Cosacak et al., 2019). The other clusters of progenitor cells provided further evidence that adult zebrafish brain contain heterogeneous progenitors that react differently to different external cues or insults. In an amyloid-toxicity model of zebrafish brain, only two progenitor cell types located at the dorsomedial region of the adult zebrafish telencephalon enhanced their proliferation (Bhattarai et al., 2020; Cosacak et al., 2019). Combined with highly divergent molecular programs of all neural progenitor cell types in the zebrafish telencephalon, this demonstrated a cellular heterogeneity within the neural stem cell pool. Some progenitors expressed genes related to astroglial functions (e.g., *aldh1l1*, *aldoc*, *ndrg2*) and some expressed ependymal markers (e.g., cilia components), indicating that either some glial are set aside as quiescent and non-neurogenic or these cells co-exist with neurogenic progenitors, represent a certain physiological state, and can be induced to become neurogenic under certain conditions (Cosacak et al., 2019). Another recent single cell transcriptomics study investigated the transcriptional profiles of early newborn neurons (Lange et al., 2020) and confirmed their heterogeneity, as

observed in the previous studies (Bhattarai et al., 2020; Cosacak et al., 2019). Finally, lineage-tracing experiments revealed that the heterogenous adult neural stem cells are hierarchically organized into deeply quiescent and self-renewing reservoir stem cells supporting constitutive neurogenesis across the zebrafish life (Than-Trong et al., 2020). Recently, a fast-growing teleost fish *N. furzerii* (killifish) was shown to contain non-glial progenitors that are rapidly dividing and contributing the quick growth of the brain (Coolen, Labusch, Mannioui, & Bally-Cuif, 2020). Non-glial progenitors were suggested to delay their entry into the quiescence and therefore can contribute to the fast growth needed for the short-living killifish (Coolen et al., 2020). Such heterochrony of neural progenitors might be an underlying determining factor for the neurogenic and regenerative properties of the teleost brains, and can be instrumental in understanding the balance between quiescence and proliferation in health and disease. Hence, understanding the mechanisms of efficient neural regeneration in zebrafish, has the potential to inspire new therapies for various neurodegenerative diseases.

3 | THE ROLE OF ASTROGLIA IN NEURAL CIRCUIT FUNCTION AND ANIMAL BEHAVIOR

Recent evidences highlight important roles of astroglia in regulating neural activity, brain states, and animal behavior, both in vertebrates (Brancaccio, Patton, Chesham, Maywood, & Hastings, 2017) and invertebrates (Ma, Stork, Bergles, & Freeman, 2016). Studies in rodents showed that astroglial cells are highly dynamic components of the brain, which respond to locomotion (Nimmerjahn, Mukamel, & Schnitzer, 2009; Sekiguchi et al., 2016; Slezak et al., 2019) or sensory stimulation (Gu et al., 2018; Slezak et al., 2019) with prominent changes in astroglial calcium levels and can regulate learning (Adamsky et al., 2018; Corkrum et al., 2020) or other state transitions (Bojarskaite et al., 2019; Cui et al., 2018; Oe et al., 2020; Poskanzer & Yuste, 2016) in the brain. Norepinephrine (Bekar, He, & Nedergaard, 2008; Oe et al., 2020; Salm & McCarthy, 1990; Shao & McCarthy, 1997) and acetylcholine (Araque, Martin, Perea, Arellano, & Buno, 2002; Pabst et al., 2016; Takata et al., 2011) are proposed to be the primary triggers for activating astroglia, yet several other molecules including glutamate (Hamilton et al., 2008; Mothet et al., 2005; Sun et al., 2013) play prominent roles in astroglial physiology. Consequently, activating astroglia triggers multiple cellular processes leading to release of gliotransmitters, such as glutamate (Fellin et al., 2004; Parpura et al., 1994; Parri, Gould, & Crunelli, 2001), adenosine triphosphate (ATP) (Newman, 2003; Pryazhnikov & Khiroug, 2008), D-serine (Henneberger, Papouin, Oliet, & Rusakov, 2010) and GABA (Kozlov, Angulo, Audinat, & Charpak, 2006; Lee et al., 2010), which in turn alter neural activity.

