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REVIEW

Adult neurogenesis in the central nervous system of teleost fish: from stem cells to function and evolution

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ABSTRACT

Adult neurogenesis, the generation of functional neurons from adult neural stem cells in the central nervous system (CNS), is widespread, and perhaps universal, among vertebrates. This phenomenon is more pronounced in teleost fish than in any other vertebrate taxon. There are up to 100 neurogenic sites in the adult teleost brain. New cells, including neurons and glia, arise from neural stem cells harbored both in neurogenic niches and outside these niches (such as the ependymal layer and parenchyma in the spinal cord, respectively). At least some, but not all, of the stem cells are of astrocytic identity. Aging appears to lead to stem cell attrition in fish that exhibit determinate body growth but not in those with indeterminate growth. At least in some areas of the CNS, the activity of the neural stem cells results in additive neurogenesis or gliogenesis – tissue growth by net addition of cells. Mathematical and computational modeling has identified three factors to be crucial for sustained tissue growth and correct formation of CNS structures: symmetric stem cell division, cell death and cell drift due to population pressure. It is hypothesized that neurogenesis in the CNS is driven by continued growth of corresponding muscle fibers and sensory receptor cells in the periphery to ensure a constant ratio of peripheral versus central elements. This 'numerical matching hypothesis' can explain why neurogenesis has ceased in most parts of the adult CNS during the evolution of mammals, which show determinate growth.

KEY WORDS: Teleost fish, Brown ghost knifefish, Zebrafish, Adult neurogenesis, Neural stem cells, Tissue growth

Introduction

Much of the twentieth century was dominated by the notion that neurogenesis in the vertebrate brain ceases at the time of birth, or shortly thereafter. This view began to be challenged in the 1960s, and only at the beginning of the twenty-first century was the idea of adult neurogenesis (see Glossary) generally accepted. In 1961, Kirsche and Kirsche reported that the optic tectum of crucian carp (*Carassius carassius*) can regenerate by production of new cells. One year later, Altman (1962) showed that, after brain lesions in adult rats, numerous mitotic cells are generated, including some that morphologically resemble neuroblasts and neurons. Subsequent studies by Altman and co-workers indicated that adult neurogenesis also takes place in the intact brain – in rodents specifically in the subgranular zone (see Glossary) of the dentate gyrus of the hippocampus and in the anterior part of the ventricular-subventricular zone (see Glossary) of the lateral ventricle from where the young cells migrate via the rostral migratory stream into the olfactory bulb (Altman, 1969; Altman and Das, 1965). In addition to these 'classical' neurogenic sites, in more recent years adult-born neurons have also been detected in several other regions of the mammalian brain (see Table 1).

However, the ideas of both Kirsche and Altman were met with great skepticism and remained largely ignored over the three decades following their discoveries. During this period, much of the progress in the area of adult neurogenesis resulted from studying the song system of birds (for review, see Nottebohm, 2002) and the optic system of teleost fish (for reviews, see Hitchcock et al., 2004; Otteson and Hitchcock, 2003). It was only after new studies employing modern cell biological techniques confirmed Altman's findings (Lois and Alvarez-Buylla, 1994; Luskin, 1993), and stem cells (see Glossary) were isolated from the adult central nervous system (CNS) of mice (Reynolds and Weiss, 1992; Richards et al., 1992), that the notion of constitutive generation of neurons in the adult mammalian brain become widely accepted. Subsequently, labeling of S-phase cells with the thymidine analog 5-bromo-2′-deoxyuridine (BrdU) (see Glossary) was introduced as a new standard technique for the study of adult neurogenesis, using glass knifefish (*Eigenmannia* sp.) (Zupanc and Zupanc, 1992); the entirety of neurogenic areas in the brain of brown ghost knifefish (*Apteronotus leptorhynchus*) was mapped (Zupanc and Horschke, 1995); and adult stem cells were isolated from the brain of brown ghost knifefish (Hinsch and Zupanc, 2006). These three achievements opened new avenues for the study of adult neurogenesis in teleost fish. The complete mapping of neurogenic sites in the brain of zebrafish (*Danio rerio*) (Grandel et al., 2006; Zupanc et al., 2005) introduced this species as an additional model for the study of adult neural stem cells.

In the following, I will summarize what is known about the identity, properties, distribution and dynamics of adult neural stem cells in the CNS of teleost fish, as well as the development of their progeny and the consequences of this process at the tissue level. I will discuss how mathematical and computational modeling can contribute to a better theoretical understanding of adult neurogenesis, and how a comparative approach can help us to gain some insight into the evolution of this phenomenon. Finally, I will consider several questions that, despite their fundamental biological importance, have remained unanswered.

At this point, it is important to note that there is a huge number of teleost fish species, but adult neurogenesis has only been investigated in a minute subset of these (Fig. 1). Most of the research in this area has focused on zebrafish and brown ghost knifefish. Zebrafish have become a premier model for genetics, biomedical research and developmental biology, including the study of adult neurogenesis, since the pioneering early work of Streisinger et al. (1981) and the subsequent large-scale screens for mutants conducted by the laboratories of Christiane Nüsslein-Volhard and Wolfgang Driever (for a personal essay, see Nüsslein-Volhard, 2012). Knifefishes (order Gymnotiformes) have been an important model in neurobiology, biochemistry, molecular biology and neuroethology for over eight decades (for review, see Zupanc

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Glossary

Additive neurogenesis
Net increase through neurogenesis in the number of neurons.
Adult neurogenesis
Process of generation of new functional neurons during adult development.
Apoptosis
Type of cell death characterized by cell shrinkage, chromatin condensation, DNA fragmentation and membrane blebbing; it is distinguished from necrosis by the absence of tissue inflammation. Apoptotic cell death occurs commonly during development to eliminate supernumerary cells.
Asymmetric stem cell division
Mitotic division of a stem cell to produce two daughter cells with different cellular fates – one clone of itself and a second daughter cell destined to develop into a differentiated cell.
BrdU labeling
Labeling of proliferating cells through incorporation of the thymidine analog 5-bromo-2′-deoxuridine (BrdU) during the S-phase of the cell cycle. BrdU-labeled cells can be detected in tissue sections through immunohistochemical techniques.
Chimera
A single organism composed of cells from two or more individuals differing in their genotypes.
Contact inhibition
A regulatory mechanism involved in the control of cellular proliferation and other developmental events by sensing the local cell density in tissue.
Cytogenesis
The formation and development of cells.
Differentiation
The process by which young, immature cells develop into specific cell types distinguished by form and function.
Ependymal layer
Layer of epithelial cells that line the ventricles of the brain and the central canal of the spinal cord.
Hyperplasia
Muscle growth due to the production of muscle fibers.
Hypertrophy
Muscle growth due to an increase in the size of already existing muscle fibers.
Lurcher mutant mice
Mice with a mutation in a gene encoding a glutamate receptor subunit. This gene is expressed predominantly by Purkinje cells in the cerebellum. The mutation converts the receptor into a leaky cation channel, thereby resulting in a chronic depolarization of the cell. In heterozygous lurcher mice, virtually all Purkinje cells have disappeared by three months of age, paralleled by subsequent (secondary) degeneration of other cell types, including granule cells in the cerebellum and neurons in the inferior olive.
Myotube
A cylindrical muscle fiber formed by fusion of myoblasts during development.
Negligible senescence
The absence of senescing with age, including a lack of reproductive senescence and cellular or functional deterioration due to intrinsic causes.
Neurogenic niche
Area in the CNS that harbors neural stem cells at high densities. It is often associated with vascular, ventricular and central-canal systems. Molecular signals derived from the circulating blood and/or the cerebrospinal fluid contained in the ventricles and the central canal are likely to play a pivotal role in the regulation of mitotic activity of the stem/progenitor cells in the neurogenic niche.
Neurosphere
A clonal cluster of spherical shape that is formed, under specific cell-culture conditions, by the progeny of a single neural stem (or progenitor) cell.
Pia
Also known as the pia mater. The innermost of the three meninges that envelope the brain and spinal cord.
Progenitor cell
An early descendent of a stem cell that can undergo only a limited number of mitotic divisions and whose tendency to differentiate increases with each cell division. In practice, it is often difficult to distinguish between stem cells and progenitors. Hence, sometimes the combined term ‘stem/progenitor cells’ is used.
Pulse–chase assay
An assay in which a label is used to follow the dynamics of a cellular process or pathway. For example, mitotic cells can be labeled with a single pulse of BrdU, followed by a variable chase period during which these cells are not exposed to BrdU. Analysis of the labeled cells after different chase periods enables investigators to reconstruct the development of the newborn cells over time.
Radial glia
Specialized glial cells that are characterized by long radial processes. These serve multiple purposes, including acting as stem cells and guiding migrating young neurons to their target sites.
Staggerer mutant mice
Mice with a deletion in a gene encoding a nuclear hormone receptor in mice. This mutation leads to degeneration of the majority of Purkinje cells in the cerebellum and a rudimentary morphology of the surviving cells. Loss of cerebellar granule cells and olivary neurons is secondary, and thought to be the result of the absence of Purkinje cells, which in wild-type mice serve as the targets of neuronal projections arising from the former two cell types.
Stem cell
A cell capable of producing, through cell division, clones of itself and, under certain physiological conditions, cells that have lost this self-renewing capacity and differentiate into specific cell types.
Subgranular zone
A thin band of cells between the granule cell layer and the hillus of the dentate gyrus of the hippocampus. It harbors adult neural stem cells that give rise to dentate granule neurons.
Symmetric stem cell division
Mitotic division of a stem cell to produce two identical copies of itself.
Ventricular-subventricular zone
A neurogenic region located along the walls of the lateral ventricles of the adult brain in rodents. The name reflects its similarity to the embryonic ventricular zone and subventricular zone. Immature neurons born during adulthood in the ventricular-subventricular zone migrate rostrally into the olfactory bulb, where they differentiate into functional interneurons.

