



Diving into the streams and waves of constitutive and regenerative olfactory neurogenesis: insights from zebrafish

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Abstract

The olfactory system is renowned for its functional and structural plasticity, with both peripheral and central structures displaying persistent neurogenesis throughout life and exhibiting remarkable capacity for regenerative neurogenesis after damage. In general, fish are known for their extensive neurogenic ability, and the zebrafish in particular presents an attractive model to study plasticity and adult neurogenesis in the olfactory system because of its conserved structure, relative simplicity, rapid cell turnover, and preponderance of neurogenic niches. In this review, we present an overview of the anatomy of zebrafish olfactory structures, with a focus on the neurogenic niches in the olfactory epithelium, olfactory bulb, and ventral telencephalon. Constitutive and regenerative neurogenesis in both the peripheral olfactory organ and central olfactory bulb of zebrafish is reviewed in detail, and a summary of current knowledge about the cellular origin and molecular signals involved in regulating these processes is presented. While some features of physiologic and injury-induced neurogenic responses are similar, there are differences that indicate that regeneration is not simply a reiteration of the constitutive proliferation process. We provide comparisons to mammalian neurogenesis that reveal similarities and differences between species. Finally, we present a number of open questions that remain to be answered.

Keywords Zebrafish · Olfactory system · Nerve cell regeneration · Stem cells · Neurogenesis

Introduction

The olfactory system is highly dynamic at the functional and structural level. Both the peripheral olfactory epithelium (OE; Graziadei and Monti Graziadei 1978; Hinds et al. 1984) and the central olfactory bulb (OB; Altman 1969; Lim and Alvarez-Buylla 2016) are sites of extensive and life-long neuronal turnover and persistent neurogenesis. New nerve cells

are constantly added to both sides of the primary synaptic circuits between olfactory sensory neurons (OSNs) and higher-order OB neurons that underlie odorant recognition and olfactory perception. More remarkably, the peripheral OE shows a capacity for self-repair and structural regeneration that is unprecedented among neuronal structures, especially in the nervous system of higher vertebrates (Schwob 2002; Ferretti 2011). As a consequence, the OB, in comparison to most other central brain structures, also maintains significant cellular and synaptic plasticity throughout life as it perpetually adjusts to the peripheral neuronal turnover (Takahashi et al. 2018).

OSNs, similar to taste receptor cells of the tongue, are directly exposed to the chemical environment to detect odor stimuli and, therefore, are unprotected from potentially harmful substances and pathogens that enter the nasal cavity during smell sensation (Moulton 1974). As a consequence, vertebrate OSNs have a limited lifespan and persist only for several weeks to a few months (Mackay-Sim and Kittel 1991; Holl 2018). Thus, constitutive OE neurogenesis reflects the persistent need of the tissue to replace dying OSNs in a rate-matched manner to maintain olfactory function over the lifespan of the

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organism. Because of its exposed structure, the OE is also vulnerable to direct physical injury, which causes damage to the overall integrity of the tissue and affects neuronal and non-neuronal cell types. Increasing insight into the cellular and molecular processes that underlie adult OSN neurogenesis supports the concept that regeneration of the OE following structural damage is not simply an accelerated mode of constitutive OSN turnover in the intact tissue (reviewed in Schwob et al. 2017). Rather, maintenance and repair neurogenesis appear to be distinct processes that depend on different stem/progenitor cells and unique inter- and intracellular molecular signals.

The steady turnover of OSNs in the intact OE and transiently increased OSN neurogenesis in the damaged tissue are matched by continuous and life-long generation of new OB interneurons, which modulate olfactory inputs from OSNs by lateral inhibition within and between OB glomeruli (Shepherd et al. 2007; Takahashi et al. 2018). In fact, one of the two most prominent and evolutionarily conserved sites of constitutive adult neurogenesis in the vertebrate CNS, the ventricular–subventricular zone (V-SVZ) of the forebrain, is almost exclusively devoted to the generation of a steady stream of newborn granule and periglomerular cells that integrate into established OB circuits (Lois and Alvarez-Buylla 1994; Figueres-Onate et al. 2019).

Due to the unusually high and incessant turnover of nerve cells, the olfactory system has often been regarded as an insightful model to identify principles, mechanisms, and molecular regulators of adult neurogenesis with candidate therapeutic relevance (Lledo and Valley 2016; Shohayeb et al. 2018). Here, we review what is known about the cellular origin, the dynamics, and the regulation of adult olfactory neurogenesis at the level of the peripheral OE and central OB in zebrafish (*Danio rerio*), a small freshwater teleost and established laboratory model. Because of its conserved structure but relative simplicity, the zebrafish olfactory system has itself been regarded as a tractable model to study olfactory function, development, and regeneration, especially in comparison to the more complex mammalian system (Yoshihara 2009; Kermen et al. 2013; Friedrich et al. 2013; Calvo-Ochoa and Byrd-Jacobs 2019). The focus of this synopsis is on regenerative phenomena in the adult system, and we have chosen to omit aspects of early olfactory system development for which excellent reviews exist on zebrafish (Whitlock and Westerfield 2000; Whitlock 2008; Miyasaka et al. 2013) and other vertebrates (Moody and LaMantia 2015; Suzuki and Osumi 2015; Sokpor et al. 2018).

While the use of zebrafish grants experimental advantages in its own right, such as reduced cost, rapid development, and easy manipulation of relevant tissue structures (Yoshihara 2009; Meyers 2018), added value in studying olfactory neurogenesis and regeneration in zebrafish may arise from a comparative view onto seemingly related anatomical

structures and cellular mechanisms in zebrafish and higher vertebrates. Despite the overall apparent similarity (Korsching et al. 1997; Kermen et al. 2013; Saraiva et al. 2015), important, and potentially insightful, structural, cellular, and molecular differences exist. We highlight these differences and peculiarities wherever relevant to provide a more holistic view on the structure and function of the olfactory system within the context of this review.

The peripheral OE of the zebrafish

Anatomical organization of the zebrafish OE

The input to the zebrafish olfactory system is formed by a pair of rosette-shaped olfactory organs located dorsally on each side of the head that project independently to one of two OBs of the rostral telencephalon (Hansen and Zeiske 1998; Fig. 1(a, b)). Analogous to the turbinate organization in mammals, which increases the sensory surface area available for odorant detection (Green et al. 2012), the zebrafish OE is formed by a convoluted sheet of neuroepithelial tissue that consists of OSNs and various non-neuronal cell types that provide structural and functional support. Each olfactory organ is organized into a bilateral array of radially projecting lamellae that originate from a central midline structure, the median raphe (Fig. 1(c, d)). Lamella formation is a continuous process and not restricted to early development with the consequence that the OE of older fish typically contains a higher number of lamellae (19–21) than the OE of young adults (12–15; Hansen and Zeiske 1998). New lamellae are added predominantly from a dedicated growth zone at the anterior end of the OE but occasionally can be observed as invaginations of the epithelial sheet between existing structures. It has been shown in rats that OE growth also persists long after birth and that cell number and surface area of the OE continue to increase for up to 12 months postnatally (Weiler and Farbman 1997). Different from the zebrafish OE, however, new cells are added from within the epithelial sheet and not from regionalized growth zones. The neotenic process of life-long olfactory organ growth in zebrafish is independent of neuronal turnover and tissue repair and adds an additional dimension to the generation and specification of OSNs that is not observed in the mammalian OE.

Each radially projecting lamella is composed of two multilayered epithelial sheets (Fig. 1(d)), which are anchored to a central lamina propria that includes blood vessels, fat cells, pigment cells, and OSN axon fascicles that converge in the ventral OE and give rise to a short olfactory nerve (Hansen and Zeiske 1998). Thus, every lamella is a bilaterally symmetric structure in which the apical epithelial surfaces are exposed to water-filled spaces between lamellae and the basal sides of the two epithelia face each other across the midline.

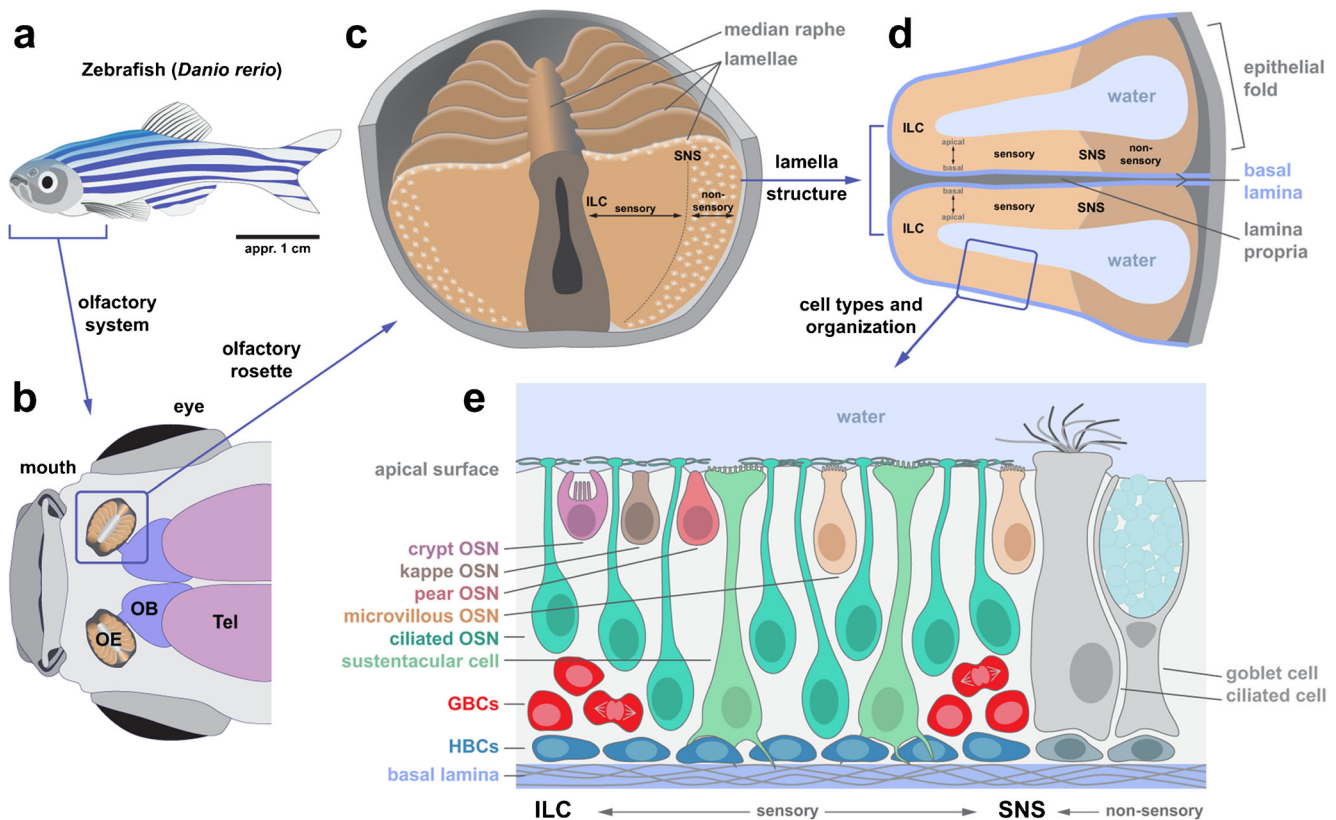


Fig. 1 Overview of the peripheral zebrafish olfactory system. (a) General habitus of the adult zebrafish, *Danio rerio*, an attractive model to study olfactory system development, function, and regeneration. (b) Overview of the peripheral olfactory organ and connectivity to the brain. The peripheral olfactory system comprises two separate olfactory epithelia (OE) located on each side of the head, halfway between the mouth and the eye. Each OE extends a short nerve, composed of olfactory sensory neuron (OSN) axons, to the olfactory bulb (OB) of the forebrain (telencephalon; Tel). (c) Structural organization of the olfactory organ. Each rosette-shaped individual olfactory organ is composed of staggered and bilaterally symmetric arrays of lamellae that extend radially from the median raphe. OSNs occupy the inner sensory regions of a lamella between the interlamellar curves (ILCs) and the sharp sensory/non-sensory border (SNS), while the non-sensory periphery is occupied by ciliated and mucus-producing non-sensory cells. (d) A single lamella is composed of two neuroepithelial sheets that are fused at their basal sides to a common lamina propria in the middle of each lamella. The epithelial sheet is

continuous between neighboring lamellae at the ILCs to form U-shaped epithelial folds. OSNs occupy the inner sensory region of each lamella (light brown) and are absent from the non-sensory (dark brown) OE. (e) Cellular composition of the zebrafish OE. The OE is composed of five types of OSNs, the ciliated (green), microvillous, (orange), crypt (magenta), kappe (brown), and pear (pale red) cells. The somata of ciliated cells occupy more basal regions of the OE, while the other cell types line the apical surface. Glial-like sustentacular cells form the apical border around OSN dendrites and extend towards the basal lamina. Globose basal cells (GBCs) are located exclusively at the ILC and SNS, whereas HBCs line the entire OE evenly. GBCs undergo active cell divisions in the intact OE to replace constantly dying OSNs, while HBCs are dormant unless the OE is damaged. Goblet cells in the non-sensory OE produce mucus, analogous to the function of duct/gland cells and large columnar cells with beating cilia generate water currents across the epithelial surface to deliver odorants to OSNs

Neighboring lamellae are connected to each other through a single epithelial sheet at the interlamellar curves (ILCs) close to the median raphe to form U-shaped epithelial folds.