Astroglia of the zebrafish brain were proposed to be the homolog of mammalian astrocytes (Grupp et al., 2010; Kizil, Kaslin, et al., 2012; Lyons & Talbot, 2014; Than-Trong & Bally-Cuif, 2015). Despite morphological differences at the first glance (Figure 4), an important finding that sets a parallelism between zebrafish and mammalian astroglia is the presence of glutamate transporter EAAT2 orthologs in Müller glial cells of the retina (Niklaus et al., 2017). This study also demonstrated that perturbing glutamate transporters alter the dynamics of glutamate-mediated neural activity, which is in line with the important role of this transporter for the clearance of excess glutamate by astroglia in mammals (Rothstein et al., 1996). In fact, mice lacking the glutamate transporter EAAT2 exhibit epileptic seizures due to excessive glutamate (Tanaka et al., 1997). In line with this, breakdown of astroglia-neuron interactions during epileptic seizures in zebrafish coincide with an excessive glutamate release (Diaz Verdugo et al., 2019).

Mammalian astroglia form an extensive functional syncytium through gap junctions, which can rapidly redistribute ions, neurotransmitters and other molecules such as ATP across large distances in the brain (Scemes & Spray, 2004; Semyanov, 2019; Volman, Bazhenov, & Sejnowski, 2012). In fact, this strongly coupled network is so effective in redistributing ions and neurotransmitters that mice lacking astrocytic gap junction connexin30 and connexin43 exhibit spontaneous seizures (Wallraff et al., 2006). Similarly, zebrafish astroglial networks have wide-spread gap junction coupling and express connexin43 (Diaz Verdugo et al., 2019). Gap junction coupling of mammalian astroglia was shown to mediate spatio-temporal synchrony of activity across neuronal and astroglial networks (Buskila, Bellot-Saez, & Morley, 2019). Similarly, zebrafish astroglia exhibit highly synchronous activity during distinct neuronal states (Diaz Verdugo et al., 2019). Future studies are needed to better understand the function of gap junction coupling within astroglial networks in zebrafish and in mammals.

Thus, from a molecular point of view, zebrafish radial glia are similar to mammalian astrocytes, and therefore can also be termed astroglia, but does zebrafish astroglia functionally interact with neurons similar to their mammalian counterparts? In fact, a recent study clearly demonstrated that astroglia in larval zebrafish hindbrain are activated by norepinephrine (Mu et al., 2019), similar to mammalian astrocytes (Bekar et al., 2008; Oe et al., 2020; Salm & McCarthy, 1990; Shao & McCarthy, 1997). These results suggest a highly conserved mechanism for recruiting astroglial networks across vertebrates. Moreover, the same study (Mu et al., 2019) also showed that activating hindbrain astroglia in several different ways leads to a transient cessation of neural activity, which is suggested to be mediated through the astroglial activation of GABAergic neurons. In parallel, another recent study (Diaz Verdugo et al., 2019) showed that activating forebrain astroglia using channelrhodopsin2 led to prominent excitation of nearby neurons mediated by glutamate and gap junctions. These results suggest that similar to mammals, zebrafish astroglial and neuronal networks directly communicate with each other via various pathways.

All these results highlight prominent astroglia-neuron interactions in zebrafish, as in mammals. Whether the function of astroglia-neuron communication is conserved across all vertebrates is to be further investigated. However, two recent studies in larval zebrafish suggest clear parallels with mammals, where astroglia-neuron interactions play a direct role in distinct state transitions of neural networks during