and Bullock, 2005). All species in this taxonomic order are distinguished by their ability to produce electric discharges with an electric organ. In the brown ghost knifefish this electric organ is formed by massively enlarged axonal terminals (referred to as electrocytes) of modified spinal motoneurons (called electromotor neurons) (Bennett, 1971; de Oliveira-Castro, 1955; Waxman et al., 1972). The electric organ produces discharges that are used for orientation (‘electrolocation’) and communication (‘electrocommunication’). The frequency of the electric organ discharges is controlled by oscillations of a pacemaker nucleus in the brainstem, and their amplitude is determined by the number and geometry of the electrocytes. Brown ghost knifefish become sexually mature at around 1 year of age, and then experience seasonal cycles of gonadal recrudescence and regression. They exhibit indeterminate growth, continuing to grow after sexual maturation.

Neurogenic areas in the CNS

Several thousand research papers and review articles published since Altman’s (1962) initial discovery have firmly established the existence of adult neurogenesis in the mammalian brain, yet have also suggested that this phenomenon is restricted to a few regions in this taxon (Table 1). By contrast, several dozen neurogenic regions (discussed in more detail below) appear to exist in the adult teleostean brain, as indicated by comprehensive brain mapping in a number of taxonomically diverse species, including brown ghost

Table 1. Adult neurogenesis in the mammalian central nervous system

Neurogenic area	Location and identity of adult neural stem/progenitor cells	Development	Proposed functional involvement of adult-born neurons	Reference
Hippocampus	RG in the subgranular zone of the dentate gyrus.	RG give rise to transit-amplifying progenitor cells, which, in turn, generate neuroblasts. The latter migrate a short distance into the granule cell layer of the dentate gyrus, where they differentiate into dentate granule neurons. In addition, RG give rise to glial cells.	Learning, memory, cognitive flexibility, pattern separation, regulation of emotional status.	Gonçalves et al. (2016); Kempermann et al. (2015); Toda and Gage (2018).
V-SVZ of lateral ventricles/ olfactory bulb	RG located in V-SVZ.	RG give rise to transit-amplifying progenitors, which divide a few times to produce neuroblasts that continue to undergo mitosis. The neuroblasts enter the RMS, where they form a chain and migrate to the olfactory bulb. Within the olfactory bulb, they differentiate into different types of interneurons.	Olfactory discrimination, sexual behavior.	Obernier and Alvarez-Buylla (2019).
V-SVZ/striatum	Two hypotheses: (i) neuroblasts derived from RMS; (ii) resident astrocytes or neural progenitors in striatum.	The newly generated neurons develop into GABAergic interneurons, a portion of which express calretinin and neuropeptide Y.	?	Farzanehfar (2018); Inta et al. (2015).
Hypothalamus	In the periventricular zone of the third ventricle, the neurogenic cells appear to be of tanycyte identity. The existence in the hypothalamic parenchyma of neurogenic cells that proliferate under physiological conditions is controversial.	The tanycytes are thought to give rise to progenitors, which, in turn, generate neuroblasts. The latter differentiate into mature neurons.	Metabolism, energy balance, weight regulation.	Migaud et al. (2016); Yoo and Blackshaw (2018).
Cortex	Several investigations have failed to reproduce earlier findings that indicated the existence of adult-born neurons in various parts of the cortex. There is some evidence that immature neurons in the adult cortex represent a reservoir of cells generated perinatally.	Studies that found evidence for newly generated neurons in the adult cortex indicated that at least some of them have a transient existence.	?	Nacher and Bonfanti (2015).

RG, radial glia-like cells; V-SVZ, ventricular-subventricular zone; RMS, rostral migratory stream.

knifefish (Zupanc and Horschke, 1995), three-spined stickleback (*Gasterosteus aculeatus*; Ekström et al., 2001), zebrafish (Grandel et al., 2006; Zupanc et al., 2005), Mozambique tilapia (*Oreochromis mossambicus*; Teles et al., 2012) and killifish (*Austrolebias* sp.; Fernández et al., 2011).

Among the neurogenic areas of the teleostean brain, the cerebellum is likely to harbor the largest number of adult-born cells. In brown ghost knifefish, ∼75% of adult-born cells in the brain are generated in the cerebellar subdivisions (Zupanc and Horschke, 1995). Notably, other neurogenic areas in the brains of teleosts include the olfactory bulb and the posterolateral region of the dorsolateral telencephalon (the latter is thought to be homologous to the mammalian hippocampus; Braford, 1995; Butler, 2000; Nieuwenhuys and Meek, 1990; Northcutt, 1995; Northcutt and Braford, 1980; Portavella et al., 2004; Rodríguez et al., 2002; Vargas et al., 2000). This observation suggests that the generation of new neurons in the olfactory bulb and in structures homologous to the mammalian hippocampus is conserved across vertebrates.

The only species in which a comprehensive quantitative cellular analysis of adult neurogenesis in the spinal cord has been performed, combined with three-dimensional reconstruction, is the brown ghost knifefish (Sîrbulescu et al., 2017). New cells arise from stem cells in specialized parts at its caudal end; the ependymal layer (see Glossary) around the central canal, and the parenchyma, which extends from the ependymal layer radially to the surface of the pia (see Glossary; Fig. 2). Qualitatively, a similar distribution of adult neural stem cells in the spinal cord has been reported for goldfish (Takeda et al., 2008) and rats (Horner et al., 2000). Unlike in teleosts, in rats, the neural stem cells in both the ependymal layer and the parenchyma give rise to astrocytes and oligodendrocytes only, but not to neurons (Beattie et al., 1997; Frisén et al., 1995; Horky et al., 2006; McTigue et al., 1998; Prayoonwiwat and Rodriguez, 1993; Yamamoto et al., 2001). Nevertheless, neuronal differentiation (see Glossary) can be induced *in vitro* (Yamamoto et al., 2001) or by transplanting stem cells to a suitable environment, such as the hippocampus (Shihabuddin et al., 2000). Thus, these cells have neurogenic potential, suggesting a continuity in the distribution of stem cells in the adult spinal cord across vertebrate taxa.

A comparison of cell proliferation rates

The differences between mammals and teleosts in adult neurogenesis are reflected by differences not only in the number of neurogenic areas but also in the number of newborn cells and the rate at which they are produced. The first vertebrate species in which