Labeling of neuronal markers, such as the pan-neuronal marker HuC/D (Iqbal and Byrd-Jacobs 2010; Bayramli et al. 2017) or the OSN-specific markers olfactory marker protein (OMP) and transient receptor potential cation channel type C2 (TrpC2), on cross sections through the OE (Celik et al. 2002; Sato et al. 2005; Bayramli et al. 2017) typically show a sharp transition between regions that contain nerve cells and regions that are composed entirely of non-neuronal cells, reminiscent of the sharp boundary between sensory and respiratory epithelia in the rodent nose (Fig. 1(c, d)). OSNs occupy the central half to two thirds (depending on the dorsal to ventral position

within the OE) and define the sensory region (Bayramli et al. 2017), while the peripheral non-sensory region is formed largely by mucus-producing cells and cells that bear motile cilia (Hansen and Zeiske 1998). The apical layers of the sensory epithelium are tightly and almost exclusively packed with nerve cell bodies, while basal regions contain the cell bodies of various non-neuronal cell types (Demirler et al. 2020; Fig. 1(e)).

Neuronal cell types in the zebrafish OE

Surprisingly, OSNs appear to be morphologically and molecularly more diverse in zebrafish than in mammals (Fig. 1(e)). The zebrafish OE comprises multiple chemosensory

subsystems, which typically occupy distinct anatomical structures in other species and includes ciliated and microvillous OSNs that are characteristic for the mammalian main OE and vomeronasal organ (VNO), respectively (Hansen and Zeiske 1998; Sato et al. 2005). Both cell types can be found in all regions across the sensory OE but segregate within the apical to basal dimension with microvillous OSNs occupying more apical strata than ciliated neurons (Sato et al. 2005).

The occurrence of ciliated and microvillous OSNs in the same olfactory organ, rather than in separate structures, seems to reflect an evolutionary ancient condition and not an adaptation to aquatic lifestyle (Eisthen 1992; Grus and Zhang 2006). Larval amphibians possess morphologically distinct main OE and VNO structures despite living under water. A true VNO occurs first in tetrapods but may have been lost subsequently in different tetrapod lineages, such as birds, aquatic reptiles, and mammals, including higher primates (Bertmar 1981). Therefore, as the zebrafish illustrates, the presence or absence of a separate VNO is independent of the cell types that form it and a more consistent relationship can be made between morphological OSN types, the molecular chemoreceptor subtypes they express, and their preference for a particular chemical ligand (Silva and Antunes 2017). The behavioral context in which ciliated and microvillous cells are active may also have changed during evolution as the same chemical class of odorants may convey different meaning in terrestrial and aquatic species. Amino acids and peptides, which are detected by V2R-type vomeronasal receptors, are food cues in zebrafish (Alioto and Ngai 2006; Nikaido et al. 2013) but may have pheromone function in rodents (Perez-Gomez et al. 2014). Amino acid-sensing microvillous cells project their axons to the lateral chain glomeruli in the zebrafish OB (Friedrich and Korsching 1997; Koide et al. 2009), which shares structural similarities with the rodent accessory OB, thus blurring the distinction between a pheromone-detecting vomeronasal system and an OE that senses common odorants.

Ciliated OSNs in zebrafish, like their mammalian counterparts, bear slender long dendrites, which fan out into a small number (3 to 7) of apical primary (= sensory) cilia that protrude into the lumen of the nasal cavity for odorant detection. Ciliated OSNs express OMP (Sato et al. 2005) along with the signal transduction components $G\alpha_{olf}$ (Hansen et al. 2004; Oka and Korsching 2011) and the cyclic nucleotide-gated channel CNGA2 (Sato et al. 2005). Each ciliated OSN also expresses a single member of a family of up to 176 classical ORs (156 of which may be functional genes; Alioto and Ngai 2005; Niimura and Nei 2005; Niimura 2009) or 112 trace amine-associated receptors (TAARs; Hussain et al. 2009). Single-cell sequencing of ciliated zebrafish OSNs suggests that each individual cell expresses only one predominant OR or TAAR gene (Dang et al. 2018; but see Sato et al. 2007 for an exception), similar to the “one neuron-one receptor” rule

that is observed in the mammalian olfactory system (Mombaerts 2004). The exact ligand for most zebrafish ORs is not known; so far, ligands for only two ORs have been characterized and these respond to the courtship-inducing pheromone prostaglandin F2 α (Yabuki et al. 2016). However, given the size and sequence diversity of the zebrafish OR family (Niimura and Nei 2005; Alioto and Ngai 2005), OR-expressing ciliated OSNs most likely respond to a wide range of chemically diverse odorants. TAAR-expressing ciliated cells preferentially respond to amine-containing compounds (Li et al. 2015). Of those, cells expressing the TAAR13c receptor exhibit high specificity for the diamine cadaverine, which is released during putrefaction and has been shown to elicit strong avoidance behaviors (Hussain et al. 2013; Dieris et al. 2017).

Microvillous cells, on the other hand, have shorter and thicker dendrites, extend apical microvilli, and express TrpC2 but not OMP (Sato et al. 2005), which is different from OMP expression in microvillous cells of the mouse vomeronasal organ (Mombaerts et al. 1996). Microvillous OSNs also express one of the 60 V2R-like Olfc (Ahuja et al. 2018) receptors and the signal transduction components $G\alpha_o$ (Oka and Korsching 2011). While neurons of the rodent VNO can be distinguished by their selective expression of V1R and V2R receptors and the associated signal transduction components $G\alpha_i$ or $G\alpha_o$, respectively (Perez-Gomez et al. 2014), expression of any of the six zebrafish V1R-like ORA receptors (Saraiva and Korsching 2007) by microvillous cells has not been demonstrated with certainty. Rather, ORA4 is expressed by TrpC2-negative crypt cells (see below), while the other five ORA genes are expressed in another, as of yet uncharacterized cell type with more slender morphological profiles (Oka et al. 2012). Similarly, expression of Gi1b, the only $G\alpha_i$ family member that is detectable by *in situ* hybridization, is restricted to a few OMP-/TrpC2-negative OSNs in the apical OE that, like ORA-expressing cells, comprise crypt neurons in addition to cells with slender profiles (Oka et al. 2012; Oka and Korsching 2011; Suzuki et al. 2015). Thus, ORA/ $G\alpha_i$ coupling could be conserved in the zebrafish OE, at least in crypt neurons, but coexpression of $G\alpha_i$ with ORA receptors has not been examined in the other cell type. Olfc-expressing cells respond to amino acids (Lipschitz and Michel 2002; Luu et al. 2004; Koide et al. 2009) and project to a specific subset of morphologically distinct glomeruli in the lateral OB, while ORA-expressing cells have been shown to be sensitive to bile acids (Cong et al. 2019). Of those, cells expressing ORA1 are also sensitive to 4-hydroxyphenylacetic acid, which acts as a pheromone and induces egg laying (Behrens et al. 2014), while ORA4 has been implicated in kin recognition (Biechl et al. 2016).

In addition to these two predominant OSN types, the zebrafish OE also contains three minor groups of presumably fish-specific OSNs, which have been termed crypt (Hansen

and Finger 2000), kappe (Ahuja et al. 2014), and pear cells (Wakisaka et al. 2017) to reflect their peculiar morphologies. These cells have in common that they are all located in the apical-most layers of the OE with a preference to be in close proximity to the ILCs, that they have very short or no dendrites, and that each cell type projects axons to a single subtype-specific glomerulus (Ahuja et al. 2013, 2014; Wakisaka et al. 2017), as opposed to groups of multiple class-specific glomeruli for ciliated and microvillous OSNs (Sato et al. 2005). In accordance with the general monospecificity of OB glomeruli (Mombaerts 2006), crypt and pear cells have been shown to express a single chemoreceptor each. Crypt cells express ORA4 (Oka et al. 2012) and pear cells have been shown to signal through an atypical A2c adenosine receptor (Wakisaka et al. 2017). While a behaviorally relevant ligand for crypt cells remains unknown, pear cells respond selectively to adenosine and secondarily to adenosine nucleotides (ATP, ADP, AMP) through enzymatic conversion to adenosine in the OE. At the morphological level, crypt cells bear some resemblance to sensory neurons of the Grüneberg ganglion, another chemosensory subsystem located at the tip of the nasal cavity of mammals (Grüneberg 1973) that responds to a host of stimuli ranging from temperature to alarm pheromones (Bumbalo et al. 2017; Chao et al. 2018; Moine et al. 2018). These cells, similar to crypt cells, have spherical morphology and possess bundles of primary cilia that are located within a pocket-shaped invagination of the soma (Brechtbühl et al. 2008) and extend axons to isolated glomeruli in the posterior OB (Fuss et al. 2005; Koos and Fraser 2005). However, the evolutionary and functional relationship between any of the non-classical OSN types in fish and the sensory neurons of the Grüneberg ganglion is speculative at best.

Non-neuronal cell types in the zebrafish OE

In addition to the various chemosensory cells, the zebrafish OE also harbors different non-neuronal cells that either support OE structure and OSN function or play a direct role in OSN neurogenesis (Fig. 1(e)). The outer non-sensory region of each lamella is largely characterized by the presence of columnar epithelial cells that are endowed with motile cilia (Hansen and Zeiske 1998), similar to cells in the respiratory OE of mammals (Morrison and Costanzo 1992). These cells generate a laminar flow of water across the surface of the epithelium to enhance odorant delivery to the sensory region and their detection by OSNs (Reiten et al. 2017). Mucus-producing goblet cells perform the function of Bowman's glands, which do not exist in the zebrafish OE (Hansen and Zeiske 1998).

The zebrafish OE also contains various supporting cells, including cells that resemble glial-like sustentacular cells (SCs; Hansen and Zeiske 1998). We have recently

characterized zebrafish SCs, which express the molecular marker SRY-Box Transcription Factor 2 (Sox2) and stain positive for intracellular filaments of the cytokeratin II class (Demirler et al. 2020). SCs are abundant and evenly spaced cells that extend from the basal lamina to the apical surface of the OE but are restricted to the sensory region. Different from other vertebrates, in which SC cell bodies form a monolayer at the apical OE surface (Hassenklöver et al. 2009; Guo et al. 2010), the cell bodies of zebrafish SCs are located in the basal OE, typically one cell layer removed from the basal lamina (Demirler et al. 2020), a feature that seems to be common for SCs in the OE of fishes (Hansen and Zielinski 2005). The cells extend foot-like basal processes to the basal lamina and fan out at their apical ends to associate with bundles of OSN dendrites (Hansen and Zeiske 1998). Junctional complexes between SCs and between SCs and OSNs contribute to the apical border of the OE that allows the tissue to maintain a distinct internal ionic milieu and protects it from osmotic challenge by the surrounding freshwater.