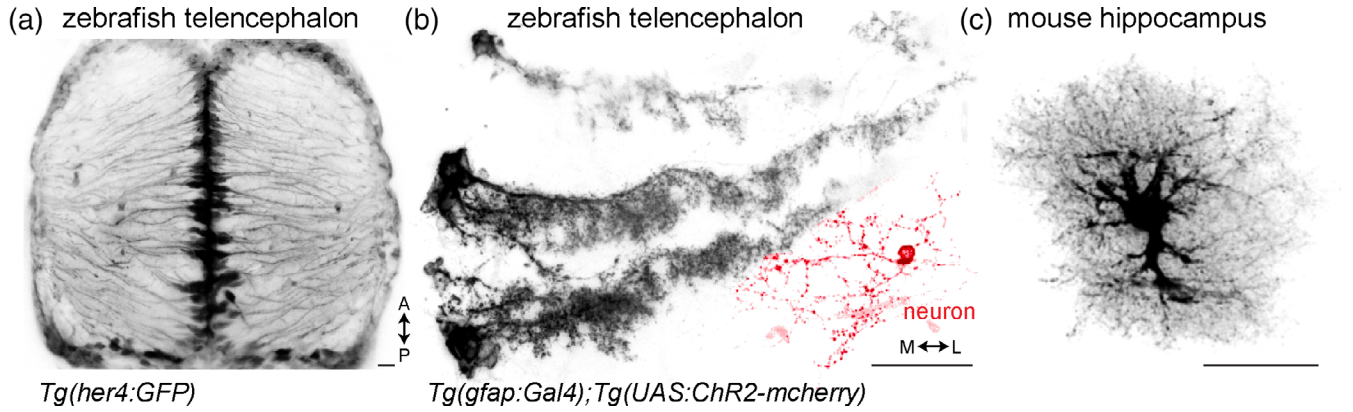

FIGURE 4 Morphology of astroglia in zebrafish versus mammals. (a, b) Confocal microscopy of astroglia in 3–5-week-old juvenile zebrafish telencephalon expressing the cytoplasmic green fluorescent protein (GFP) *Tg(her4:GFP)* (Yeo et al., 2007) or membrane-bound Channel-Rhodopsin2-mCherry *Tg(gfap:Gal4);Tg(UAS:ChR2-mCherry)* (Diaz Verdugo et al., 2019) in astroglia. (a) Astroglia have a radial morphology with their nuclei located at the midline of the telencephalon and their radial processes reaching the pial surface. (b) Sparse expression of membrane-bound Channel-Rhodopsin2-mCherry reveals bushy processes in zebrafish astroglia, similarly to mammalians astrocytes shown in panel C. Note the different morphology of an individual zebrafish telencephalic neuron (red) in comparison with astroglia (black). (c) Dye-filled mouse hippocampal astrocyte from (Wilhelmsson et al., 2006) A: anterior, P: posterior, M: medial, L: lateral. Scale bar: 25 μm

both physiological and pathophysiological states. One of these studies (Mu et al., 2019) showed a clear role for astroglial networks in evidence accumulation and altering neural activity in a way to suppress unsuccessful attempts to swim. Another study (Diaz Verdugo et al., 2019) showed that interactions between astroglia and neurons are not stationary but highly dynamic, and breakdown of these interactions lead to spreading of epileptic seizures. Combined with the previous demonstrations for the functional roles of other glial types in zebrafish (Baraban, Koudelka, & Lyons, 2018; Kegel et al., 2019), all these studies are likely the beginning of a whole series of follow up work to dive deeper into the mechanisms and functions of astroglia-neuron interactions in the zebrafish brain. As in mammalian astrocytes, these interactions are likely to be mediated by multiple processes and molecules that act in parallel, which in turn can serve several roles. Thanks to the transparency, small size, and optogenetic amenability of zebrafish, we are confident that future studies in zebrafish will complement rodent work and provide important insights on the cellular and physiological processes underlying astroglial function for modulating neural activity and animal behavior.

4 | FUNCTION OF GLIA IN BRAIN HOMEOSTASIS AT THE BRAIN BARRIERS AND VENTRICULAR SURFACE

It is well accepted that glial cells play essential roles in brain homeostasis by regulating the content and movement of the fluid surrounding the brain, particularly at the level of the blood–brain barrier (BBB) and at the CSF–brain interface. (Abbott, 2005; Abbott, Pizzo, Preston, Janigro, & Thorne, 2018; Alvarez, Katayama, & Prat, 2013; Fame & Lehtinen, 2020; Jimenez, Dominguez-Pinos, Guerra, Fernandez-Llebrez, & Perez-Figares, 2014). Here, we will specifically review glial contribution at the BBB and the ependyma because (a) astrocytes have been ascribed critical roles in the function of the BBB, and (b) the ependymal layer in zebrafish is primarily made of radial glia and thus different from mammals. By summarizing the similarities and differences at these two brain barriers between the zebrafish and mammalian brains, our aim is to pinpoint evolutionary aspects of how glia may contribute to brain homeostasis.

4.1 | Astroglial feet at the BBB

The BBB separates the brain parenchyma from the blood supply and restricts the passage of solutes and water from the blood, thus maintaining neurons in a controlled environment known as interstitial fluid (ISF) (Abbott, 2005). BBB has been the subject of extensive research mainly due to its impermeability to a range of molecules leading to prevention of proper drug delivery for the treatment of neurological diseases and conditions (Abbott, Ronnback, & Hansson, 2006; Wolak & Thorne, 2013).