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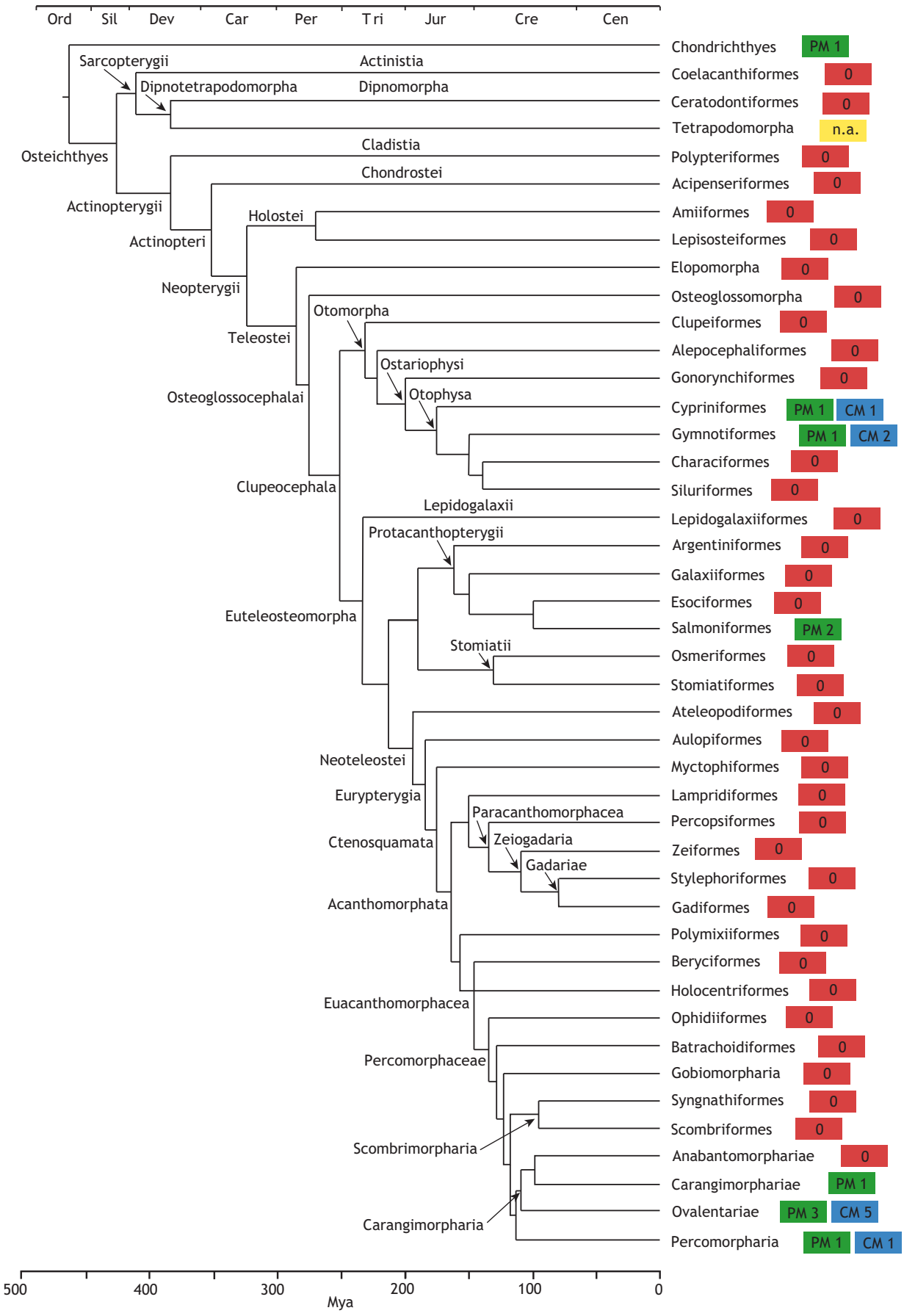

Fig. 1. See next page for legend.

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Fig. 1. Overview of research on adult neurogenesis in fishes. The number of species for which partial mapping (PM; green boxes) or complete mapping (CM; blue boxes) of neurogenic regions in the adult brain has been carried out is indicated for each terminal clade (order or supraordinal taxon) in the phylogenetic tree, with the exception of Tetrapodomorpha, for which the literature has not been analyzed (n.a., yellow box). The phylogenetic classification is based on molecular and genomic data (Betancur-R. et al., 2013, 2017). Divergence times can be related to the geological time periods or eras shown along the top of the phylogenetic tree (Ord, Ordovician; Sil, Silurian; Dev, Devonian; Car, Carboniferous; Per, Permian; Tri, Triassic; Jur, Jurassic; Cre, Cretaceous; Cen, Cenozoic), or to the time scale shown below the tree (Mya, million years ago). Mappings are categorized as 'complete' if neurogenic areas have been described in detail throughout the neuroaxis of the brain, and at least some analysis of the identity of the stem cells and their progeny has been performed. If only select brain region(s) of a species have been examined, and/or the development of the progeny of mitotically dividing cells has not been further characterized, the mapping is considered to be 'partial'. Terminal clades in which adult neurogenesis has not been studied in any species are indicated by red boxes with a '0'. Of the estimated 32,000 living fish species (Nelson et al., 2016), adult neurogenesis has been studied in 19 species, concentrated in 7 of the 43 terminal clades shown. They are: *Scyliorhinus canicula* (PM) among Chondrichtyes (Docampo-Seara et al., 2020); *Carassius auratus* (PM) (Delgado and Schmachtenberg, 2011; Otteson et al., 2001) and *Danio rerio* (CM) (Grandel et al., 2006; Zupanc et al., 2005) among Cypriniformes; *Eigenmannia* sp. (PM) (Zupanc and Zupanc, 1992), *Apteronotus leptorhynchus* (CM) (Zupanc and Horschke, 1995) and *Gymnotus omarorum* (CM) (Olivera-Pasilio et al., 2017) among Gymnotiformes; *Oncorhynchus masou* (PM) (Pushchina et al., 2013) and *Oncorhynchus mykiss* (PM) (Ausas et al., 2019) among Salmoniformes; *Scophthalmus maximus* (PM) (Taboada et al., 2018) among Carangimorphariae; *Odontesthes bonariensis* (PM) (Strobl-Mazzulla et al., 2010), *Oryzias latipes* (PM) (Kuroyanagi et al., 2010), *Nothobranchius furzeri* (PM) (Tozzini et al., 2012), *Austrolebias charrua* (CM) (Fernández et al., 2011; Torres-Pérez et al., 2017), *Austrolebias affinis* (CM) (Fernández et al., 2011), *Austrolebias reicherti* (CM) (Fernández et al., 2011), *Oreochromis mossambicus* (CM) (Teles et al., 2012) and *Astatotilapia burtoni* (CM) (Maruska et al., 2012) among Ovalentariae; and *Sparus aurata* (PM) (Zikopoulos et al., 2000) and *Gasterosteus aculeatus* (CM) (Ekström et al., 2001) among Percomorpharia.

the overall cell proliferation rate was determined in the adult brain was the brown ghost knifefish (Zupanc and Horschke, 1995). As revealed by BrdU labeling, 100,000 cells on average enter mitotic S-phase within a given 2 h period in this organism. This represents ∼0.2% of all brain cells. Similar proliferation rates have been estimated in the zebrafish brain (Hinsch and Zupanc, 2007). In mammals, estimations of cell proliferation rates have been obtained only for individual neurogenic brain regions. In adult mice, ∼30,000 cells a day are produced in the ventricular-subventricular zone (Lois and Alvarez-Buylla, 1994). This represents 0.03% of the estimated 110 million cells (Williams, 2000) in the adult mouse brain. Adult rats are thought to produce 9000 cells a day in the dentate gyrus of the hippocampus (Cameron and McKay, 2001). This represents 0.003% of the ∼330 million cells (Herculano-Houzel and Lent, 2005) in the adult rat brain. In the human dentate gyrus, it has been estimated that ∼700 new neurons are produced per day, equivalent to 0.004% of the neuronal population in the human brain (Spalding et al., 2013).

These figures suggest that the rate of cell proliferation in the adult brain is, qualitatively, significantly higher in brown ghost knifefish and zebrafish (and possibly teleosts in general) than in rodents and other mammals. However, quantitative interpretation of these inter-taxa differences is not currently possible, given that proliferation rates may be affected by differences in cell cycle times in different regions of the CNS and/or of the age of the animals used in different studies (see 'Age-related changes in the dynamics of adult neurogenesis', below), as well as by the lack of standardization of mitotic cell labeling protocols and data analysis. However, with the recent development of standardized mitotic cell labeling, tissue processing and data analysis protocols (Lindsey et al., 2017; Zhao and van Praag, 2020), it is likely that at least some of these difficulties will be overcome in the foreseeable future.

Although the rates of constitutive cell proliferation in the adult teleostean CNS are remarkably high, they can be further increased by both endogenous and exogenous factors. Among these factors, a particularly strong modulator is injury. Studies in brown ghost knifefish and zebrafish have shown that neurogenesis induced by experimental lesions plays a key role in rebuilding tissue lost to injury and in recovery of function (for reviews, see Kizil et al., 2012; Sîrbulescu and Zupanc, 2011; Sîrbulescu and Zupanc, 2013; Zupanc, 2019; Zupanc and Sîrbulescu, 2013). In the cerebellum, dorsal telencephalon and spinal cord of zebrafish and brown ghost knifefish, mitotic rate begins to increase 1 day after injury and peaks after ∼1 week (Ayari et al., 2010; Dervan and Roberts, 2003; Kishimoto et al., 2012; Kroehne et al., 2011; Kyritsis et al., 2012; März et al., 2011; Reimer et al., 2008; Sîrbulescu et al., 2009; Takeda et al., 2008; Zupanc and Ott, 1999). In the cerebellum of brown ghost knifefish, the rate of cell proliferation returns to normal by 2 weeks post-lesion (Zupanc and Ott, 1999); by contrast, in the spinal cord after tail amputation, baseline levels of proliferation are still not achieved after 7 weeks (Sîrbulescu et al., 2009).