Of particular interest for the regenerating capacity of the OE are resident stem and progenitor cells that are located in the basal OE, underneath the layers formed by OSNs and SCs (Fig. 1(e)). In rodents, two major types of basal cells, the globose (GBCs) and horizontal basal cells (HBCs), have been characterized in detail (for an exhaustive review, see Schwob et al. 2017). GBCs are a heterogeneous group of stem cells, committed progenitor cells, transit-amplifying cells, and immediate neuronal precursors, some of which undergo frequent cell divisions in the intact tissue (Guo et al. 2010; Chen et al. 2014). GBCs have also been shown to respond with an increase in mitotic cycling when OSNs are selectively lost from the OE (Leung et al. 2007). In contrast, HBCs remain dormant in the intact OE and are activated when the structural integrity of the OE is more severely compromised and includes loss of or damage to non-neuronal cells (Leung et al. 2007; Packard et al. 2011). The different behavior of GBCs and HBCs has led to the concept that GBCs, in particular *Lgr5*-positive, mitotically active cells (Chen et al. 2014), contribute to constitutive OSN turnover in the intact OE, while HBCs represent a pool of "reserve stem cells" (Schnittke et al. 2015; Herrick et al. 2017) that selectively contribute to OE regeneration after damage. However, the contribution of HBCs to constitutive OSN neurogenesis in the intact OE remains controversial (Leung et al. 2007; Iwai et al. 2008).

Far less is known about the identity, origin, and regulation of GBCs and HBCs in zebrafish. However, analysis of constitutive OSN neurogenesis (Bayramli et al. 2017) and responses to tissue injury (Iqbal and Byrd-Jacobs 2010; Demirler et al. 2020) suggest that a dual GBC/HBC system exists as well. Cells with HBC characteristics form a continuous band of cells with flat horizontal profiles that are in direct contact with the basal lamina (Fig. 1(e)) and stain positive for the HBC markers Sox2, keratin 5, and tumor protein 63 (p63;

Demirler et al. 2020). Like their mammalian counterparts, these cells become activated when the OE is damaged, which establishes a pattern of proliferating cells across the sensory OE (Demirler et al. 2020). In contrast, GBC-like cells occur only at the ILC and the sensory/non-sensory border (SNS) but appear to be absent from the sensory OE (Fig. 1(e)). These cells express Delta A, Ascl1, and neuronal differentiation (NeuroD) markers that are characteristic for the progenitor, transit-amplifying and immediate neuronal precursor stages of the GBC lineage, respectively (Bayramli et al. 2017). In line with their contribution to neuronal turnover, clusters of dividing cells in the intact OE are observed exclusively at the ILC and SNS but not within the sensory region. Thus, the tissue distribution of GBCs and HBCs in zebrafish is fundamentally different from the rodent system, in which HBCs and GBCs occupy different basal strata but have otherwise identical distribution (Schwob et al. 2017). The unique occupancy of distinct OE regions by GBC- and HBC-like cells in zebrafish may facilitate studies of their selective contribution to OSN neurogenesis under different experimental conditions.

The difference in tissue distribution suggests that zebrafish GBCs and HBCs constitute distinct and independent cell lineages (Demirler et al. 2020). HBCs within the mid-sensory OE, because of their physical distance to the ILC and SNS, are unlikely to be GBC-derived. GBCs at the ILC and SNS, at least in theory, could be derived from HBCs that are under the influence of position-specific signals that trigger HBC cycling and GBC production in these regions. The zebrafish OE, similar to the mammalian OE, originates from the olfactory placode at the edge of the antero-lateral neural plate (Torres-Paz and Whitlock 2014; Aguillon et al. 2016). Recently, it has been suggested in the mouse that distinct HBC subpopulations descend from two different developmental origins, the olfactory placode and the migratory neural crest (Suzuki and Osumi 2015), eventually to give rise to functionally distinct HBC pools. While a selective neural crest contribution to microvillous OSNs has been suggested to occur in the developing zebrafish OE (Saxena et al. 2013), the neural crest origin of zebrafish OE cells has been questioned in more recent lineage-tracing studies (Torres-Paz and Whitlock 2014; Aguillon et al. 2018).

Constitutive neurogenesis in the peripheral OE

OSNs are unique among central and other sensory neurons because of their high and life-long intrinsic turnover rate (Schwob 2002; Ferretti 2011). Part of the reason why the olfactory system displays such a high degree of built-in structural and functional recovery may arise from the unprotected nature of OSNs and the need to counter the constant loss of individual OSNs due to their environmental exposure (Moulton 1974). OSNs have been reported to have a limited lifespan that ranges from weeks to several months (Moulton

1975; Hinds et al. 1984; Mackay-Sim and Kittel 1991) and which depends not only on the chemical composition of the environment and toxicant load but also on OSN activity (Watt et al. 2004; Santoro and Dulac 2012; Zhao et al. 2013), trophic support from the OE (Francois et al. 2013), the OB (Schwob et al. 1992; Sultan-Styne et al. 2009), or age (Kondo et al. 2010). However, the lifespan of individual OSNs is difficult to assess in the heterogeneous OE tissue, which contains multiple morphological OSN types and distinct OSN subpopulations expressing different chemosensory receptors (Zhang and Firestein 2009). To complicate matters, in the literature half-life is often confused with lifespan or lifetime and the terms are used interchangeably despite their difference in meaning.

A recent study, using tamoxifen-inducible labeling from the OMP promoter in the mouse, measured OSN half-life under pathogen-free conditions to be around 26 days, which corresponds to a mean lifetime of ($\tau = t_{1/2} / \ln(2)$; τ : mean lifetime, $t_{1/2}$: half-life) of 37.5 days, although a subpopulation of 7.8% of labeled cells persisted for more than a year (Holl 2018). Longer half-lives of 85–90 days have been reported following injection of labeled thymidine analogs (Mackay-Sim and Kittel 1991; Tsai and Barnea 2014). The difference may be explained by the fact that thymidine labeling marks additional, proliferating, and long-lived cell types (Jang et al. 2014) or that genetic cell-tracing labels all OMP-expressing OSNs, irrespective of their age, at the time of the tamoxifen pulse. We have measured a half-life of mature zebrafish OSNs in adult zebrafish (≥ 1 year of age) in clean tank water by selectively following HuC/D-positive mature OSNs after a 24-h BrdU pulse to be around 19.8 days, which is equivalent to a mean lifetime of 28.5 days (Bayramli et al. 2017). This is not only shorter than the lifetime of rodent OSNs but also much shorter than the average expected lifespan of the zebrafish in captivity of about 3.5 to 5.5 years (Gerhard et al. 2002). This suggests that the zebrafish OE, much as the OE of other species, undergoes multiple rounds of complete turnover between birth and death of the animal.

It is less clear, however, how much OSN lifespan is determined by intrinsic molecular programs and inherently limited. Even though OSN lifespan may be extended, cell death also occurs in the absence of high concentrations of environmental toxicants and under clean and controlled environmental conditions (Hinds et al. 1984). While apoptotic OSNs can be easily detected in the intact rodent OE (Cowan and Roskams 2002), we were not able to identify OSNs that stain positive for activated caspase-3 in the intact zebrafish OE despite their presence in embryonic or damaged tissue (Bayramli et al. 2017). However, a large number of terminal deoxynucleotidyl transferase dUTP nick end labeling- (TUNEL-) positive cells can be detected, suggesting that alternative, non-apoptotic cell death mechanisms (Tonnus et al. 2019) may be more prominent in aged zebrafish OSNs.

Labeling of mitotic activity using cell cycle markers (Iqbal and Byrd-Jacobs 2010; Bayramli et al. 2017) or labeled thymidine analogs (Byrd and Brunjes 2001; Oehlmann et al. 2004; Bayramli et al. 2017) reveals a distinctive pattern of cell division in the intact zebrafish OE. In contrast to the even distribution of proliferating cells across all regions of the rodent OE (Schwob et al. 1992), mitotic activity is restricted to the ILC and the SNS, while the sensory OE is essentially devoid of dividing cells in zebrafish. OSNs generated at the ILC and SNS successively invade the sensory OE and move towards each other in the center of the lamella as they age and adopt their functional maturity (Bayramli et al. 2017). The lateral (= radial along the lamella) migration of young maturing and old functional OSNs in zebrafish is different from the mammalian OE in which newborn OSNs originate from basal OE strata and ascend vertically within the OE as they mature (Iwema and Schwob 2003). Consistent with the unusual lateral direction of cell migration in zebrafish, older cells, identified by NeuroD, GAP-43, and OMP expression, or successive labeling of adult-born cells with different thymidine analogs, are found increasingly further away from the ILC and SNS (Bayramli et al. 2017). The lateral movement of zebrafish OSNs is, therefore, conceptually more similar to neurogenesis in the rodent VNO, where new cells arise predominantly, yet not exclusively, from marginal proliferation zones and shift laterally to more central positions over time (Giacobini et al. 2000; Martinez-Marcos et al. 2005; Chang and Parrilla 2016).

As newborn OSNs age, they run into each other in the center of the tissue, where they are subsequently eliminated, as indicated by the high density of TUNEL-positive cells in the mid-sensory OE (Bayramli et al. 2017). TUNEL-positive cells also seem to be enriched around the ILC and SNS suggesting that some newborn OSNs fail to mature or to make successful connections to their OB target, an observation that has also been made in rodents (Carr and Farbman 1992). Interestingly, the speed of lateral progression of about 3–5 $\mu\text{m}/\text{day}$ correlates well with the mean average lifespan of zebrafish OSNs of about 30 days, which would allow newborn cells to reach the midpoint of the sensory OE, which is about 100–130 μm away from the ILC or SNS (Bayramli et al. 2017). The elimination of old OSNs in mid-sensory regions could serve as a sink for incoming OSNs, but it remains to be examined whether OSNs move laterally by active and directed migration or if they are passively displaced and pushed towards the center by subsequently generated cells.

The number of mitotically active cells in the zebrafish OE is quite high and we have counted about 12,000 BrdU-labeled cells in a single OE over a 24-h incorporation period (Bayramli et al. 2017). However, not all of these cell divisions directly or indirectly contribute to the neuronal population. Especially cell divisions that occur within the extreme non-sensory periphery of the OE may also generate non-neuronal

cell types. In addition, BrdU labeling highlights not only terminal cell divisions but also mitotic events that occur within any stage of the GBC lineage to amplify or to maintain the progenitor pool. Simultaneous staining against the mature neuronal marker HuC/D and BrdU showed that over a 24-h period around 5500 new HuC/D-positive OSNs are generated (Bayramli et al. 2017). This is still an incredibly high number, given the small size of the zebrafish OE, which, by conservative estimates, has been suggested to contain 25,000 (Baier et al. 1994) to 40,000 (Barth et al. 1996) mature OSNs. However, our OSN lifetime estimates of ~ 30 days, together with the number of newborn cells, suggest a much higher number of $\sim 150,000$ OSNs per zebrafish OE. While we did not evaluate OSN survival beyond 3 months, 8.1% of long-lived OSNs were still present at that time point (Bayramli et al. 2017), which correlates well with the number of 7.8% of long-lived OSNs that were observed in the mouse OE (Holl 2018).

One of the seminal findings shortly after the discovery of the OR genes (Buck and Axel 1991) was the observation that OSNs expressing individual ORs segregate within spatial domains of the OE (Ressler et al. 1993; Vassar et al. 1993). While the actual number of “expression zones” in the rodent OE is still under debate (Miyamichi et al. 2005; Zapiec and Mombaerts 2020), these studies agree that each OR is expressed only within a relatively narrow region along the dorso-ventral axis of the OE. The functional significance of zonal OR expression is still unclear but a contribution to odorant detection (Coppola et al. 2013) or establishment of axonal projections from the OE to the OB have been suggested (Mori et al. 2000; Vassalli et al. 2002). In zebrafish, OSNs expressing individual ORs (Weth et al. 1996), Olfc/V2Rs (Ahuja et al. 2018), and TAARs (Hussain et al. 2009) have been shown to occupy overlapping concentric domains with varying peak distributions on cross sections through the OE, which, on a first glance, resembles zonal organization in the mammalian OE.