The gold standard experiments to assess the function and integrity of the BBB consist of injecting tracers of different size into the blood stream and monitoring their location within the brain parenchyma (Chow & Gu, 2015) together with electron microscopy analyses of the ultrastructure of the BBB. Such experiments revealed the presence of a BBB in many vertebrates including zebrafish (Jeong et al., 2008; Quinonez-Silvero, Hubner, & Herzog, 2020) and even invertebrates (Abbott, 2005). In zebrafish, experiments using dyes of different molecular weight or transgenic reporter proteins revealed that the functional BBB is established at larval stage between 3 and 10 days post-fertilization (dpf) (Fleming, Diekmann, & Goldsmith, 2013; Jeong et al., 2008; O'Brown, Megason, & Gu, 2019; Quinonez-Silvero et al., 2020; Xie, Farage, Sugimoto, & Anand-Apte, 2010). Similar to mammals, the zebrafish BBB is more permeable in specific parts of the brain including circumventricular organs, for

example, the hypophysis (Jeong et al., 2008; Umans et al., 2017), due to the presence of leaky blood vessels known as fenestrated capillaries (Gordon et al., 2019).

The BBB is composed of multiple cell types including endothelial cells, pericytes, and glia, collectively referred to as the neurovascular unit. In most vertebrates, the barrier effect is provided by the endothelial cells which are connected to each other by tight junctions restricting paracellular diffusion (Zihni, Mills, Matter, & Balda, 2016). The tight junction protein Claudin 5 (Greene, Hanley, & Campbell, 2019) is of particular importance as it is highly expressed in the cerebral vessels in rodents (Morita, Sasaki, Furuse, & Tsukita, 1999), humans (Virgintino et al., 2004), and zebrafish from 3 dpf to adulthood (Jeong et al., 2008; van Leeuwen et al., 2018; Xie et al., 2010), and plays a crucial role in the BBB integrity (Nitta et al., 2003). Beside tight junctions, the BBB properties can also be regulated by controlling the endothelial transcytosis, which is a vesicular-based transport across the cells existing in mammals (Ben-Zvi et al., 2014; Chow & Gu, 2015) and zebrafish (O'Brown et al., 2019).

While the endothelium plays a major role in BBB function, pericytes and glia also contribute to the formation and plasticity of the BBB (Alvarez et al., 2013). Indeed, loss of pericytes results in hemorrhages and BBB leakage in zebrafish mutants (Y. Wang, Pan, Moens, & Appel, 2014), similarly to rodents (Armulik et al., 2010). The presence and function of glia at the BBB are more diverse across animals raising some interesting question on the evolution of the BBB and the importance of glial cells in the physiology of the BBB (Abbott, 2005). For instance, in elasmobranch (sharks and rays) and some invertebrates, the BBB is established mainly by a perivascular glial barrier (Abbott, 2005), in contrast to the endothelial barrier of mammals and zebrafish. Importantly, in rodents, astrocytic endfeet ensheat more than two third of the blood vessels in the brain (Korogod, Petersen, & Knott, 2015; Mathiisen, Lehre, Danbolt, & Ottersen, 2010) and plays crucial role in the establishment and modulation of the endothelial barrier properties of BBB (Alvarez et al., 2013).

The presence and function of astroglial endfeet in the BBB of zebrafish remains poorly understood. GFAP-positive processes have been observed next to blood vessels within the brain parenchyma of larval zebrafish at 10 dpf (Fleming et al., 2013) and adults (Jeong et al., 2008). However, the extent of blood vessels coverage is highly reduced in zebrafish, with no apparent ensheating (Fleming et al., 2013; O'Brown et al., 2019) in comparison with mammals (Korogod et al., 2015; Mathiisen et al., 2010). Water transporter aquaporin 4 is highly expressed in mammalian astrocytic endfeet (King, Kozono, & Agre, 2004; Nielsen et al., 1997) and plays key roles in water homeostasis and ISF clearance (Nagelhus & Ottersen, 2013) without affecting BBB integrity (Haj-Yasein et al., 2011). In zebrafish, aquaporin 4 is expressed along the radial extensions of glia, but not compartmentalized within the endfeet as described in mammals (Grupp et al., 2010). Its importance in water homeostasis in the zebrafish brain remains to date poorly studied (Gleiser et al., 2016).

Taken together, these studies suggest both similarities and differences in the identity and function of glial endfeet at the BBB between zebrafish and mammals. At this point, further work is needed to understand the glial contribution to the establishment and function of the zebrafish BBB before further parallelism with the mammalian brain can be made.