Neural stem cells as sources of adult-born cells

Teleostean neural stem cells are the source of adult-born cells, and they have been isolated from the brains of brown ghost knifefish (Hinsch and Zupanc, 2006) and zebrafish (Lopez-Ramirez et al., 2016). Under the correct culture conditions, these isolated cells can form neurospheres (see Glossary), produce differentiated cells (including both neurons and glia; Fig. 3), and self-renew through mitotic division. These characteristics are representative of true stem cells (Doe et al., 1998; Gage, 2000; Temple, 2001; Weiss et al., 1996; Weissman et al., 2001).

Live imaging and lineage tracing of adult stem cells in the zebrafish telencephalon revealed that these cells divide rarely; the majority stay quiescent for several weeks (Barbosa et al., 2015; Dray et al., 2015; Lange et al., 2020). As in mammalian neurogenic zones (Bonaguidi et al., 2011; Doetsch et al., 1999; Laywell et al., 2000; Seri et al., 2001) (Table 1), many of the adult neural stem cells in the teleostean brain assume properties of radial glia (see Glossary). In brown ghost knifefish, such stem cells, identified by expression of the stem cell marker Sox2, co-express the astrocytic markers S100, glial fibrillary acidic protein (GFAP) and vimentin in both the medullary pacemaker nucleus (Sîrbulescu et al., 2014) and the cerebellum (Sîrbulescu et al., 2015) (Fig. 4). However, although in the pacemaker nucleus almost all Sox2-immunopositive cells co-express the radial glial marker S100, in the cerebellum, only about half of the Sox2-immunopositive cells express this marker. It is unclear whether these two cellular populations correspond to the two lineages of adult stem cells previously identified in the zebrafish brain (Kaslin et al., 2009, 2013). One of these two lineages is derived from ventricular zone progenitor cells (see Glossary) on the ventral side of the fourth ventricle and expresses glial markers. The other originates from upper rhombic lip progenitors located on the dorsomedial part of the fourth ventricle that are of epithelial origin and characterized by nestin expression. Stem cells are similarly heterogeneous in terms of their cellular identity in the spinal cord. In brown ghost knifefish, only half of the Sox2-immunopositive spinal cord cells co-express S100 (Sîrbulescu et al., 2017), thus lending support to the notion that, besides the glia-like

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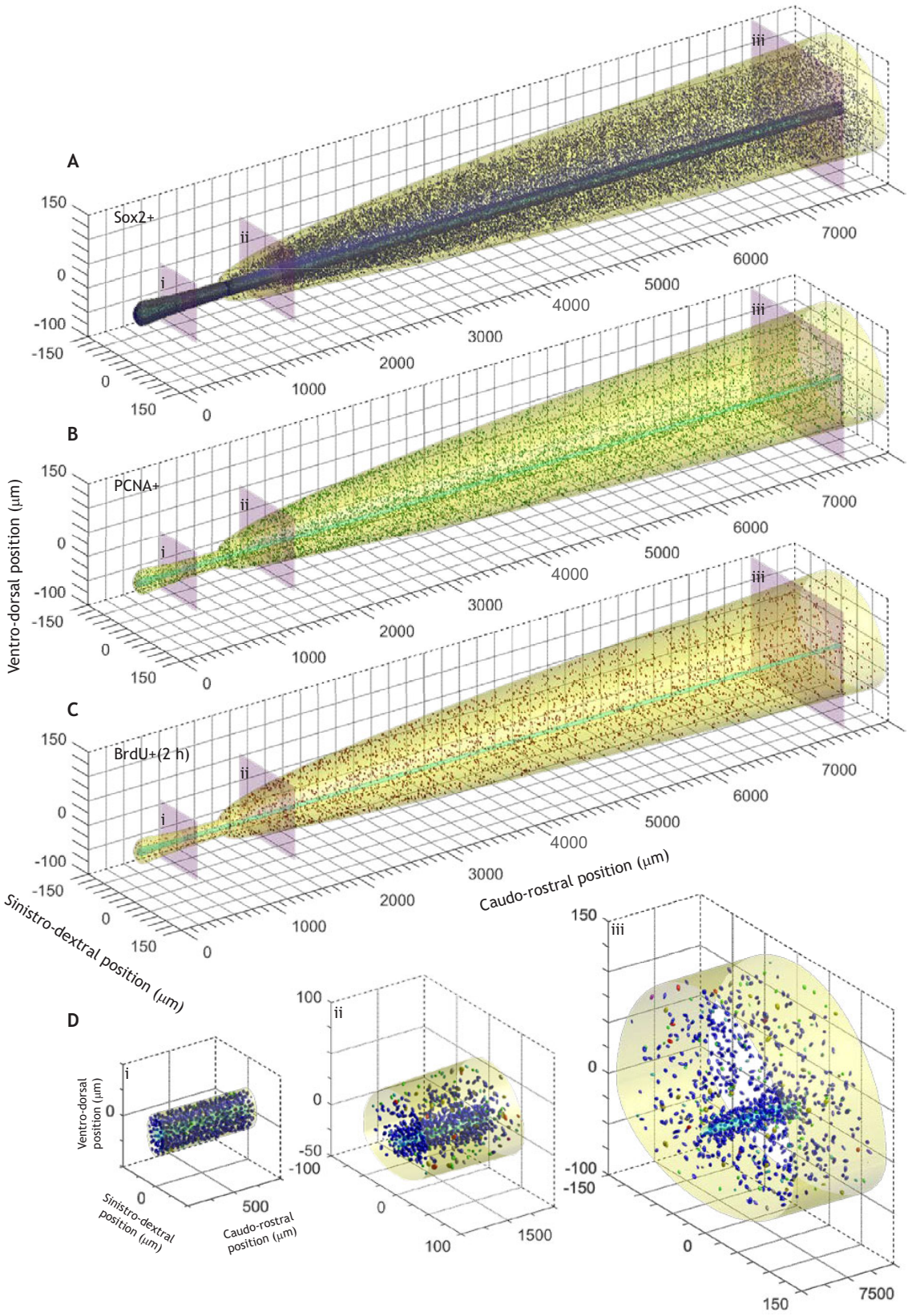

Fig. 2. Distribution of stem cells and proliferating cells in the caudal-most 8 mm of the adult spinal cord of brown ghost knifefish. The 3D distribution of these cells was determined using a statistical mapping approach. (A) Cells expressing the stem cell marker Sox2. (B) Proliferating cells expressing proliferating cell nuclear antigen (PCNA, a protein involved in DNA replication). (C) Proliferating cells labeled with a single pulse of BrdU, followed by a 2 h chase. (D) Planes i, ii and iii show close-up views of 100 μm thick transverse sections at the three positions indicated in A–C. Individual markers and marker combinations are represented as follows: blue, Sox2+; green, PCNA+; red, BrdU+; teal, Sox2+/PCNA+; dark yellow, PCNA+/BrdU+; purple, Sox2+/BrdU+; gray, Sox2+/PCNA+/BrdU+. From Sîrbulescu et al. (2017).

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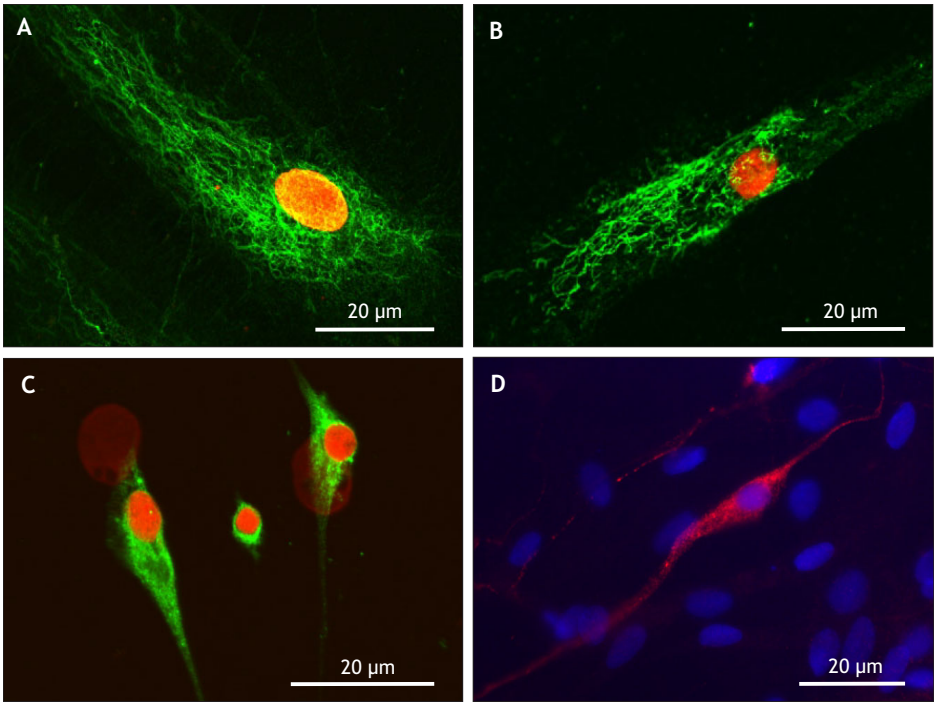