The concept of fixed and spatially organized expression domains, however, does not fit well with the generation of OSNs from two opposing proliferation zones at the ILC and SNS and the progressive lateral movement of adult-born OSNs in zebrafish. Newborn OSNs express ORs, V2Rs, and the mature OSN markers OMP and TrpC2 as early as 4 days, thus shortly after they are generated and while they are still close to the ILC or SNS, making it unlikely that positional cues along the lamella pattern OR expression (Bayramli et al. 2017). Instead, we could show that spatial segregation of OSNs expressing different ORs can be explained entirely by simple non-molecular parameters, such as the relative number of cells created at each proliferation zone, their migration speed towards the center of the sensory OE, and their survival time. Thus, peak distributions of OSNs expressing a given chemoreceptor appear to be a consequence of their movement rather than being determined by positional morphogens,

questioning whether segregated OR patterns in zebrafish bear any functional relevance. In contrast, lateral movement of OSNs is negligible in the rodent OE, as seen from clonal analysis in the HBC and GBC lineages (e.g., Leung et al. 2007; Chen et al. 2014). A comprehensive understanding of how zonal OR expression is established in rodents is still missing, but it is likely specified at some level by localized molecular factors either to generate position-specific sets of restricted progenitors or to bias the output of multipotent progenitors towards specific OSN fates within a zone (Coleman et al. 2019).

While differences in the generation of microvillous OlfC-expressing OSNs have not been investigated formally, similar principles seem to apply. OlfC-expressing OSNs also occupy concentric domains with “centers of gravity” for each receptor (Ahuja et al. 2018). Most of the studied OlfC genes showed peak distributions with bias towards the ILC and only OlfCc1- (previously also known as v2rl1) expressing cells occupies a more symmetrical distribution around the mid-sensory OE (Ahuja et al. 2018). OSNs expressing this receptor, the mammalian homolog of which functions as a coreceptor in V2R-expressing vomeronasal neurons (Silvotti et al. 2007), are generated at high and equal numbers and from the ILC and SNS, which may explain the more symmetric distribution in line with our model (Bayramli et al. 2017). The model also predicts that cells expressing any of the other six OlfC genes studied may be preferentially, but not necessarily exclusively, generated from the ILC.

The presence of two distinct proliferation zones also raises the question whether the stem/progenitor cell niches at the ILC and SNS are equivalent or if the same progenitor cell can generate different OSN subtypes and chemoreceptor populations. Generally, the SNS appears to be more active than the ILC, and about 1.5 to 2 times more cells are generated at the SNS (Bayramli et al. 2017). While proliferative activity at the SNS may also contribute to the generation of non-neuronal cell types that are destined for the peripheral non-sensory OE, Delta A- and Ascl1-positive transit-amplifying cells of the GBC lineage are also more frequent at the SNS, suggesting that neurogenic activity is indeed about two-times higher at the SNS. However, a somewhat different picture emerges for different OSN subtypes. TrpC2-positive microvillous OSNs are generated more frequently at the SNS, while generation of OMP-positive ciliated cells shows an opposite bias towards the ILC. Surprisingly, the generation of OSNs that express specific chemoreceptor genes does not follow the same rule as the morphological cell type in which they are expressed, and cells expressing individual receptors can be generated more frequently at the ILC, at the SNS, or equally from both proliferation zones (Bayramli et al. 2017). The origin of crypt, kappe, and pear OSNs has not been investigated but a positional bias of these cells towards the ILC has been reported (Oka et al. 2012; Ahuja et al. 2014; Wakisaka et al. 2017).

Thus, similar to zonal OR expression in the rodent main OE, the ILC and SNS either contain distinct GBC progenitors that are committed to generate specific OSN subsets or the two niches are under the influence of distinct positional morphogens that bias chemosensory receptor expression. On a larger scale, it remains to be investigated whether the same GBC-like cell can generate morphologically distinct OSN subtypes or if separate GBC lineages exist for ciliated, microvillous, crypt, pear, and kappe cells.

Recovery of the OE from traumatic injury

In addition to the constitutive high proliferation rate observed in the intact OE, even severe traumatic damage to the tissue is repaired with remarkable speed and accuracy. The OE is capable of regenerating from conditions in which essentially the entire OSN population has been lost (Schwob et al. 1992; Konzelmann et al. 1998; Iqbal and Byrd-Jacobs 2010). Different experimental paradigms can be used to induce OE damage to different degrees or with different cellular specificity, such as blunt physical trauma (Var and Byrd-Jacobs 2019), olfactory nerve transection (Graziadei et al. 1978), bulbectomy (Carr and Farbman 1992), obstruction of the naris (Farbman et al. 1988; Scheib et al. 2019), genetic manipulation (e.g., Ma et al. 2014; Herrick et al. 2017), treatment with cytotoxic drugs (Bergström et al. 2003), and exposure to cytotoxic solutions (Cancalon 1982, 1983; Iqbal and Byrd-Jacobs 2010) or gas (Hurt et al. 1988). Full recovery of the OE occurs within several days to months and depends largely on the type and extent of damage that has been created, although species-specific differences and age-dependent influences (reviewed in Brann and Firestein 2014) have been described.

Chemical lesion of the OE with ZnSO₄, which disrupts the structural integrity of the OE and kills OSNs and other OE cell types, can be restored within 30 days in rabbits (Mulvaney and Heist 1971) or around 70 days in mouse (Matulionis 1975) and frogs (Smith 1951). Adult rats recover from methyl bromide-induced OE ablation within 4 to 6 weeks (Schwob et al. 1995). Nerve transection and olfactory bulbectomy, i.e., removal of the OB, predominantly affects the OSN population in the OE, which dies retrogradely from the severed axons (Carr and Farbman 1992). Morphologically normal OEs can be seen 60 days after nerve transection in squirrel monkeys (Graziadei et al. 1980) or 30 days in neonatal mice (Graziadei et al. 1978), while only incomplete restoration of epithelial thickness was reported in the hamster after 6 months (Costanzo and Graziadei 1983). An unrivaled champion in terms of OSN regeneration is the zebrafish OE, which can recover from loss of the near entire OSN population (Iqbal and Byrd-Jacobs 2010; Hentig and Byrd-Jacobs 2016) or even the entire olfactory organ structure (Scheib et al. 2019) within only 5 to 7 days.

The cellular mechanisms that contribute to regeneration largely depend on which cell types have been affected and need to be regenerated. Selective loss of OSNs preferentially, if not exclusively, stimulates GBC activity (Suzuki et al. 1998; Leung et al. 2007), while damage to non-OSN cell types is required for HBC activation (Leung et al. 2007; Herrick et al. 2017). Since structural damage affects all OE cell types, the regeneration response most likely involves simultaneous activation of HBCs and resident GBCs. Since activated HBCs generate additional progenitor cells that are indistinguishable from resident GBCs (Leung et al. 2007), HBC activity expands the proliferative GBC pool and the OE is ultimately restored by GBC activity.

In zebrafish, a robust experimental method to damage the OE is simple irrigation with the detergent Triton X-100 (Iqbal and Byrd-Jacobs 2010). The severity of the damage can be adjusted by changing the detergent concentration or through repeated application (Paskin et al. 2011). A single exposure to 0.7% Triton X-100 leads to loss of more than half of the HuC/D-positive neuronal population within 24 h, along with signs of inflammation and structural changes, such as the fusion of neighboring lamellae (Iqbal and Byrd-Jacobs 2010). Over the next 2 to 5 days the number of HuC/D cells and the thickness of lamella returns to pre-injury conditions, indicating that the OSN population has been largely restored. Repeated application of Triton X-100 more severely affects the OE extending the recovery period to 21 days (Paskin et al. 2011). Recently, we have shown that removable wax plug insertions into the naris results in severe atrophy of the OE (Scheib et al. 2019). Despite the observation that the entire structure is virtually absent, the OE reconstitutes within 1 week after removal of the plugs, including the reformation of a multilayered epithelium and a clear rosette structure, although the number of lamellae may be reduced. The OE appears to be largely normal and fully restored by 3 weeks after the insult.

Irrigation with chemicals that are applied to the external surface of the OE, such as ZnSO₄ and Triton X-100, seem to have a selective impact on ciliated OSN, while microvillous cells are largely spared (Paskin and Byrd-Jacobs 2012; Hentig and Byrd-Jacobs 2016). This observation is somewhat counterintuitive given the more apical distribution of microvillous somata compared to ciliated cells (Sato et al. 2005). It may be that the larger cilia (2–3 µm in length; Hansen and Zeiske 1998) are more vulnerable to chemical exposure than the short (0.5–0.8 µm) microvilli and that ciliated OSNs die preferentially because their cilia have been damaged, while microvilli more robustly sustain chemical exposure (Cancalon 1983).

One of the more remarkable features of the regeneration response to damage is a change in the pattern and tissue distribution of proliferating cells. As described above, proliferative activity in the intact OE is high at the ILC and SNS but not within the sensory OE (Iqbal and Byrd-Jacobs 2010; Bayramli et al. 2017). Following Triton X-100-induced damage,

increased proliferative activity can also be observed within the sensory OE, thus, between the marginal proliferation zones at the ILC and SNS (Iqbal and Byrd-Jacobs 2010; Demirler et al. 2020). Mitotic activity in the sensory OE stays high for the first 3 days after the lesion but declines to lower levels after 5 days indicating that the damage-induced proliferation pattern is a transient response (Iqbal and Byrd-Jacobs 2010). Colabeling with the HBC marker keratin 5 indicates that 1 day after damage, the otherwise dormant HBC population in the sensory OE is induced (Demirler et al. 2020), similar to the activation of HBCs in the injured rodent OE (Leung et al. 2007). While only occasional BrdU/keratin 5-double positive cells can be observed in the intact OE, Triton treatment increased the number of mitotically active HBCs about 15-fold (Demirler et al. 2020). Preliminary findings from our group support the concept that the HBC response includes the transient generation of Ascl1-positive GBCs in the sensory OE and that the activity is neurogenic. Thus, stem cell responses in the zebrafish OE follow the same rules as in higher vertebrates, despite the different distribution of GBCs and HBCs within the tissue.

Signaling molecules and molecular pathways regulating OSN neurogenesis

The high rate of OSN neurogenesis in the intact and damaged OE not only is remarkable but also requires a tight level of regulation to avoid fluctuations in sensitivity to odorants or imbalances in tissue size and cellular composition of the OE. Excessive cell proliferation would result in a larger than normal number of OSNs that provide sensory input to higher olfactory circuits and, therefore, may change odor perception. If uncontrolled, the process could result in neuroblastoma-like forms of cancer, which, however, appear to be rare in the nose of mammals (Bailey and Barton 1975; Yamate et al. 2006; Parker et al. 2010) and fish (Torikata et al. 1989; Vigliano et al. 2011; Gould et al. 2020). Even during recovery from severe damage, the OE does not overgrow and cell proliferation ceases as soon as or slightly before pre-injury conditions have been reestablished. In contrast, if OSN neurogenesis would be too low to catch up with the rate of OSN loss in the intact OE, the consequence would be progressive decline, eventually complete loss, of smell sensation. Thus, it is plausible to assume that the rate of OSN neurogenesis must be somehow linked to the density of intact OSNs, the rate of dying cells, or other aspects of structural OE integrity to match GBC and HBC proliferation rates with the number of OSNs that need to be replaced.

At the molecular level, a large number of diverse signaling molecules, ranging from growth (Plendl et al. 1999; Beites et al. 2005; Fukuda et al. 2018) and neurotrophic factors (Buckland and Cunningham 1998; Simpson et al. 2003) to peptides (Jia and Hegg 2012) and small molecules, such as

dopamine (Feron et al. 1999), nitric oxide (Sülz et al. 2009), and purines (Jia et al. 2009), have been demonstrated to stimulate or to repress OSN neurogenesis in vivo or in vitro. However, with the exception of purines (Demirler et al. 2020; see below), none of these molecules or signaling pathways have been functionally investigated in the zebrafish OE.