4.2 | Glial composition and function of the ependyma

The ependyma is the cellular layer lining the surface of the brain ventricles. In the adult mammalian brain, the ependyma is made primarily of post-mitotic glia-like cells known as multiciliated ependymal cells (Del Bigio, 2010; Jimenez et al., 2014). Ependymal cells, which originate from radial glial cells and differentiate during the perinatal and postnatal periods (Ortiz-Alvarez et al., 2019; Redmond et al., 2019), carry large brushes of cilia on their apical surface that contribute to CSF flow (Faubel, Westendorf, Bodenschatz, & Eichele, 2016; Ringers et al., 2020; Sawamoto et al., 2006; Spassky & Meunier, 2017), similar to multiciliated cells in other organs such as the nose (Reiten et al., 2017), lung epithelium, and reproductive tract (Spassky & Meunier, 2017). Beyond ependymal cells, other cell types of the mammalian ependyma are the glial neurosecretory tanycytes of the hypothalamus (Prevot et al., 2018) and the subventricular neurogenic niche of the lateral ventricles (Doetsch, Caille, et al., 1999; Mirzadeh, Merkle, Soriano-Navarro, Garcia-Verdugo, & Alvarez-Buylla, 2008).

In zebrafish, the ependymal lining is substantially different than in mammals due to the continuous neurogenesis throughout life (Kizil, Kaslin, et al., 2012). In fact, zebrafish ependyma resembles the ependyma of embryonic mammalian brain with mainly radial glia and neuroepithelial cells located at the ventricular surface (Dirian et al., 2014; Galant et al., 2016; Ganz, Kaslin, Hochmann, Freudenreich, & Brand, 2010; Ito et al., 2010). Multiciliated cells akin the ependymal cells of mammals have only been reported in adult zebrafish brain, along the ventral telencephalic and diencephalic ventricles (Kishimoto et al., 2011; Ogino et al., 2016), the telea choroida located on the top of the telencephalic ventricle (Lindsey, Darabie, & Tropepe, 2012; Ogino et al., 2016), and the medulla oblongata of the brainstem (Grimes et al., 2016; Konjikusic et al., 2018), where they generate a directional CSF flow (Grimes et al., 2016; Ogino et al., 2016). Interestingly, the ventricles of the optic tectum appear to be devoid of multiciliated cells (Corbo & Fulop, 2020). Taken together, these anatomical differences call for caution when denominating cells lining the zebrafish ventricle as ependymal cells, since ependymal cells in mammals usually refers to multiciliated cells lining the ependyma.

In the adult zebrafish telencephalon, radial glia cells harbor a single cilium that extend into the ventricular cavity (Kishimoto et al., 2011; Ogino et al., 2016), similarly to the neuroepithelium of the embryonic brain of mouse (Paridaen, Wilsch-Brauninger, & Huttner, 2013) and zebrafish (Borovina, Superina, Voskas, & Ciruna, 2010; J. N. Hansen et al., 2020; Olstad et al., 2019), and the neural stem cells of the SVZ (Mirzadeh et al., 2008). The cilium of progenitors is in direct contact with CSF, which provides the niche and growth factors necessary for the stem cells to retain their stemness

(Fame & Lehtinen, 2020; Lehtinen et al., 2011; Silva-Vargas et al., 2016). Interestingly, Kishimoto et al. observed that the cilia of radial glia on the adult telencephalic wall have a 9 + 2 microtubule organization (Kishimoto et al., 2011), which is mostly observed in motile cilia (Ringers et al., 2020) and suggest that these cilia may be motile. These cells may therefore have flow-producing properties similar to the motile monociliated cells of the larval zebrafish brain ventricles (Fame, Chang, Hong, Aponte-Santiago, & Sive, 2016; Olstad et al., 2019; van Leeuwen et al., 2018) and spinal cord (Kramer-Zucker et al., 2005; Ringers et al., 2020; Sternberg et al., 2018; Thouvenin et al., 2020). Of note, motile monociliated cells described at larval zebrafish are not radial glia, but instead, they constitute other cell types (Olstad et al., 2019; van Leeuwen et al., 2018). Altogether, these findings suggest that the zebrafish ependyma undergoes some important transformations between 5 days of age and adulthood, yet the mechanisms and impact of such changes remain unknown.

In mammals, multiciliated ependymal cells are connected by adherence junctions, which maintain the integrity of the ependyma (Jimenez et al., 2014). Since they lack tight junctions (Fame & Lehtinen, 2020), the ependyma of the mammalian adult brain allows the diffusion of molecules and water between ISF and CSF (Abbott, 2005; Abbott et al., 2018; Ghersi-Egea, Finnegan, Chen, & Fenstermacher, 1996; Pizzo et al., 2018). Moreover, mammalian ISF-CSF exchange is suggested to be enhanced by other mechanisms including the convection of CSF in the perivascular spaces (Abbott et al., 2018; Pizzo et al., 2018; Rennels, Gregory, Blaumanis, Fujimoto, & Grady, 1985; Wardlaw et al., 2020) driven by the cardiac cycle (Mestre et al., 2018), and the glia-dependent glymphatic system (Abbott et al., 2018; Iliff et al., 2012). As a result, the CSF and ISF are considered to be of similar composition. Yet, the dynamics of exchange of molecules between CSF and ISF may vary according to their molecular properties, such as size, interactions with extracellular matrix of the brain parenchyma, binding to specific receptors, aggregation state (e.g., amyloid plaques), and permeability through the BBB (Abbott et al., 2018; Jimenez et al., 2014; Wolak & Thorne, 2013). Other factors may also influence the accessibility of molecules to specific location of the brain parenchyma and include the distance from the CSF filled cavities and properties of the brain barriers (Abbott et al., 2018; Ghersi-Egea et al., 1996; Jimenez et al., 2014; Pizzo et al., 2018; Prevot et al., 2018).