Fig. 3. Differentiated progeny of adult neural stem cells isolated from the brain of brown ghost knifefish. These stem cells are pluripotent; their progeny can differentiate into two major cell types in the CNS: neurons and glia. (A) Glial fibrillary acidic protein (GFAP)-immunopositive astrocyte. (B) Vimentin-immunopositive glial cell. (C) Hu C/D-expressing neuron. (D) Microtubule-associated protein 2 (MAP2) (2a+2b)-immunoreactive neuron. Nuclei were stained with either propidium iodide (red) or 4′6-diamidino-2-phenyl-indole-dihydrochloride (DAPI) (blue). From Hinsch and Zupanc (2006).

Sox2-expressing stem cells, there is at least one additional Sox2-immunopositive stem cell population characterized by the lack of S100 expression.

After stem cell division, one of the resulting daughter cells becomes more committed toward a non-stem cell fate (e.g. neuron or glial cell), and it typically leaves its neurogenic niche (see Glossary). Such a transit-amplifying progenitor performs symmetric or asymmetric stem cell divisions (see Glossary), amplifying the number of differentiated cells produced. In the cerebellum of both zebrafish and brown ghost knifefish, several of these divisions occur (Fig. 4) (Sîrbulescu et al., 2015; Zupanc et al., 2005). By contrast, in the dorsal telencephalon of zebrafish, the amplification appears to be minimal, with at most one or two divisions (Furlan et al., 2017; for review, see Labusch et al., 2020; Rothenaigner et al., 2011).

There is some controversy about the identity of the intermediate progenitor cells that amplify the progeny of adult radial glial stem cells in the dorsal telencephalon of zebrafish. Based on live imaging, Dray et al. (2015) proposed that the intermediate progenitors are primarily non-radial glial precursors; however, single-cell sequencing in the zebrafish telencephalon (Lange et al., 2020) suggests that cells with radial glia characteristics assume this role.

Development of the progeny of adult neural stem/progenitor cells

In this section, I will discuss four pillars of the further development of the progeny of the adult stem cells: cellular migration, differentiation, survival and death. None of these is unique to adult neurogenesis in the teleostean CNS – they are the cornerstones of adult and embryonic neural development across all vertebrate taxa.

Migration

In the teleostean CNS, adult development involves migration of newborn cells in some regions, whereas in others there is no indication of active migration. For example, newborn cells in the optic tectum do not migrate. Here, most of the adult-born cells arise at the caudal pole, where they remain during subsequent development (Candal et al., 2005; Ekström et al., 2001; Grandel et al., 2006; Mansour-Robaey and Pinganaud, 1990; Meyer, 1978; Nguyen et al., 1999; Raymond and Easter, 1983; Wullimann and Puelles, 1999; Zupanc et al., 2005). Consequently, the optic tectum grows asymmetrically from its caudal end.

Absence of active migration does not necessarily result in absence of any movement of cells. In the spinal cord of brown ghost knifefish, stem cells are found at high densities in the ependymal layer, and at much lower densities (although higher absolute numbers) in the adjacent parenchyma (Sîrbulescu et al., 2017). Computational modeling has suggested that the stem cells in the parenchyma originate from the ependyma, having drifted radially away from the latter as a result of population pressure (Lehotzky et al., 2021) (see also ‘Mathematical and computational modeling of stem cell-driven tissue growth’, below).

Active migration during adult development has been demonstrated in the cerebellum of several teleostean species, including brown ghost knifefish (Zupanc et al., 1996, 2012), zebrafish (Grandel et al., 2006; Zupanc et al., 2005) and Mozambique tilapia (Teles et al., 2012). In the corpus cerebelli, most of the new cells arise from stem cells in the molecular layer, from where they migrate into the granular layer (Fig. 4). In the course of their migration, the young cells are guided by radial glial fibers (Fig. 5) (Zupanc and Clint, 2003; Zupanc et al., 2012). Most of these fibers co-express GFAP and vimentin, similar to radial glia in rodents, along which neurons migrate during early brain development (for review, see Cameron and Rakic, 1991).

Differentiation

What types of cells do the progeny of the adult neural stem cells in the teleostean CNS develop into? Immunohistochemical staining, combined with a pulse–chase assay (see Glossary) using BrdU, has demonstrated that in the adult brain of zebrafish, ∼50% of new cells born 9 months earlier express the neuron-specific marker protein Hu (Hinsch and Zupanc, 2007; Zupanc et al., 2005). These neurons are especially common in the dorsal telencephalon, including the area

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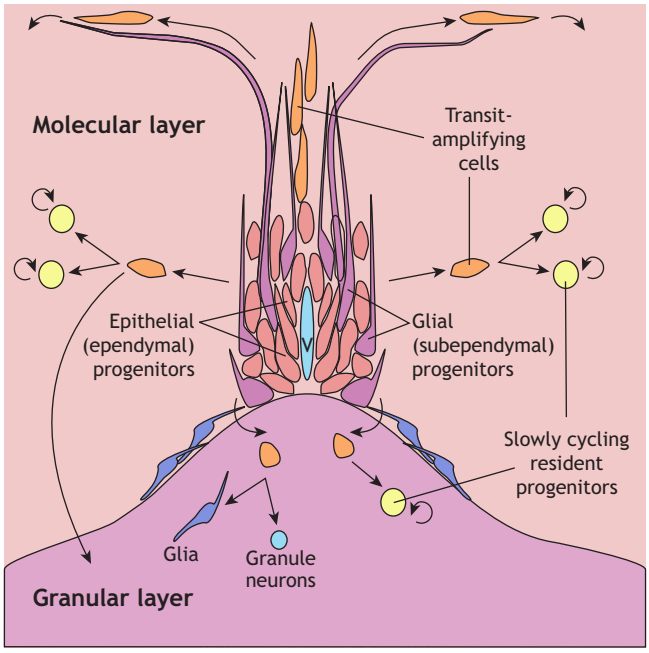

Fig. 4. Model of the developmental dynamics of the neural stem/progenitor cells in the corpus cerebelli of brown ghost knifefish. Stem and progenitor cells comprise a heterogeneous population in the neurogenic niche, which is formed by the area around the remnant of the ventricle (V) at the midline of the cerebellum. Around half of these cells do not express glial markers; they are thought to be ependymal (or epithelial) and are situated immediately next to the lumen of the ventricle. The other cells express glial markers; they are thought to be equivalent to subependymal radial glia. All of these stem/progenitor cells (those which express glial markers and those which do not) produce progenitors that are more fate restricted. These progenitors undergo a few mitotic divisions while moving away from the neurogenic niche, thus acting as transit-amplifying cells. Most of the new cells migrate along particular routes, often guided by radial glia, until – after a period of ~5–10 days – they reach the granule cell layer. Presumably, most of the progeny originating from the neurogenic niche in the corpus cerebelli eventually differentiate into granule cell neurons and glia. However, some of them appear to remain undifferentiated and continue to express stem cell markers. These cells form a quiescent resident progenitor cell population in both the molecular and granular layers. From Sîrbulescu et al. (2015).

thought to be homologous to the mammalian hippocampus. The radial glia-like stem cells in the ventricular zone of this area give rise to neurons that migrate a short distance into the adjacent periventricular zone, where they develop into glutamatergic projection neurons (Furlan et al., 2017; Ganz et al., 2012, 2010; Kroehne et al., 2011; Lange et al., 2020). In the ventral telencephalon, a second population of neural progenitors exists that are distinguished by expression of nestin. Their progeny undergo long-distance migration into the telencephalic parenchyma and develop into GABAergic interneurons (Ganz et al., 2012, 2010; März et al., 2010).

In the cerebellum, most new cells differentiate into granule cell neurons (Fig. 4) (Kaslin et al., 2009; Zupanc et al., 2005, 1996), the most abundant cell type not only in the cerebellum but also in the entire brain. In the corpus cerebelli, Hu is expressed when the migrating immature cells reach the granular layer (Zupanc et al., 2012). The new granule cells then develop axonal projections from the granular layer into the molecular layer (Zupanc et al., 2005, 1996), suggesting that they integrate into the cerebellar neural network.