Selective loss of OSNs stimulates GBC activity but has no effect on HBCs in rodents (Leung et al. 2007). It has been shown that leukemia inhibitory factor (LIF) is expressed by OSNs and strongly upregulated after bulbectomy (Bauer et al. 2003). GBCs but not HBCs express the LIFR β receptor and LIF knockout reduces progenitor proliferation in the intact OE, suggesting a stimulatory effect of OSNs on GBCs (Kim et al. 2005). There is also strong evidence for negative regulation by factors derived from intact OSNs to restrain GBC activity when OSN density reaches optimal levels to prevent overproduction of cells. Growth and differentiation factor 11 (GDF11; also known as BMP11) is expressed by OSNs and inhibits cell cycle progression and self-renewal in immediate neuronal precursors of the late GBC lineage (Wu et al. 2003). Consistent with its function as a negative feedback regulator, GDF11 knockout results in supernumerary OSNs, whereas transgenes carrying a deletion of the natural GDF11 antagonist follistatin show reduced OSN numbers.

HBC activation, on the other hand, requires structural changes in the OE that are more extensive and affects non-OSN cell types. Indeed, selective ablation of SCs by overexpression of diphtheria toxin in transgenic mice triggers HBC activity (Herrick et al. 2017). The contact between HBCs and SCs in the intact tissue activates Notch signaling in HBCs through its ligand Jagged1, which is expressed by SCs. Notch activity, in turn, positively regulates expression of p63, a master regulator of HBC dormancy (Fletcher et al. 2011; Schnitke et al. 2015). Thus, loss of SCs in the damaged OE tunes down Notch signaling and subsequently p63 expression and, thereby, activates HBC proliferation.

Damage-associated molecular patterns (DAMPs), on the other hand, comprise a heterogeneous class of molecules that are liberated from damaged or dying cells and stimulate non-infectious inflammatory responses and other molecular processes, such as cell death and proliferation (Venereau et al. 2015). Thus, DAMPs could be involved in regulating OE neurogenesis when they are released from OSNs that reach the end of their lifespan or from damaged cells after OE injury. This is an attractive model because the momentary concentration of the DAMP would correlate directly with the number of cells that need to be replaced and could provide a match between the rate of OSN loss and neurogenesis.

In particular, adenosine triphosphate (ATP) has emerged as a DAMP that positively modulates regeneration in various tissues (Burnstock 2016a, 2016b), including the adult neurogenic niches at the ventricular-subventricular zone of the forebrain (Suyama et al. 2012) and the hippocampus (Cao et al.

2013). In the olfactory system, ATP stimulation has been shown to trigger Ca²⁺ transients in SC and basal cells in mouse and *Xenopus* (Hegg et al. 2009; Hassenklöver et al. 2008). Thus, SCs that span the thickness of the OE and make cell–cell connections with basal cells could function as “antennae” to detect ATP or other DAMPs that are released from dying cells in more apical strata and convey the signal to basal progenitors. Both constitutive and ATP-stimulated ATP release from SCs and its pro-proliferative effect on basal progenitors has been demonstrated (Hayoz et al. 2012). In addition, ATP stimulation of the OE upregulates expression of TGF- α in OSNs, FGF2 in OSNs and SCs (Jia et al. 2011), and NPY in SCs (Jia and Hegg 2010), for all of which proliferation-promoting activity has been shown.

We have recently demonstrated that ATP stimulation of the zebrafish OE induces selective cell proliferation and neurogenesis from GBCs at ILC and SNS but not from HBCs (Demirler et al. 2020). In the fish OE, ATP stimulation evokes Ca²⁺ transients in HBCs, SCs, and GBCs; however, the different cell populations have unique ATP sensitivity and purine receptor complements that may be linked to different outcomes. Despite their high sensitivity to ATP, HBCs did not respond with increased mitotic activity. Because zebrafish SCs also span the vertical dimension of the OE and are in contact with HBCs, this suggests that ATP-sensing and signal transmission to HBCs does not occur in the fish. Yet, the zebrafish OE is relatively small (~500 μ m diameter) and the radial length of the sensory region (180–230 μ m) is only twice the vertical height of the mouse OE, which is on average about 98 μ m (McIntyre et al. 2008). Thus, the GBC-containing proliferation zones at the ILC or SNS are similarly distant from the center of the OE as the basal cell layer from the apical surface of the OE in mice.

The selective impact of ATP on GBC-like cells (Demirler et al. 2020) is consistent with increased GBC activation that is seen after selective loss of OSNs (Leung et al. 2007), further supporting the hypothesis that purine DAMPs can function to communicate the need to replace dying OSNs in a rate-matched fashion. Blocking P2 receptor-mediated signaling by suramin treatment not only prevents ATP-stimulated OSN neurogenesis but also slows down progenitor cycling at the ILC and SNS in the intact OE, suggesting that ATP-mediated signaling may occur naturally in zebrafish to modulate the rate of GBC cycling (Demirler et al. 2020).

Even though far less is known about detailed molecular events that participate in and regulate cellular turnover, OSN neurogenesis, and organ regeneration in zebrafish, interesting similarities and differences are beginning to emerge. The speed with which the zebrafish OE regenerates, even from extreme structural degeneration stands out among vertebrate model organisms. The OE, however, defines only the first level of odorant sensing and olfactory processing and de- and regeneration events in the OE likely affect higher-order

neuronal circuits in the OB, which is itself a site of continuous cellular turnover and neurogenesis.

The central olfactory bulb of the zebrafish

Anatomical organization of the zebrafish olfactory bulb and telencephalon

The zebrafish brain continues to grow way into adulthood and possesses a total of 16 active neurogenic niches with high proliferative activity that are scattered throughout the brain (Grandel et al. 2006). This is in stark contrast to the limited neurogenic capacity of adult mammals, in which active cell proliferation can consistently be identified only in a few brain regions. Among those, the most prominent and most widely studied neurogenic areas are the granular cell layer of the hippocampus and the V-SVZ of the forebrain ventricle across different organisms (Gage 2000). Two relevant regions that contribute new neurons to the olfactory system in zebrafish can be localized to the OB and the adjacent telencephalon, which is functionally similar to the V-SVZ (Byrd and Brunjes 2001; Zupanc et al. 2005; Grandel et al. 2006). These neurogenic niches are maintained by a population of highly proliferative neural progenitors that give rise to different subtypes of neurons destined for the telencephalic parenchyma and the OB (Adolf et al. 2006; Grandel et al. 2006; Kaslin et al. 2008). Newborn cells that arrive in the OB develop into GABAergic granule and dopaminergic periglomerular cells (Byrd and Brunjes 2001), as has been reported in rodents (Petreanu and Alvarez-Buylla 2002).

Our group and others have characterized the anatomical and morphological organization of the zebrafish OB (Baier and Korsching 1994; Byrd and Brunjes 1995; Fuller et al. 2005, 2006; Braubach et al. 2012), which is a paired structure located at the rostralmost region of the forebrain. Each OB is connected to the ipsilateral OE by a short olfactory nerve, while OB output neurons project axons to higher olfactory processing centers via olfactory tracts (Figs. 1(b) and 2(a, b)). Different from the clear and distinct layering of the rodent OB (Shepherd 1972), the OB of zebrafish is diffusely organized into three concentric layers: (1) a superficial olfactory nerve layer, formed by olfactory axons; (2) a glomerular layer containing olfactory axon termini as well as apical dendrites and somata of mitral and ruffed cell output neurons along with periglomerular cell interneurons; and (3) an internal cell layer consisting predominantly of granule cell interneurons (Fig. 2(c); Baier and Korsching 1994; Byrd and Brunjes 1995; Edwards and Michel 2003; Fuller et al. 2005, 2006). The OB receives olfactory input from OSN axon terminals that form synaptic complexes with OB output and interneurons in spherical neuropil structures, the olfactory glomeruli (Baier and Korsching 1994). Granule cells form reciprocal

dendro-dendritic synapses with mitral cells, while periglomerular cells are more heterogeneous: a subset receives direct OSN input while another forms axo-dendritic synapses onto more distant mitral cells (Crespo et al. 2013). Both cell types provide lateral inhibition within and between glomeruli to modulate OSN input and odorant discrimination (Shepherd et al. 2007; Takahashi et al. 2016).

Glomeruli in zebrafish are distributed throughout the glomerular layer but, different from their homogeneous distribution in the mammalian OB (Royet et al. 1988; Zapiec et al. 2017), are organized into isolated regional clusters that are defined by OSN cell type and expression of their cognate chemosensory receptors (Sato et al. 2005; Koide et al. 2009; Braubach et al. 2012). A total of ~140 glomeruli have been described and classified in zebrafish based on their location and molecular marker expression (Braubach et al. 2012). Ciliated and microvillous OSNs innervate the OB in a mutually exclusive fashion, where the former project axons to dorsal, ventral, and medial glomerular domains and the latter project to morphologically distinct glomeruli in the lateral OB (Sato et al. 2005; Koide et al. 2009; Braubach et al. 2012).

Output neurons that receive sensory input from medial and lateral glomerular clusters tend to project axons through the medial and lateral olfactory tracts, respectively, as opposed to the presence of a single lateral tract in mammals (Fig. 2(c); Fuller et al. 2006; Gayoso et al. 2012; Miyasaka et al. 2014). While functional segregation of olfactory tracts remains unclear in zebrafish, in other teleosts, the medial olfactory tract relays sensory information from ciliated OSNs that are responsive primarily to bile salts and pheromones, while the lateral olfactory tract processes microvillous OSN responses to amino acids (Von Rekowski and Zippel 1993; Sorenson et al. 1991). The olfactory tracts connect the OB to the telencephalon, located posterior to the OBs and formed by two lobes with an extensive ventricular surface along the rostrocaudal axis (Fig. 2(b, d); Gayoso et al. 2012).

The telencephalon is the most widely studied proliferative zone and neurogenic niche in the zebrafish brain and contains multiple regions that show abundant cell proliferation (Labusch et al. 2020). During development, the teleost telencephalon forms by eversion (outward folding) instead of evagination (inward folding) as observed in mammals (Folgueira et al. 2012). A consequence of this characteristic process is that the ventricle and associated proliferative zones are found along the outer surfaces of the ventral and dorsal telencephalon, rather than being embedded inside the brain (Fig. 2(d); Hodos and Butler 1997; Folgueira et al. 2012). In a transverse section of the anterior region of the telencephalon, two ventricular surfaces can be observed: a prominent ventral v-shaped zone and a smaller dorsal t-shaped zone, separated by a medial anterior commissure through which the two lobes are connected. In the posterior telencephalon, the ventricular surface angles dorsally, giving rise to a larger dorsal

ventricular zone. There is a gradient of proliferation along the rostrocaudal axis of the telencephalic ventricular region, with the rostral domain presenting proliferation throughout the ventricular surface, while proliferation in caudal regions is restricted to isolated domains (Grandel et al. 2006; Wullmann and Mueller 2004).

The anterior telencephalon can be roughly divided into two subdomains, the dorsal pallium and ventral subpallium (Fig.