In zebrafish, little is known about the circulation of ISF and CSF in the adult brain, beside the characterization of the anatomy of the brain ventricles (Figure 3) (Wullimann et al., 1996), the identification of motile ciliated cells generating fluid flow (Fame et al., 2016; Grimes et al., 2016; Kishimoto et al., 2011; Konjikusic et al., 2018; Lindsey et al., 2012; Ogino et al., 2016; Olstad et al., 2019; Ringers et al., 2020; van Leeuwen et al., 2018) and the description of brain lymphatic endothelial cells scavenging molecules from the brain (Shibata-Germanos et al., 2020; van Lessen et al., 2017). In fact, there is very limited knowledge on the existence of perivascular space allowing ISF-CSF exchange or glymphatic system, on the anatomy of arachnoid and meningeal structures, on the physiological properties of the mature ependyma and choroid plexus, and the glial contribution to these processes. It is very likely that CSF and ISF are distributed across the zebrafish brain through non-ventricular ways, similarly to mammals. This is supported by results obtained upon the injection of dyes or amyloid peptide at the surface of the optic tectum under the skull which reach the distant telencephalic ventricular wall within 10 min (Kizil & Brand, 2011) before diffusing into the brain parenchyma (Bhattarai et al., 2016). Yet, the mechanisms underlying this large-scale transport of molecules across the brain parenchyma remain poorly understood. It may involve canals and gating structures as identified on the tectal ventricle (Corbo & Fulop, 2020) or other mechanisms that remain to be discovered. In fact, most of our knowledge of CSF circulation in zebrafish comes from the study of the larval brain, where various physiological factors contributes to the movement of CSF within the brain ventricles, such as ciliary beating, heartbeat (Fame et al., 2016; Olstad et al., 2019), and bodily movement (Olstad et al., 2019). It is important to note that at those early developmental stages up to 4 dpf, the CSF system is not fully developed. The choroid plexus is not yet functional (Bill & Korzh, 2014) and most of the CSF may be produced by neuroepithelial cells (Fame, Cortes-Campos, & Sive, 2020; Fame & Lehtinen, 2020; Lowery & Sive, 2005) or diffuse through the leaky BBB (O'Brown et al., 2019). Thus, it is expected that major changes happen in the physiology of brain barriers as the animal develops and the brain matures.

Altogether, our understanding of the brain barriers in the zebrafish remains limited. The evidences from other animal models and humans supporting the involvement of glia at the brain barriers in the physiology of the brain in health and disease therefore call for further work addressing these important questions in the zebrafish. We emphasize that understanding how glia contribute to the overall ependymal function in the highly neurogenic zebrafish may reveal novel function of the brain-CSF interface in neurogenesis with therapeutically benefits for human diseases.

5 | OPEN QUESTIONS AND OPPORTUNITIES

5.1 | Radial glia/astroglia in zebrafish: How similar are they to mammalian astroglia?

Radial glia/astroglia of the zebrafish brain were proposed to be the homologue of mammalian astrocytes (Grupp et al., 2010; Kizil, Kaslin, et al., 2012; Lyons & Talbot, 2014; Than-Trong & Bally-Cuif, 2015). While growing number of evidences are supporting this thought, zebrafish astroglia are also in many ways similar to radial glia of mammals (Kizil, Kaslin, et al., 2012; Marz et al., 2010) and therefore often called radial glia, rather than astroglia. The radial glia/astroglia in zebrafish express markers of mammalian astrocytes (e.g., S100beta, Gfap) and serve many functions of the mammalian astrocytes, reviewed in Section 3. While most of the studies in zebrafish radial glia/astroglia focused on the contribution of these cell class in neural development (reviewed in Section 2), several

recent works showed extensive parallels between zebrafish radial glia/astroglia and mammalian astroglia. Most radial glia/astroglia a in zebrafish exhibit morphological characteristics of mammalian radial glia with radial extensions form the ventricular surface to the pial surface (see Figures 2 and 4a). However, these radial extensions are also decorated with diffuse processes that are somewhat similar to mammalian astrocytes (Figure 4b,c) Moreover, star-shaped cells labeled by glial markers that morphologically resemble mammalian astrocytes were shown in zebrafish (Kawai, Arata, & Nakayasu, 2001) and in other teleost fish (Alunni et al., 2005). Similarly, we also observed star-shaped astroglia especially at later developmental stages in the forebrain of juvenile (4 weeks old) and adult zebrafish (*unpublished data*).