Overall, in the adult brain of zebrafish (and probably other teleosts), neurogenesis dominates over gliogenesis; however, in certain brain regions, the majority of the newly generated cells may differentiate into glia. For example, in the pacemaker nucleus of brown ghost knifefish (which determines the frequency of electric organ discharge), stem cells give rise to new cells that differentiate into astrocytes and small interneurons at a ratio of 4:1 (Sîrbulescu et al., 2014). It is thought that the dominance of gliogenesis in the pacemaker nucleus is part of a glial mechanism that evolved as an adaptation to the high-frequency oscillations (at frequencies of up to 1000 Hz) generated throughout the fish's life (for reviews, see Zupanc, 2017a, 2020). Neurons constituting the oscillatory network are embedded in a dense meshwork of astrocytes (Zupanc et al., 2014). A major function of these astrocytes might be to buffer excess potassium ions that accumulate in the extracellular space during the continuous high-frequency firing (Zupanc, 2017a, 2020).

Cell death and survival

There is ample evidence from studies of brain systems that apoptosis (see Glossary) is a key mechanism for regulation of cell numbers during both embryonic and adult development. In the cerebellum of brown ghost knifefish and Mozambique tilapia, apoptotic cell death occurs in waves, both after the initial stem cell division and after each of the subsequent rounds of mitosis performed by the progenitor cells (Sîrbulescu et al., 2015; Teles et al., 2012; Zupanc et al., 1996). Most of the apoptosis takes place in the target areas of the migrating young cells (for example, in the corpus cerebelli in the granular layer) (Soutschek and Zupanc, 1996). Similar mechanisms have been observed in mammals during embryonic development (for reviews, see Raff, 1992; Raff et al., 1993). It appears that cell death is largely due to the failure of the young cells to properly connect with other neurons at their target site and a lack of specific survival factors produced by other cells in the region. In three teleostean species (brown ghost knifefish, zebrafish and Mozambique tilapia), approximately half of the newborn cells present at 10 days of age survive long term, and probably for the rest of the fish's normal life span (Hinsch and Zupanc, 2007; Ott et al., 1997; Teles et al., 2012; Zupanc et al., 2005, 1996).

Age-related changes in the dynamics of adult neurogenesis

In mammals, the relative rates of cell proliferation and neuronal differentiation in the hippocampus decline exponentially with age (Amrein et al., 2011). In rodents, cell proliferation in the hippocampal dentate gyrus is reduced 5- to 10-fold over the first half of adult life (Amrein et al., 2004; Ben Abdallah et al., 2010; Rao et al., 2005, 2006). Similarly, the rate of neuronal differentiation decreases 6- to 40-fold over the same period (Aizawa et al., 2011; Morgenstern et al., 2008; Rao et al., 2005, 2006).

In teleost fish, the effect of age on stem cell dynamics appears to depend on the organism's overall body growth. Some teleosts exhibit determinate body growth, characterized by rapid growth during juvenile stages but cessation of any significant further growth after reaching puberty, whereas other species display indeterminate body growth, distinguished by continued growth beyond puberty and until the end of life. Examples of fishes with determinate growth are some killifish (order Cyprinodontiformes), which live in ephemeral ponds and flood plains (Blažek et al., 2013; Genade et al., 2005). These fish typically survive for less than 1 year in their natural habitat, and they display age-related degenerative changes of the body, eyes and scales (Liu and Walford, 1969; Walford and Liu, 1965). The short-lived turquoise killifish (*Nothobranchius furzeri*), shows a 5-fold decrease in mitotic activity in the germinal layer of the optic tectum of aged individuals compared with young adults (Tozzini et al., 2012). Similarly, there is a marked age-related decline in adult-born

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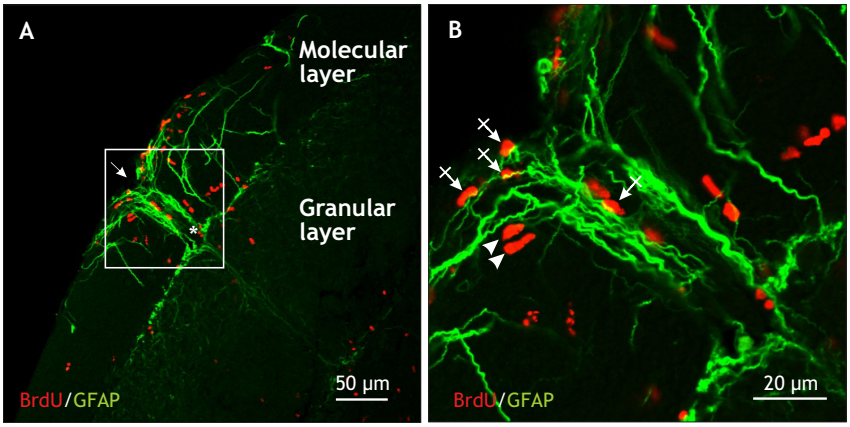

Fig. 5. Guidance by radial glia of adult-born cells in the cerebellum of brown ghost knifefish. (A) The confocal image depicts the dorsal tip (asterisk), a neurogenic niche at the interface of the granular layer and molecular layer in the corpus cerebelli. Stem cells in this niche give rise to new cells (labeled with BrdU; red), which are shown here at 2 days of age. They migrate along radial glial fibers (immunostained against GFAP; green) that emerge from the dorsal tip to run parallel to the midline (arrow) in the dorsal direction, but then bifurcate immediately underneath the pial surface to continue their course in a lateral direction in each hemisphere. (B) Magnified view of the boxed area in A. Several of the migrating young cells are either closely apposed to (arrowheads) or partially overlapping with (arrows with cross), the radial glial fibers. From Zupanc et al. (2012).

neurons in the ventricular zone of the telencephalon and the olfactory bulb of zebrafish, which also exhibits determinate growth of the body (Singleman and Holtzman, 2014). The decrease in neuronal numbers is associated with an increase in the number of radial glia-like progenitor cells entering quiescence (Edelmann et al., 2013). The reduction in adult neurogenesis occurs alongside impairments in cognitive ability in aging zebrafish (Yu et al., 2006).

This age-related decline in adult neurogenesis of teleosts with determinate body growth contrasts with the situation in brown ghost knifefish. As discussed above, this fish shows indeterminate growth not only of the body (Ilieş et al., 2014) but also of the brain (Zupanc and Horschke, 1995) and spinal cord (Sîrbulescu et al., 2017). In its brain, there is no evidence for any significant age-related decline in the absolute levels of stem cell proliferation, neuronal and glial differentiation, nor are there age-related changes in the long-term survival of newborn cells, or in the amount of GFAP or the number of apoptotic cells (Traniello et al., 2014). These features are hallmarks of species exhibiting negligible senescence (see Glossary). Such organisms are characterized by continued growth beyond sexual maturation and lack of reproductive senescence, even though their lifespans may be finite (Finch, 1990). It has been hypothesized that such indeterminate growth protects against senescence (Bidder, 1932).

Global consequence of adult neurogenesis: tissue growth and behavioral function

What are the consequences of adult neurogenesis at the tissue level? In mammals, experimental data and results of modeling studies do not paint a clear picture. In Wistar rats, Bayer (1985) and Boss et al. (1985) found a progressive increase with age in the number of granule cells in the hippocampus, as a result of neurogenesis (‘additive neurogenesis’; see Glossary). However, similar measurements in Sprague–Dawley rats failed to demonstrate any marked change in total granule cell numbers in the hippocampus (Boss et al., 1985) and olfactory bulb (Bayer, 1985) during the first 12 months of life. Genetic fate mapping in mice suggested that in the glomerular layer of the olfactory bulb there is a constant net addition of adult-born neurons, whereas in the granule cell layers of the olfactory bulb and the dentate gyrus of the hippocampus, the proportion of newly generated neurons increases within the first few weeks of life but plateaus ∼2 months after birth (Ninkovic et al., 2007). Conversely, by genetically labeling neural stem cells in mice, Imayoshi et al. (2008) found that continued neurogenesis results in a turnover of granule cells in the olfactory bulb but a substantial addition of granule neurons in the hippocampal dentate gyrus. Similarly, the findings of studies modeling the effect of adult neurogenesis in the mammalian hippocampus are rather inconclusive (Appleby et al., 2011; Appleby and Wiskott, 2009; Choi et al., 2016).