2(d)). The pallium encompasses the dorsal, dorsomedial, and lateral regions, which have been described to be homologous to the neocortex, amygdala, and hippocampus, respectively (Wullmann and Mueller 2004), while the subpallium is located in the medial and ventromedial areas of the telencephalon. Based on its cellular and molecular components, this region is further subdivided into the ventroventral (Vv) and ventrodorsal (Vd) subdomains, which have been described

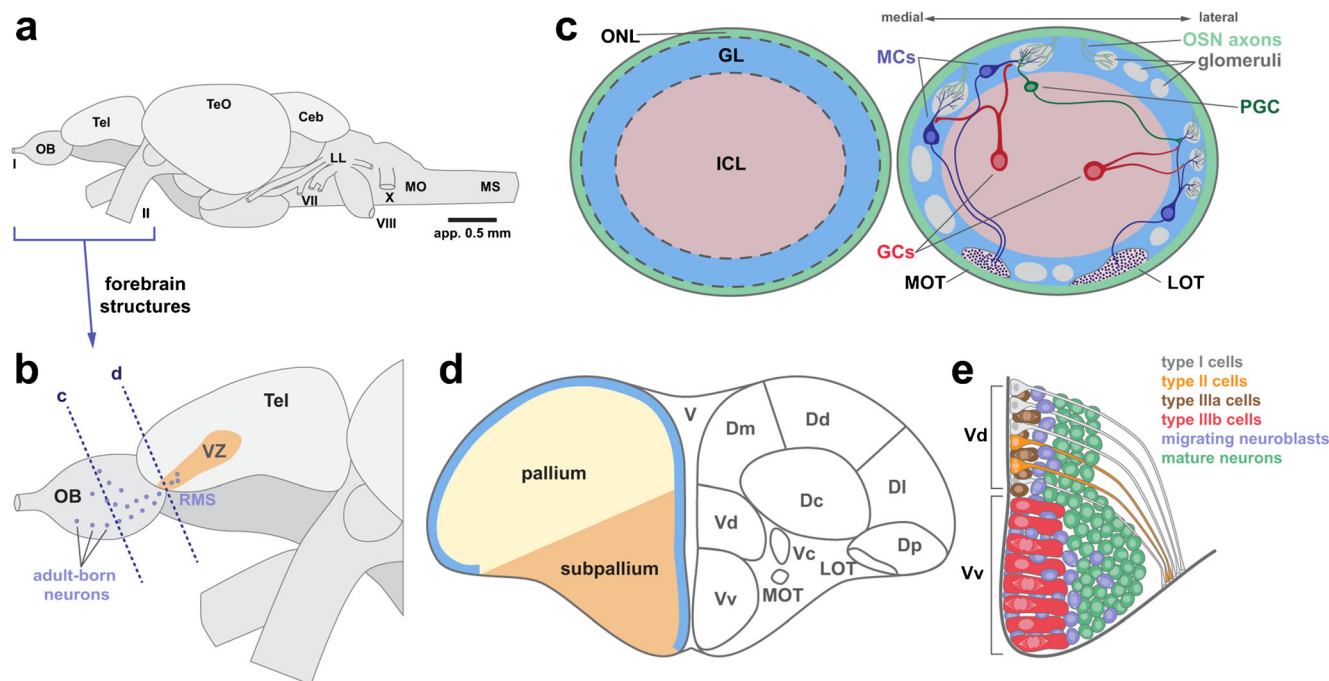


Fig. 2 Overview of the zebrafish olfactory bulb and telencephalon. (a) Lateral view of the full zebrafish brain (adapted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Anatomy and Embryology, The zebrafish brain: a neuroanatomical comparison with the goldfish, Rupp et al. 1996). The olfactory bulb (OB) and adjacent telencephalon (Tel) are located rostrally (left); TeO: optic tectum, Ceb: cerebellum, LL: nerve trunks of lateral line, MO: medulla oblongata, MS: medulla spinalis, roman numbers depict various cranial nerves. (b) Detailed view of olfactory-related forebrain structures. Neuroblasts generated along the ventricular zone (VZ) within the telencephalon (orange) enter the OB through the rostral migratory stream (RMS) and give rise to adult-born neurons (blue dots). The dotted lines show the positions of coronal sections through the OB and telencephalon shown in (c) and (d), respectively. (c) Overview of laminar organization (left) and cellular composition (right) of a coronal section through the OB. Three concentric layers can be observed. The outermost olfactory nerve layer (ONL; green) contains axons of olfactory sensory neurons (OSNs) from the OE, while the glomerular layer (GL, light blue) is composed of synapses between OSN axons and mitral cell (MC, dark blue) dendrites in olfactory glomeruli (gray blobs). MC bodies are also located predominantly within the GL. Most MCs extend dendritic branches to a single glomerulus (left) but multiglomerular MCs (right) have also been described in the lateral OB. Periglomerular cells (PGCs, green) also receive sensory input from OSN terminals and extend axons that form inhibitory synapses on MCs of neighboring glomeruli. Granule cells (GGs, red) are axonless cells that occupy the inner cell layer (light red) and form dendrodendritic inhibitory synapses between different MCs or dendritic trunks of the same cell that target different glomeruli. MC axons from the medial

and lateral OB exit from the medial (MOT) and lateral (LOT) olfactory tract, respectively, and transduce olfactory signals to higher olfactory centers in caudal brain structures. (d) Overview of a coronal section of the anterior telencephalon (adapted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Neural Development, Neurogenesis in zebrafish—from embryo to adult, Schmidt et al. 2013). The gross telencephalic anatomical divisions are shown in the left half of the panel: pallium (yellow), subpallium (orange). The blue line depicts the neurogenic periventricular zone, which is in direct contact with the ventricle (V). Detailed anatomical subdivisions are shown in the right half of the panel. The pallium is further subdivided into dorsal domains: dorsomedial (Dm), dorsodorsal (Dd), dorsocentral (Dc), dorsolateral (Dl), and dorsoposterior (Dp). The subpallium is divided into ventrodorsal (Vd), ventroventral (Vv), and ventrocentral (Vc) domains. The olfactory tracts (MOT, LOT) stemming from the MC axons in the OB are also shown. (e) Neurogenic niches in the ventral half of the anterior telencephalon. The Vd domain contains two types of radial glial progenitors lining the ventricular surface. Type I (quiescent, gray) and type II (proliferating, orange), which both extend radial processes to the pial lateral surface. Type IIIa proliferating neuroblasts (brown) and migrating neuroblasts (blue) are found laterally in the parenchyma, as well as mature neurons (green). The Vv domain is formed by neuroepithelial-like progenitors (red), characterized by their elongated shape and their high proliferation rate. In addition, a great number of migrating neuroblasts (blue) and mature neurons (green) are found flanking this niche. Note that some of the neuroblasts originating from the Vv also migrate to the OB to give rise to GGs and PGCs

to be functionally similar to the V-SVZ of mammals (Fig. 2(d); Kaslin et al. 2008; Ganz et al. 2010). These highly proliferative ventricular regions comprise a variety of neuronal progenitor cells and precursors that give rise to adult-born neuroblasts, which invade the adjacent telencephalic parenchyma or migrate to the OB (Adolf et al. 2006; Grandel et al. 2006; Kishimoto et al. 2011). Out of the scope of this review is the pallial neurogenesis, which has been reviewed in detail elsewhere (Labusch et al. 2020).

Characteristics of neuronal precursors and neurogenic niches of the adult OB and anterior telencephalic subpallium

Adult-born neurons in the V-SVZ of the hippocampus of mammals are generated from a subset of specialized astrocytes that function as neural stem cells (NSCs). These astrocytes are derived from radial glia cells, which act as progenitors throughout early CNS development (Fuentetaja et al. 2015). Radial glial cells are not found in the adult brain, although astrocytic NSCs are often referred to as “radial glial-like,” given their location and progenitor function (Rakic 1998). In the V-SVZ, NSCs (B1 cells) give rise to transit-amplifying cells (C cells) through asymmetrical divisions (Doetsch et al. 1999; Kriegstein and Alvarez-Buylla 2009). Type C cells further divide to generate migrating neuroblasts (A cells), which in turn reach the OB through the rostral migratory stream (RMS; Doetsch and Alvarez-Buylla 1996; Lois et al. 1996; Lim and Alvarez-Buylla 2016). Neuroblasts that arrive at the OB disperse radially and differentiate into mature interneurons (Luskin 1993; Alfonso et al. 2015).

Unlike in mammals, radial glia cells persist throughout adulthood in zebrafish and are bona fide NSCs since they are able to both self-renew and generate different types of progenitors (Zupanc and Clint 2003; Marz et al. 2010; Rothenaigner et al. 2011). These cells are found along the outer ventricular surfaces where the cell bodies are in direct contact with the cerebrospinal fluid and extend radial processes through the parenchyma to contact the pial surface (Fig. 2(d, e); Ganz et al. 2010; Marz et al. 2010; Kishimoto et al. 2011; Rothenaigner et al. 2011). In the telencephalic subpallium, four types of progenitor cells have been described, based on molecular marker expression, activation state, and pattern of cell division: quiescent radial glial cells (type I cells), dividing radial glia (type II cells), radial glia-derived cycling neuroblasts (type IIIa cells), and dividing neuroblasts that lack the expression of glial markers (type IIIb cells; Ganz et al. 2010; Marz et al. 2010; Chapouton et al. 2010). In contrast, type I, II, and IIIa cells all express canonical markers of radial glia, such as brain lipid-binding protein (BLBP; Adolf et al. 2006; Marz et al. 2010; Diotel et al. 2016), glial fibrillary acidic protein (GFAP; Lam et al. 2009; Ganz et al. 2010; Marz et al. 2010; Kishimoto et al.

2011), S100 calcium-binding protein beta (S100 β ; Ganz et al. 2010; Marz et al. 2010; Rothenaigner et al. 2011), vimentin (Ganz et al. 2010), glutamine synthase (GS; Ganz et al. 2010), and aromatase B (Ganz et al. 2010; Pellegrini et al. 2007; Diotel et al. 2016). Type II progenitors, which are actively proliferating, can divide symmetrically to expand the pool of type II cells or asymmetrically to give rise to fast-cycling type IIIa neuroblasts (Chapouton et al. 2010; Marz et al. 2010). The latter can be identified by expression of GFAP (Marz et al. 2010), BLBP (Marz et al. 2010), and the polysialylated-neural cell adhesion molecule (PSA-NCAM; Grandel et al. 2006; Adolf et al. 2006; Marz et al. 2010; Chapouton et al. 2010), which is an established marker for migrating neuroblasts (Kishimoto et al. 2011). In contrast, the ventral fast-proliferating type IIIb neuroblasts are considered to be neuroepithelial-like cells, given their polarized morphology (Ganz et al. 2010; Kishimoto et al. 2011) and presence of interkinetic nuclear migration during mitosis (Ganz et al. 2010), in addition to their lack of glial marker expression (Ganz et al. 2010; Marz et al. 2010; Kishimoto et al. 2011). Both IIIa and IIIb type cells in the zebrafish subpallial telencephalon undergo one or two rounds of cell division followed by a terminal symmetric division that give rise to migrating neuroblasts (Rothenaigner et al. 2011). The majority of proliferating precursors express the NSC markers Nestin and Sox2 (Adolf et al. 2006; Lam et al. 2009; Ganz et al. 2010; Chapouton et al. 2010; Marz et al. 2010), although a small percentage of progenitors present a mosaic expression pattern that differs from the majority of precursors, suggesting that NSC subtypes in the zebrafish telencephalon may be more diverse (Kizil et al. 2012; Diotel et al. 2015; Cosacak et al. 2019; Labusch et al. 2020).

Surprisingly, we and others have found that the zebrafish OB itself, unlike the mammalian OB, presents constitutive proliferation throughout adulthood and that most of these proliferating cells can be found scattered within the olfactory nerve and glomerular layers of the OB (Byrd and Brunjes 1998, 2001; Grandel et al. 2006; Adolf et al. 2006; Villanueva and Byrd-Jacobs 2009; Trimpe and Byrd-Jacobs 2016). Nevertheless, despite local OB neurogenesis, the function of the VZ as the primary source for new OB neurons appears to be conserved. It has been suggested that the posterior ventrolateral region of the OB, near the interphase with the ventral telencephalon, could be considered a neurogenic niche given the presence of BrdU-positive profiles in this region and their ultrastructural similarity in cell morphology to type II and IIIa progenitors of glial origin (Lindsey et al. 2014). It is noteworthy, however, that bona fide radial glia or astrocytes have not been described in the zebrafish OB; instead, GFAP-, S100 β -, and GS-positive fibers can be found extensively in the olfactory nerve and glomerular layers, thus, the regions of the adult OB where proliferation takes place (Byrd and Brunjes 1995, 1998; Alonso et al. 1998;

Grupp et al. 2010; Lazzari et al. 2014; Scheib and Byrd-Jacobs 2020).

BrdU pulse-chase assays label cells in the periphery of the OB a few hours after the pulse and newly generated neurons are present in the internal cell layer within 1 week (Byrd and Brunjes 1998, 2001; Adolf et al. 2006; Lindsey et al. 2014). These neurons express dopaminergic and GABAergic markers, suggesting that they develop into granule and periglomerular interneurons similar to VZ-derived cells. Even though it is likely that most of the adult-born neurons in the internal cell layer are derived from progenitors that are located outside of the OB, a subset of neurons may be produced in situ, given that the rate of proliferation in the OB can be regulated by changes in sensory input or damage (see below). In addition, PSA-NCAM, a molecule required for neuroblast migration, is found in the peripheral olfactory nerve layer (Lazzari et al. 2014). A similar pattern of intrabulbar proliferation and neurogenesis has been described in other teleost fishes, in which NSCs are found in the peripheral layers and the newly divided cells subsequently migrate to more internal positions (Alonso et al. 1989; Zupanc and Horschke 1996; Zupanc et al. 2005; Fernandez et al. 2011; Teles et al. 2012). In line with this, the two related sialyltransferases enzymes STX and PST, which are required for the formation of PSA-NCAM, are expressed abundantly throughout the zebrafish OB, suggesting that both local and distant neuroblast migration can occur in the zebrafish OB (Rieger et al. 2007).