Given the diversity of markers labeling distinct radial glial populations in zebrafish brain (Cosacak et al., 2019; Lange et al., 2020), it is reasonable to name some zebrafish radial glial populations as astroglia, based on their functional role in regulating brain activity and homeostasis. We propose that naming the astroglial subpopulations should be based on both functions and genetic markers as this will improve comparative analysis across animal species. For this, we call for further work in identifying specific functions and markers for the diverse populations of mammalian (Batiuk et al., 2020; Bayraktar et al., 2020) and zebrafish (Cosacak et al., 2019; Lange et al., 2020) astroglia recently characterized by single cell transcriptomics.

5.2 | Can we learn from zebrafish glia how to tweak the mammalian glia?

Zebrafish has a unique chance to teach us the molecular and cellular programs by which we can modulate mammalian glia for various clinical applications. These include increasing neurogenesis in neurodegenerative diseases, modulating the immune response in traumatic injury, regulating brain activity via neuro, and gliotransmitters, tackling disorders through regulation of content and distribution of CSF, or validating drugs in a pre-clinical setting.

The studies on adult zebrafish brain have already provided important new candidates through which the mammalian glial cells could be made more proliferative and neurogenic (Cosacak et al., 2020; Cosacak et al., 2015; Gama Sosa, De Gasperi, & Elder, 2011; Kizil, 2018; Kizil & Bhattarai, 2018; Lieschke & Currie, 2007; Tincer et al., 2016). For instance, IL4, initially identified in zebrafish, enhanced proliferation and neurogenesis of human neural stem cells in 3D human neural stem cell (NSC) cultures, and induced Alzheimer's disease model (Papadimitriou et al., 2018) similar to zebrafish (Bhattarai et al., 2020; Bhattarai, Thomas, Cosacak, et al., 2016). Alternatively, zebrafish was utilized for drug development as pre-clinical models for neurodegenerative diseases (Reinhardt et al., 2019). It is important to note that comparative studies revealed difference in neurogenic responses in mammalian models following specific cues identified in zebrafish. For example, type 1 IL signaling obliterated astroglia in mouse brains (Mashkaryan et al., 2020) and *gata3* failed to induce a neurogenic output after traumatic injuries despite enhanced neurogenic capacity (Celikkaya et al., 2019). Likewise, BDNF fails to enhance neural stem cell or astrocyte proliferation in mouse brains during homeostatic and Alzheimer's disease (AD) conditions (Bhattarai et al., 2020; Choi et al., 2018). Taken together, these comparative studies suggest that the neuron–glia interactions that make pathology-induced neuroregeneration possible in zebrafish brain culminate a complex interplay between immune system, astroglia and neurons, which are lost in mammalian brains and led to the poor neuroregenerative ability. Thus, we are confident that by further understanding the difference between zebrafish and mammalian models, we will not only reveal key molecular and cellular processes underlying brain development and physiology, but also pave the way for novel clinical paradigm for brain diseases in human.

5.3 | Limitations and opportunities

Zebrafish is evolutionarily related to humans and around 70% of the protein-coding genes in humans have orthologues in zebrafish (Howe et al., 2013). Despite this similarity, zebrafish is still a distant vertebrate to humans. Some physiological, cellular and molecular aspects of astroglia might differ between zebrafish and humans considering even rodents cannot fully recapitulate certain aspects of human physiology (Hodge et al., 2019; Qiu et al., 2016). It is too early to jump to conclusions from zebrafish studies for mammalian systems, yet comparative studies that will be undertaken will significantly increase the value of new findings both in rodents and in zebrafish.