In contrast to the situation in mammals, quantitative analysis in brown ghost knifefish has clearly demonstrated additive neurogenesis in the CNS. The body (Ilieş et al., 2014), brain (Zupanc and Horschke, 1995) and spinal cord (Sîrbulescu et al., 2017) grow continuously throughout the lifespan, with increases in both the total number of cells and the total tissue volume. The long-term survival of many of these adult-born cells, in combination with the continuous generation of new cells through the mitotic activity of the neural stem cells, has a profound effect not only on tissue growth but also on behavioral function. By 2–3 years of age, an individual brown ghost knifefish will have reached a total length of 150 mm, and the spinal cord will contain ∼18,900 electromotor neurons (Sîrbulescu et al., 2017). Over the next 100 days, the fish will gain ∼10 mm in length, which is associated with the addition of an estimated 1260 new electromotor neurons. This corresponds to a 7% increase in total electromotor cell number, and probably a similar increase in the number of electrocytes, which are formed by the axonal terminals of the electromotor neurons (see ‘Introduction’). At the behavioral level, this additive neurogenesis in the electromotor system results in a continuous increase in the amplitude of the electric organ discharge over time (Sîrbulescu et al., 2017).

Mathematical and computational modeling of stem cell-driven tissue growth

Despite the fair amount of experimental data available on adult neurogenesis in teleost fish, the theory of this phenomenon is surprisingly poorly understood. Recent mathematical and computational modeling of the stem cell dynamics has implicated several factors that are crucial for sustained stem cell-driven growth of the tissue and correct formation of CNS structures, such as the spinal cord (Ilieş et al., 2018; Lehotzky et al., 2021). The first two factors are sufficiently high probabilities of symmetric stem cell division and cell death of progenitor cells. Low rates of symmetric cell division and progenitor cell death result in the abortion of tissue growth and/or aberrant spinal cord formation. Each of these two processes plays a particularly important role during phases of accelerated tissue growth, such as those occurring during the early stages of development or as part of an organism’s regenerative response to injury. Under such conditions, symmetric division plays a key role in amplifying the populations of stem and/or progenitor cells. It is, therefore, not surprising that a shift from asymmetric to symmetric stem cell division in response to injury has been found in the spinal cord of axolotls, where the cells surrounding the injury site induce a transcriptional program that promotes increased cell

proliferation, symmetric divisions and rapid cell cycles (Rodrigo Albors et al., 2015).

The hypothesis that an increased cell death rate has a growth-promoting effect may seem counterintuitive. However, analysis of simulated tissue growth reveals that, under conditions of low cell death probability, stem/progenitor cells are frequently surrounded by a high density of cells ('encapsulation'), thereby reducing or even abolishing the proliferative activity of the stem/progenitor cells through contact inhibition (see Glossary) (Lehotzky et al., 2021). By contrast, induction of apoptotic cell death of a sufficiently large number of progenitor cells and subsequent removal of their corpses through phagocytosis reduces this risk by reducing the likelihood of encapsulation, thereby promoting sustained growth. Work on the spinal cord of brown ghost knifefish provides support for this hypothesis. For example, following an experimentally induced lesion, the number of apoptotic cells at the injury site increases substantially within hours, and the number of apoptotic cells remains high when cell proliferation is upregulated in response to the injury (Sîrbulescu et al., 2009; Sîrbulescu and Zupanc, 2009).

A third factor critically involved in sustained tissue growth and correct morphogenesis, as suggested by computational modeling, is the ability of cells to drift radially (see 'Migration' section of 'Development of the progeny of adult neural stem/progenitor cells', above). This property is especially important in the spinal cord, as the cords of both brown ghost knifefish (Sîrbulescu et al., 2017) and rat (Horner et al., 2000) show no active migration of cells born during adulthood. Using such a passive mechanism, cells can still move, although typically over shorter distances and at slower time scales than is the case when cells employ active migration mechanisms. It will be worth considering cell drift as a developmental mechanism in future studies on embryonic and postnatal development.

Why is adult neurogenesis more pronounced in teleost fish than in mammals? An evolutionary perspective

Why does the generation of new neurons cease in all but a few regions of the mammalian CNS during early stages of development but persist, throughout life, in many areas of the teleost fish CNS? And why is additive neurogenesis far more pronounced in teleosts than in mammals? In a Review published in *Journal of Experimental Biology* in 1999, I hypothesized that these differences in adult neurogenesis are related to a fundamental difference between the two taxa in how muscles and sensory organs grow (Zupanc, 1999). During postnatal life, all vertebrate species grow. In mammalian species, somatic growth is rapid in early stages of postnatal development but declines dramatically as the organism approaches its adult body size – mammals exhibit determinate growth. By contrast, in many fish, somatic growth is indeterminate. Moreover, whereas in mammals, postnatal muscle growth is the result of hypertrophy (see Glossary) of already existing fibers (Rowe and Goldspink, 1969), in fish, the increase in muscle mass is due to both hyperplasia (see Glossary) and hypertrophy (Koumans and Akster, 1995; Weatherley and Gill, 1985; Zimmerman and Lowery, 1999) (for review, see Rowlerson and Veggetti, 2001). Similarly, cytogenesis (see Glossary) in the retina of mammals ends at, or shortly after, birth, but the eye, including the retina, continues to grow postnatally (for review, see Kuhrt et al., 2012). In the mammalian cochlea, hair cells undergo terminal mitosis during embryonic development, as shown in mice (Ruben, 1967). This contrasts with the development of these two sensory organs in fish. Throughout postnatal development, new retinal cells are formed in the eyes of goldfish (Johns and Easter, 1977), and new hair cells are generated in the inner ear of sharks (Corwin, 1981).

The numerical matching hypothesis of adult neurogenesis states that hyperplasia of muscle fibers prompts a concomitant increase, through proliferation, in the number of motoneurons and other nerve cells functionally involved in neural control of the respective muscle fiber activity (Fig. 6) (Zupanc, 1999, 2017b). Conversely, this hypothesis predicts that loss of motor fibers results in corresponding cell death of related central neurons. These adjustments through cell proliferation and cell death ensure that the interconnected populations of peripheral muscle fibers and central neurons are maintained at a constant ratio. Similar arguments can be applied to the growth dynamics of sensory systems. The continuous increase in the number of sensory cells during postnatal stages of development in fish induces the generation of new neurons involved in the processing of sensory information, thereby achieving numerical matching of peripheral sensory elements and corresponding central neurons.

As a corollary of the numerical matching hypothesis, it is proposed that, when in the course of mammalian evolution the growth of muscles and sensory organs shifted from a pattern of indeterminate growth to determinate growth, the neurogenic potential of central structures forming part of the corresponding motor and sensory pathways was reduced in parallel. This notion can also provide an explanation for the olfactory bulb and the dentate gyrus as two major sites where integration of new neurons into neural circuits occurs in the adult mammalian brain. The primary sensory neurons of the olfactory epithelium are the only sensory cells in mammals that continue to be formed during adulthood (Graziadei and Graziadei, 1979). They arise from globose basal cells that function as adult stem cells in the olfactory epithelium (Costanzo and Graziadei, 1983; Huard and Schwob, 1995; Schwartz Levey et al., 1991). There is controversy about whether neurogenesis results in a constant turnover of olfactory receptor cells during adulthood, or whether new receptor cells are primarily added to older ones, although more recent investigations favor the latter hypothesis (for review, see Breipohl et al., 1986).

The olfactory sensory neurons project to the olfactory bulb where they make glutamatergic synaptic contacts with dendrites of mitral and tufted cells. Adult-born sensory neurons appear to develop proper synaptic connections in the olfactory bulb, as suggested by a combination of labeling of mitotic cells and retrograde tracing (Barber, 1981). Axons of mitral and tufted cells travel to the olfactory cortex, including the lateral entorhinal cortex. The latter structure, in turn, projects, via the lateral perforant path, to the hippocampus where synaptic connections are formed with the distal dendrites of the dentate gyrus granule cells (Carlsen et al., 1982; Insausti et al., 2002; van Groen et al., 2002, 2003). Thus, two of the major regions in which neurogenesis occurs within the adult mammalian brain – the olfactory bulb and dentate gyrus – are part of the central olfactory pathway.