The cytoarchitecture of the ventral telencephalic Vv and Vd domains is complex, and the two domains can be distinguished by the presence of different progenitor types (Fig. 2(e)). The Vv domain is formed by a large number of tightly packed fast-cycling, neuroepithelial-like type IIIb precursors lining the medial ventricular surface, most of which are constitutively proliferating (Kishimoto et al. 2011; Rothenaiger et al., 2011). These precursors give rise to dividing intermediate neuroblasts that migrate laterally to constitute a massive cell layer that extends deep into the adjacent parenchyma but also contains non-proliferative precursors and other supporting cells. The neurogenic ventricular layers are flanked by a dense population of mature neurons, none of which present active proliferation markers. Noteworthy, however, some of these neurons retain BrdU labeling for weeks following a BrdU pulse, suggesting that neurogenesis in the Vv region contributes at least two types of newborn cells: those that migrate rostrally into the OB and others that migrate radially and remain within the Vv (Ganz et al. 2010; Marz et al. 2010; Kishimoto et al. 2011; Lindsey et al. 2014). In contrast, the Vd domain is narrower than the Vv and contains fewer proliferating cells. It is comprised of scattered quiescent type I radial glia, type II slow-cycling proliferating precursors lining the ventricular surface, and type IIIa progenitors adjacent and intermixed within this layer. All of these glial cells extend

individual radial projections to the dorsolateral pallium. The neurogenic region of the Vd is flanked by a population of parenchymal mature neurons and migrating neuroblasts (Adolf et al. 2006; Grandel et al. 2006; Marz et al. 2010; Lindsey et al. 2014). While much is known about the molecular differences of the various proliferating precursors, additional work will be needed to shed light onto the molecular regulation of constitutive and regenerative neurogenesis under different tissue conditions.

Constitutive neurogenesis in the OB and telencephalon

Adult neurogenesis in the zebrafish brain is remarkable for various reasons: it persists throughout the organism's lifespan, it takes place in multiple distinct niches along the CNS, and it contributes a striking number of newborn cells to the existing neuronal population. It has been estimated that up to 100 times more neurons are produced in the teleost CNS than in the mammalian brain (Zupanc and Horschke 1996; Hinsch and Zupanc 2007; Zupanc and Sirbulescu 2011). The constitutive and life-long neurogenesis in the adult OB and telencephalon supports several processes and brain functions, which include postlarval growth and basal replacement of lost neurons, in addition to sensory and behavioral plasticity (Takahashi et al. 2018). The presence of active neurogenic niches in the adult organism also provides a cellular basis for the vast capacity for regeneration and repair that has been reported. Contrary to the documented decline of neurogenic activity in mammals throughout life (Luo et al. 2006; Shook et al. 2012; Paredes et al. 2018), aging does not significantly affect the innate proliferative and neurogenic ability of the teleost brain (Olivera-Pasilio et al. 2014; Traniello et al. 2014; Rosillo et al. 2010; Trimpe and Byrd-Jacobs 2016).

Newborn cells that arise from the Vv reach the OBs via a migratory route that resembles the RMS between the V-SVZ and the OB in rodents (Altman 1969; Lois and Alvarez-Buylla 1994; Kishimoto et al. 2011). Different from mammals, however, the RMS in zebrafish is not lined by a corridor of glial cells (Kishimoto et al. 2011). Nevertheless, the occurrence of a RMS is conserved among taxa, such as teleosts, birds, and mammals, despite differences in cellular makeup, distance to be traveled, and organization (Nottebohm et al. 1994; Olivera-Pasilio et al. 2014, 2017; Malik et al. 2012; Orechio et al. 2018). In zebrafish, migration of newly born progenitors from the Vv takes place in three stages: (1) type IIIa and IIIb progenitors move radially from the lumen of the ventricle towards the telencephalic parenchyma; (2) then they turn rostrally and migrate through the ventromedial interphase between the OBs and the telencephalon; and finally (3) they migrate again radially across the inner cell layer of the OB, similar to their trajectory in rodents and other teleosts (Terzibasi et al. 2007;

Rosillo et al. 2010; Kishimoto et al. 2011; Olivera-Pasilio et al. 2014; Lim and Alvarez-Buylla 2016).

The incorporation of newborn cells in the OB of zebrafish and other teleost fishes shows remarkable plasticity in response to environmental factors (Zupanc and Zupanc 2006; Lindsey et al. 2014) and interesting inherent differences across similar organisms with different lifestyles or life spans. For instance, killifishes, which have a short annual lifecycle, show a very rapid OB neuronal turnover and can integrate newly born neurons in the OBs just 24 h after a BrdU pulse (Fernandez et al. 2011; Rosillo et al. 2010). On the other hand, in teleosts with longer lifespans, the proliferation, migration, and integration of newborn neurons in the OB occurs over a longer time period. In zebrafish and turquoise killifish (*Nothobranchius furzeri*), mature neuron profiles can be found in the VZ and the OB at 3 and 7 days after a BrdU pulse, respectively (Byrd and Brunjes 1995, 1998; Terzibasi et al. 2007). Although BrdU-labeled cells occur relatively soon in the OB of both groups, cellular maturation and functional integration into bulbar circuits may take up to several weeks (Villanueva and Byrd-Jacobs 2009; Trimpe and Byrd-Jacobs 2016). BrdU-labeled cells are found to be integrated into bulbar circuits for months after the pulse, suggesting that they are long-lived (Zupanc et al. 2005; Hinsch and Zupanc 2007; Teles et al. 2012). Adaptation to changing environments and the need for behavioral plasticity can also affect the rate of OB and Vv proliferation and neurogenesis. In an interesting example, the annual killifish (*Austrolebias charrua*) relies heavily on olfaction when their freshwater habitat becomes murky and mating and reproduction suddenly needs to take place in complete darkness (Rosillo et al. 2010; Passos et al. 2014). This need for increased olfactory acuity, but also olfactory sensory enrichment, can accelerate neurogenesis and integration of newborn neurons in the OB (Lindsey et al. 2014; Rosillo et al. 2010). Interestingly, in this fish, the posterior region of the OBs is lined by an enlarged ventricular surface comprising a neurogenic niche equivalent to the Vv zone of other teleosts. The presence of the neurogenic niche within the OB itself allows for more rapid neurogenesis, shorter migration distance, shorter time of integration into OB circuitries, and ultimately improved plasticity and adaptation to environmental changes. These examples showcase the many advantages that zebrafish and other teleosts present to study aspects of constitutive and sensory-modulated neurogenesis, which are only marginally understood in higher vertebrates (Zupanc and Zupanc 2006; Pinto and Götz 2007; Strobl-Mazzulla et al. 2010; Lindsey et al. 2012).

Recovery of the OB from traumatic injury and disease

Physical and chemical lesions in the mammalian CNS cause cell death and sustained functional loss of the damaged site since neurogenesis in the V-SVZ and hippocampus does not

contribute significantly to the replacement of lost neurons in other brain regions. Brain lesions are typically followed by an inflammatory response that involves activation of astrocytes (astrogliosis) and recruitment of microglia to the injured site. This often results in excessive inflammation, the formation of astroglial scars, and the exposure of myelin-derived factors that hinder repair of the lesioned site directly or prevent the regrowth of axons that connect across the site of injury (Hernandez-Ontiveros et al. 2013; Johnson et al. 2013; Karve et al. 2016). Interestingly, while inflammatory signals in the mammalian brain largely preclude regeneration, pro-inflammatory cytokines have been shown to activate radial progenitors and promote neuron replacement (Kyritsis et al. 2012). Thus, zebrafish features an astrocytic and microglial inflammatory response that is different from related events in mammals and which has been suggested to be a key contributor to successful regeneration and repair of lost neurons following CNS damage.

To study the mechanisms that underlie regeneration and repair of the zebrafish brain, a widely used model of traumatic brain injury involves unilateral stab wounds in the dorsal telencephalon (Kroehne et al. 2011; Marz et al. 2010). The lesion, unlike what has been documented in mammals, shows complete recovery, including the presence of mature newborn neurons within the injured region. Following the insult, a large number of damaged neurons undergo apoptosis, in contrast to necrosis, which is predominantly observed in mammals (Karve et al. 2016). The injured site is then repaired in three distinct phases that include (1) an acute but transient inflammatory response by microglia and astroglia; (2) an increase in radial progenitor proliferation and subsequent neurogenesis; and finally (3) migration of an increased number of neuronal precursors to the lesioned areas and repopulation of the damaged site with functional neurons (Kroehne et al. 2011; Marz et al. 2010; Kishimoto et al. 2011; Kyritsis et al. 2012; Skaggs et al. 2014). Physical lesions initially promote a systemic response of precursor proliferation within pallial and subpallial regions of both telencephalic hemispheres but with increased and sustained presence of neurogenesis on the side ipsilateral to the lesion. A large number of newly born neurons can be found within the parenchyma for up to several months after the lesion, suggesting that they have functionally integrated and replaced lost neurons (Kroehne et al. 2011; Marz et al. 2010; Baumgart et al. 2012; Kyritsis et al. 2012; Skaggs et al. 2014).

Inflammation acts as key modulator of neuronal replacement and tissue repair following damage in zebrafish (Keightley et al. 2014; Kizil et al. 2015). An astrocytic response following damage appears to be necessary and sufficient for enhancing neurogenesis in the ventricular zone via the activation of radial glial progenitors by CysLT1/LTC4 signaling and activation of non-glial progenitors by interleukin 4 (IL-4; Marz et al. 2010; Baumgart et al. 2012; Kyritsis

et al. 2012; Bhattarai et al. 2016). The astroglial inflammatory response of zebrafish, which promotes regeneration and neurogenesis, differs from that in mammals since teleosts lack the canonical GFAP-positive, stellate-shaped astrocytes and, instead, a range of morphologically distinct astroglial cells have been described throughout the CNS (Kizil et al. 2015; Zambusi and Ninkovic 2020). These cells express a combination of various glial markers (e.g., GFAP, vimentin, BLBP, GS, S100 β) and exhibit different regional morphologies (Cuoghi and Mola 2009; Clint and Zupanc 2001; Grupp et al. 2010; Lyons and Talbot 2014; Jurisch-Yaksi et al. 2020; Scheib and Byrd-Jacobs 2020). Even though an astroglial response occurs early in the lesioned hemisphere, it resolves quickly without leaving a permanent astroglial scar that obstructs regeneration and repair (Scheib and Byrd-Jacobs 2020).

In addition, microglial activation also modulates brain regeneration (Keightley et al. 2014). We have shown that microglia in adult zebrafish exhibit similar morphology, activation states, and phagocytic properties as their mammalian homologs (Var and Byrd-Jacobs 2019, 2020). Following damage, both resident microglia and infiltrating peripheral macrophages increase in the ipsi- and contralateral hemisphere, with a concentration of activated microglia around the lesioned region (Zupanc and Clint 2003; Marz et al. 2010; Baumgart et al. 2012; Var and Byrd-Jacobs 2019). Microglia remove neuronal debris and promote tissue repair by secreting various neurotrophic factors (Mazaheri et al. 2014; Herzog et al. 2019; Villani et al. 2019; Var and Byrd-Jacobs 2020). It has been shown that tumor necrosis factor (TNF), TGF β -1, C-C motif chemokine receptor 2 (CCR 2), chemokine (C-X-C motif) receptor 4b (cxcr4b), IL-4, and activated Wnt signaling are associated with regeneration (Nguyen-Chi et al. 2015; Bhattarai et al. 2016). A noticeable characteristic of zebrafish microglial cells is that they become transiently activated during a critical time frame but that the inflammatory response resolves quickly. It has been hypothesized that this specific and succinct activation period also underlies some of the regenerative properties conferred by microglia (Marz et al. 2010; Carrillo et al. 2016; Var and Byrd-Jacobs 2019, 2020).