Advantages that can be attributed to zebrafish includes its easy maintenance, established genetic and molecular biology techniques, large repertoire of transgenic lines, transparent embryonic development that allows extensive imaging, large and interactive community that embraces more than 1,500 laboratories around the world, extraordinary regenerative ability in almost all tissues, and 3R compatible experimental procedures. Besides, investigations of neural circuit activity in zebrafish have been very effective in elucidating neural computations underlying animal behavior. Neural circuit research has been spearheaded by the discovery of genetically encoded fluorescent reporters and improved imaging techniques enabling functional imaging of the whole zebrafish brain with single cell resolution (Ahrens et al., 2012; Kim et al., 2017; Marques, Li, Schaak, Robson, & Li, 2020; Vladimirov et al., 2014). Together with whole brain connectome (Hildebrand et al., 2017), single-cell transcriptomics profiling of neurons (Raj et al., 2018) and glia (Cosacak et al., 2019; Lange et al., 2020), and knowledge on the identities, morphologies, and long-range projections of cell populations (Kunst et al., 2019), it is now possible to study the function and development of neuronal networks in an entire vertebrate brain with single cell resolution. Moreover, registration of transgenic and experimental brains on standardized atlases (Kunst et al., 2019; Randlett et al., 2015; Tabor et al., 2019) enables scientists to identify neuronal populations involved in specific behaviors (Haesemeyer, Robson, Li, Schier, & Engert, 2018; Randlett et al., 2015; Wee et al., 2019) or

TABLE 1 Studying the brain in zebrafish and mammals

	Zebrafish	Mammals
Neural tube patterning	Eversion (large ventricular surface, accommodates glia)	Invagination (small ventricular surface)
Genetic tools	Advanced, easy to perform large numbers of transgenics	Advanced, generation of transgenics costly
Maintenance	Easy, cost-effective	Difficult, cost-intensive
Behavioral analyses	Expanding number of assays	Well established
Neuroregeneration	Extensive, majority of neuronal types can regenerate	Poor, very limited regenerative ability
Neural stem cells	Widespread rostrocaudally	Restricted locations in the forebrain
Response to neurodegeneration	Activation of astroglia, neuroregeneration	Gliotic response, scar formation, low neurogenic ability
Neural circuits	The architecture and the functional units of the vertebrate brain are evolutionarily conserved	
Functional imaging and opto-/chemogenetics	Expanding number of tools and approaches are available for detailed in vivo investigations and optical and chemical perturbations	
Single cell transcriptomics	Established tools available	
Heterogeneity of neural stem cells	Heterogenous, co-existence with non-neurogenic astroglia	
Astroglia-neuron interactions	Present, associated with sensory processing, locomotion, learning, epilepsy, and so forth	
Neurotransmitter release/uptake in glia	Glutamate transporter EEAT2 mediates glutamate clearance	
Neurotransmitter responsiveness in glia	Present, mediates neuron–glia interactions	
Gap junctions in glia	Gap junctions mediate small molecule transport across glia	
Neurovascular unit	Present, astroglial contribution poorly understood	Present
Cellular composition of ependyma	Primarily radial glia and neuroepithelial cells, some motile ciliated cells	Primarily glia and neuroepithelial cells (prenatal), primarily multiciliated ependymal cells (postnatal)
Ependymal cells	Present, monociliated (larvae), multiciliated (adult)	Present, multiciliated
Choroid plexus	Present, complexity not well understood	
Fluid circulation of CSF	Present, complexity not well understood	

diseases (Thyme et al., 2019) in an unbiased manner. Beside investigations at larval stages, recent studies at juvenile zebrafish (2–5 weeks) showed that this relatively transparent (Fore, Cosacak, Verdugo, Kizil, & Yaksi, 2019) development stage allows non-invasive imaging (Jetti, Vendrell-Llopis, & Yaksi, 2014; Vendrell-Llopis & Yaksi, 2015) and exhibit cognitively demanding behaviors such as learning (Palumbo, Serneels, Pelgrims, & Yaksi, 2019; Valente, Huang, Portugues, & Engert, 2012; Yashina, Tejero-Cantero, Herz, & Baier, 2019) and social interactions (Dreosti, Lopes, Kampff, & Wilson, 2015; Hinz & de Polavieja, 2017; Larsch & Baier, 2018; Tunbak, Vazquez-Prada, Ryan, Kampff, & Dreosti, 2020). Altogether, we are certain that applying the wide range of methodologies described above to measure and interfere with astroglia activity will reveal exciting findings on the mechanisms and dynamics underlying neuro-glia interactions in the context of complex behaviors and brain diseases.

In conclusion, as summarized in Table 1, zebrafish emerged as an exciting and promising model organism for many fields of neuroscience, and glia biology of zebrafish has been rising above the horizon in these last years. We argue that this tiny teleost fish has the potential to provide important insights into the role of astroglia in development, homeostatic physiology, and complex diseases as a reductionist vertebrate model, thus paving the way to new paradigms relevant for humans.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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