Support for the notion that the size of a neuronal target population is influenced by interactions with its cellular source population comes from a variety of quantitative morphometric studies in mammals. For example, in chick embryos, the number of motoneurons in the brachial lateral motor column that survive after a period of regulatory cell death is proportional to the volume of wing bud-derived muscle present (Lanser and Fallon, 1987). An excellent correlation has also been observed between the number of myotubes (see Glossary) and the number of motoneurons in the hindlimb of embryos of chick, quail and chick–quail chimeras (see Glossary) (Tanaka and Landmesser, 1986). Such target–source

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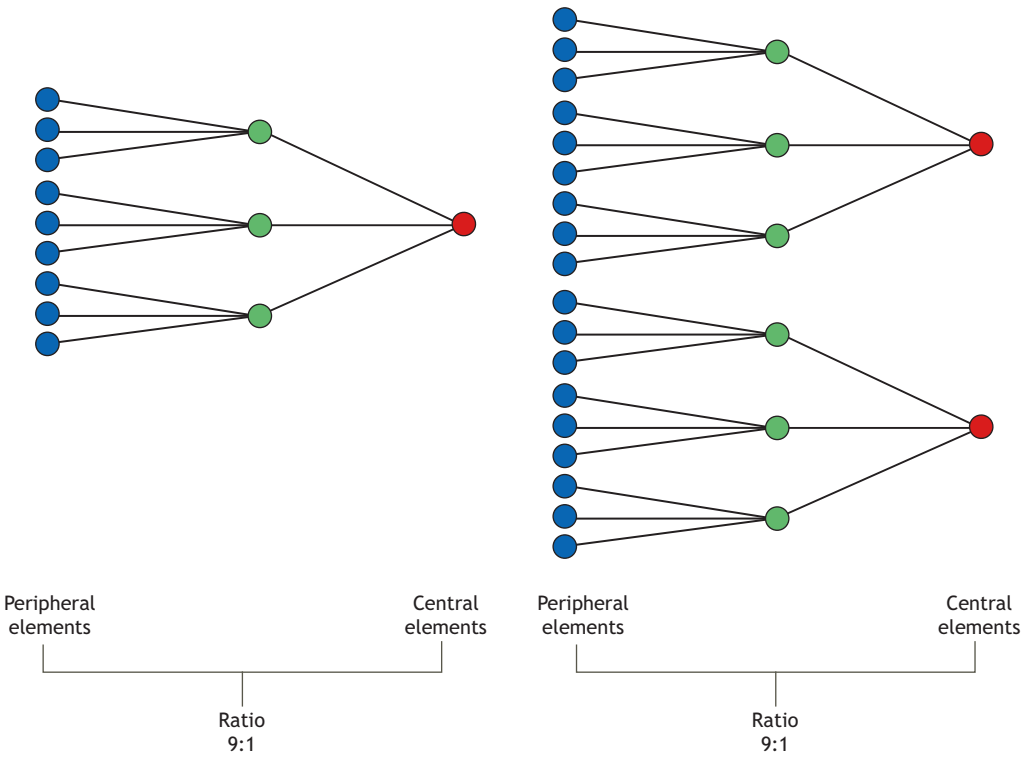

Fig. 6. Numerical matching of peripheral and central elements. Observations in various brain systems suggest that the ratio of peripheral elements (i.e. muscle fibers or sensory receptor cells) and central elements (i.e. neurons involved in central control of the corresponding motor activity or in central processing of the corresponding sensory information, respectively) is relatively constant. When the number of peripheral elements changes – for example, through muscle hyperplasia – there is a concurrent increase in the number of corresponding central neurons through adult neurogenesis. From Zupanc (2017b).

matching is also evident in several regions of the CNS. In neural circuits consisting of neurons projecting from the inferior olive to cerebellar Purkinje cells in chimeras of lurcher mutant mice (see Glossary) and wild-type mice, the number of the neuronal source population is a linear function of the number of the neuronal target population (Herrup et al., 1996). Similarly, using chimeric cerebella of wild-type mice and staggerer mutant mice (see Glossary), Herrup and Sunter (1987) discovered a linear relationship between the number of granule cells and the number of their projection target, Purkinje cells.

In fish, evidence in support of the numerical matching hypothesis has been obtained in the visual system. Early experiments in the killifish *Fundulus heteroclitus* by White (1948) revealed that complete or partial removal of one eye during embryonic development results in reduced size of the contralateral optic tectum, the target site to which retinal ganglion cells project in the intact visual system of teleosts. The notion that the size of the eye (or, more precisely, the number of ganglion cell axons) modulates the size of tectal tissue was further substantiated by a study in adult goldfish, *Carassius auratus* (Raymond et al., 1983). The authors found that permanent removal of one eye led to sustained depression of mitotic activity in the tectal proliferation zone on the denervated side, compared with the intact one. Temporary denervation by optic nerve crush had initially a similar effect. However, upon reinnervation of the tectum by the regenerating ganglion cell axons, proliferation was enhanced in the experimental hemisphere, compared with the control hemisphere.

Conclusions and future directions

A comparative understanding of the biological principles of adult neurogenesis is highly desirable, yet vastly lacking (for review, see Lindsey and Tropepe, 2006). An analysis of papers published on adult neurogenesis in 2010 demonstrates that ∼95% of them were based on mammals (most of them on laboratory rats and mice), and only 5% focused on non-mammalian vertebrates (Bonfanti et al., 2011). Since then, the situation has not improved – and perhaps has even worsened – as indicated by a PubMed search using the string ‘adult neurogenesis’. Out of 300 papers indexed in 2019, only 7 focused on non-mammalian vertebrates and 2 on invertebrates. Such a restriction to essentially two ‘model’ organisms, studied exclusively under laboratory conditions, is dictated largely by funding agencies and comes at a high price. From a biological perspective, it prevents us from gaining an understanding of the evolution of adult neurogenesis.

Although teleosts represent roughly half of all extant vertebrates, our knowledge about the possible existence of adult neural stem cells, and their properties and roles in adult CNS development is frustratingly fragmented, with not a single species examined in most of the taxonomic orders (Fig. 1). Even worse from a comparative perspective, the possibility of neurogenesis in the adult CNS has never been examined in any clade of Osteichthyes besides teleosts; these neglected clades include coelacanths, lungfishes, bichirs, reedfishes, sturgeons, paddlefishes, gars and bowfins. And it was only very recently that the first study was published on adult neurogenesis in the brain (telencephalon) of a chondrichthyan species (Docampo-Seara et al., 2020), whereas hagfishes, lampreys, rays and chimaeras are still waiting to be examined. Unless we widen and intensify a comparative exploration of adult neurogenesis targeting key taxa, we will not understand how this phenomenon has evolved in vertebrates.

The restriction of the vast majority of studies to essentially two mammalian model systems also limits the ability of investigators to develop a broad appreciation for the function of adult neurogenesis. Traditionally, researchers have focused on examining the role of adult-born neurons in spatial learning and memory in the hippocampus, and in olfactory discrimination and memory in the olfactory bulb (see Table 1) – functions generally associated with these two brain structures. However, despite a multitude of sophisticated approaches and an impressive body of experimental data, the results are frequently contradictory and, overall, have failed

to provide a clear holistic view of the function of adult neurogenesis (for a critical review, see Lledo et al., 2006).

At the same time, this narrowly defined strategy has prevented investigators from considering alternative notions, such as the potential involvement of adult neurogenesis in the numerical matching of central neurons and peripheral motor/sensory cells, as discussed above. This last hypothesis could provide novel clues to explain the dramatic exponential decline with age in cell proliferation and neuronal differentiation in the dentate gyrus (and likely other neurogenic areas) in any mammalian species examined (Amrein et al., 2011), observations that have led to the suggestion that 'adult' neurogenesis is primarily a 'juvenile' phenomenon (Barker et al., 2011). This decline correlates with the dramatic deceleration in somatic growth rate with age during postnatal development. It is unknown whether the correlation of somatic growth rate and degree of adult neurogenesis also extends to differences between species. Do fast-growing species produce adult-born neurons at higher rates than slowly growing species? Do species with larger adult body sizes generate larger numbers of postnatally generated neurons than species with smaller bodies? Teleosts, with their enormous diversity in growth patterns, provide an excellent resource to address these questions.

Furthermore, teleost fish are particularly well suited to examine the traditionally considered functions of adult neurogenesis, such as its involvement in the formation and maintenance of spatial memory. Do fish that orient in two-dimensions, such as bottom-dwelling species, differ from fish that orient in three dimensions in terms of adult neurogenesis in brain structures homologous to the mammalian hippocampus? Are similar differences in adult neurogenesis evident among coral reef fishes differing in the size of their home ranges? Such behavioral differences are well established based on field studies (Cowlishaw, 2014); for example, some species (such as the damselfish *Pomacentrus chrysurus*) have home ranges of less than one square meter, whereas the home ranges of others (such as the butterflyfish *Chaetodon melannotus*) extend over several hundred square meters. With nearly 30,000 species, teleost fish account for roughly half of all extant vertebrates. This huge number is paralleled by a tremendous diversity affecting morphology, physiology, ecology and ethology. Together with an unprecedented degree of adult neurogenesis, defined by both the number of neurogenic regions and the relative number of adult-born neurons, this variability makes it particularly attractive to study, in teleosts, questions related to structural and functional adaptations of this phenomenon. It is down to us to make use of this treasure trove.

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