We have developed different experimental models of direct lesion to the zebrafish OB that have shed light on mechanisms of regeneration, repair, and inflammation (Var and Byrd-Jacobs 2019; Calvo-Ochoa and Byrd-Jacobs, unpublished). Following direct bulbar chemical lesion, initial decreases in OB volume and alterations in olfactory axonal morphology can be observed. These alterations revert to pre-injury conditions within 21 days; the tissue appears fully recovered, including the restoration of most neurons, some of which are glutamatergic, suggesting that under these conditions, output neurons can also be generated in addition to GABAergic and dopaminergic interneurons. The paradigm also increases proliferation in the Vv domain of the VZ (Calvo-Ochoa and

Byrd-Jacobs, unpublished). In addition, the loss of OB output neurons also causes loss of OSNs in the OE, which is followed by induction of proliferation and recovery over the same time frame. Direct injury by stab wounds to the OB also promotes swift microglial migration through the ventricular zone, with a robust ipsilateral response 4 to 12 h following damage that subsides by 24 h (Var and Byrd-Jacobs 2019; Var and Byrd-Jacobs, unpublished).

Our group has also extensively studied the effects of sensory deafferentation on OB regeneration and neurogenesis by developing various reversible physical and chemical OE lesion paradigms. OE degeneration caused by these lesions also promotes OB degeneration, observed as a reduction in volume (Byrd 2000; Paskin et al. 2011), alterations in mitral cell dendritic morphology (Pozzuto et al. 2019), apoptotic loss of granule and periglomerular interneurons in the internal cell layer (Vankirk and Byrd 2003), and glomerular defasciculation (Paskin and Byrd-Jacobs 2012; White et al. 2015). In particular, there is a stark reduction in staining for dopaminergic somata and dendritic processes, which indicates a reduction in the number of periglomerular cells (Byrd 2000; Fuller et al. 2005; Paskin et al. 2011). As a result of the degeneration observed in both the OE and OB, we found that olfactory acuity is compromised, as assessed in behavioral assays. A swift recovery of normal OB morphology is observed within 10 days following OSN ablation while complete glomerular innervation and olfactory function are restored by 21 days (Vankirk and Byrd 2003; Paskin et al. 2011; Paskin and Byrd-Jacobs 2012; White et al. 2015; Hentig and Byrd-Jacobs 2016).

Interestingly, we have reported that unilateral bulbar deafferentation also activates a systemic response by inducing proliferation in the glomerular layer of both the ipsi- and contralateral OB, with an increase in cell survival on the lesioned side. Newborn cells are found in the internal cell layer of the OB 3 weeks after the lesion, and it has been suggested that the integration of these newly born cells contributes to the recovery of OB volume and morphology to pre-lesion conditions (Villanueva and Byrd-Jacobs 2009; Trimpe and Byrd-Jacobs 2016). In addition, activation of astroglial cells and microglia is observed immediately after deafferentation, but expression of inflammatory markers decreases rapidly and a glial scar does not form in the OB potentially contributing to the overall permissive environment for regenerative neurogenesis (Var and Byrd-Jacobs 2019; Scheib and Byrd-Jacobs 2020).

In contrast, irreparable peripheral damage by permanent OE ablation causes cell proliferation in the glomerular layer of the OB and telencephalic Vv region immediately after injury (Villanueva and Byrd-Jacobs 2009). While OB volume continues to decrease, OB and Vv proliferation is still active after 1 week, and newborn neurons can be found throughout all OB layers. However, 3 weeks later, when complete degeneration of the OB is observed due to the lack of afferent input,

all newborn neurons are lost, presumably by apoptosis (Vankirk and Byrd 2003; Villanueva and Byrd-Jacobs 2009). These results differ from those reported after telencephalic lesions and suggest that newborn OB neurons require afferent input or trophic support from the OE in order to survive, to form synapses, and to integrate into lesioned areas. Given the severity of this type of lesion, the microglial response in the OB is more robust and sustained but ultimately decreases to control levels (Var and Byrd-Jacobs 2019).

In addition to experimental injury and deafferentation, models of neurodegenerative disease, which cause sustained and progressive neuron loss, can also be used to study the regenerative and neurogenic response of the zebrafish brain. Intracerebroventricular injection of the amyloid peptide A β 42 recapitulates synaptic deterioration and neuron loss, inflammation, and learning impairment, as reported in rodent models of Alzheimer's disease (Bhattarai et al. 2017a). Interestingly, contrary to the well-documented reduction of neurogenesis under similar experimental conditions in rodents (Haughey et al. 2002; Scopa et al. 2020), the neurodegenerative paradigm increases a neurogenic response in the Vv domain. The anti-inflammatory cytokine IL-4 acts as a key regulator for type IIIb progenitor proliferation and neurogenesis, suggesting that glia-neuron crosstalk regulates regeneration in this model (Bhattarai et al. 2016; Bhattarai et al. 2020). Collectively, these results add to the mounting evidence that microglia play a pivotal role in the regenerative response of the zebrafish brain following damage or disease (Keightley et al. 2014; Cosacak et al. 2019; Var and Byrd-Jacobs 2020).

A striking feature learned from these different injury and neurodegeneration models is that the regenerative capacity of the zebrafish OB and telencephalon does not decrease over the organism's lifespan, as is the case in rodents (Shook et al. 2012; Traniello et al. 2014). While constitutive proliferation and neurogenesis is reduced in the aging brain of zebrafish due to increased quiescence of radial glia, injury promotes inflammation and results in (re-)activation of radial glia progenitors to stimulate proliferation and neurogenesis in the OB and adjacent ventral telencephalon (Edelmann et al. 2013; Trimpe and Byrd-Jacobs 2016; Bhattarai et al. 2017b).

Signaling molecules and molecular pathways regulating OB and telencephalic proliferation and neurogenesis

Generally, neurotrophic factors and signaling pathways that govern cell differentiation during development also regulate proliferation and neurogenesis in the adult telencephalon and OB of the zebrafish. A major switch between quiescent and proliferative states in neurogenic niches in both mammals and zebrafish involves Notch signaling. Quiescent type I radial glia progenitors typically show high constitutive Notch activity (Chapouton et al. 2010). When Notch signaling is blocked

experimentally, type I cells transition to dividing progenitors, and vice versa (Chapouton et al. 2007; Chapouton et al. 2011; Alunni et al. 2013; de Oliveira-Carlos et al. 2013; You et al. 2019). Quiescent progenitors with high Notch activity negatively affect Notch signaling in neighboring cells through lateral cell–cell interactions, leading to a pattern of intermingled quiescent and dividing radial glia progenitors along the ventricular surface of the Vd domain (Chapouton et al. 2010; Kizil et al. 2012; Than-Trong et al. 2018). Unlike what is known in mammals, Notch signaling in zebrafish progenitors regulates proliferation state, but does not appear to affect cellular fate decisions (Ables et al. 2011).

Brain-derived neurotrophic factor (BDNF), which supports the growth, survival, and differentiation of neurons is upregulated and secreted following brain trauma. In zebrafish and other teleosts, BDNF is abundantly expressed in neuronal clusters located in neurogenic niches in the telencephalon and the OB and plays an important role in regeneration, by enhancing telencephalic neurogenesis (Dalton et al. 2009; Bhattarai et al. 2020). BDNF mRNA levels increase in mature neurons of the telencephalic parenchyma following CNS trauma and neurodegeneration in a rapid and transient fashion (Cacialli et al. 2018a, 2018b). In particular, BDNF activates nerve growth factor receptor a (NGFRA) signaling in zebrafish radial glia, promotes proliferation, and augments neurogenesis (Bhattarai et al. 2020), unlike in rodents, where it activates non-regenerative gliosis and tropomyosin receptor kinase B/neurotrophic tyrosine kinase, receptor 2 (TrkB/Ntrk2) signaling (Klein et al. 1991; Galvao et al. 2008). In addition, BMP2b is a morphogen factor that regulates NSC fate and progenitor cell proliferation in the telencephalic ventricular zone by activating quiescence of radial glia type I progenitors through regulation of inhibitor of DNA binding 1 (id1) expression during constitutive and regenerative neurogenesis (Diotel et al. 2013; Ghosh and Prakash Hui 2016; Zhang et al. 2020).

Another class of growth factor with known neurogenic properties in adult mammals and zebrafish brains are fibroblast growth factors (Fgfs), which promote proliferation, migration, and survival of several cell types, including neurons (Jin et al. 2003). Following damage in zebrafish, Fgfs activate radial glia to promote repair and proliferation in a region-dependent manner. Fgfs are required for proliferation of radial glial progenitors in the telencephalic Vv niche, but not in the Vd region (Ganz et al. 2010), reflecting the differences in the progenitor populations that are found in these domains.

Interestingly, aromatase B, the rate-limiting enzyme in estrogen biosynthesis, is expressed and presents high activity in telencephalic radial glial progenitors, which synthesize and are the target of neurosteroids, including estrogen and progesterone (Pellegrini et al. 2005, 2007; Tong et al. 2009; Diotel et al. 2011). In rodents, estradiol modulates constitutive and post-injury proliferation and neurogenesis (Soustiel et al.

2005; Suzuki et al. 2007). Surprisingly, estradiol inhibits cell proliferation in telencephalic neurogenic niches and migration of newborn neurons to other telencephalic regions or to the OB and reduces cell survival (Diotel et al. 2013; Makantasi and Dermon 2014). Intriguingly, the expression of aromatase B is greatly reduced in the ventral telencephalon following injury, while it is expressed in parenchymal neurons near the lesion site (Diotel et al. 2013). These results highlight the complexity of the NSC regulation by positive and negative signals, which are involved in mediating both regeneration and repair following CNS damage.

Although the inherent neurogenic potential of the teleost brain is vast, it can also be negatively affected by the presence of stressors and metabolic disease. In a model that recapitulates chronic hyperglycemic states of diabetes mellitus, both constitutive and regenerative OB and telencephalic neurogenesis in zebrafish are impaired (Dorsemans et al. 2017). A paradigm of chronic stress, due to social subordination, results in sustained elevated cortisol levels in various teleosts. Increased cortisol leads to reduced proliferation in the Vd neurogenic niche, while neurogenesis in the Vv zone remains unaltered. Because of the impairment in Vd neurogenesis, a reduced number of newborn neurons are observed in the telencephalic parenchyma. Moreover, the degree of neurogenesis impairment is correlated with the severity of the social stressor (Dunlap et al. 2006; Sorensen et al. 2011, 2012; Johansen et al. 2012; Tea et al. 2019).

Conclusions and open questions

The processes and cell types that govern constitutive and regenerative neurogenesis in the adult zebrafish OE share many similarities with related phenomena in mammals; however, important and potentially insightful differences exist. Similar to mammals, OSN turnover in the intact OE and en masse generation of new cells following structural damage are interwoven processes that originate from two molecularly distinct progenitor/stem cell populations, the GBCs and HBCs. The differences in tissue distribution of GBC- and HBC-like cells in zebrafish offer valuable opportunities to tackle the contribution of these cells under different tissue conditions and in different experimental paradigms. Regeneration of the damaged zebrafish OE occurs with remarkable speed and is complete, even after ablation of the entire OE structure, within only 7 days, which makes zebrafish a very powerful experimental model to study not only the initial but also the later stages of tissue regeneration.

The zebrafish OB is also a brain region of extraordinary plasticity despite the presence of only four major neuronal cell types that have cell bodies within the OB. Constitutive and regenerative plasticity in OB is key to maintenance and recovery of persistent olfactory perception and plastic changes,

which underlie vital fish behaviors. The OB exhibits constant neuronal turnover, morphological remodeling, and the remarkable ability to regenerate and repair following damage. These regenerative abilities are feasible given the presence of proliferative and neurogenic niches within the OB itself and the adjacent rostroventral telencephalic regions. Different from the exposed nature of the peripheral OE, the central OB is largely protected from external damage, suggesting that persistent OB neurogenesis is predominantly involved in constant remodeling of central olfactory circuits or responds to changes in synaptic input to the OB from OSNs. It remains an open question why generation of new interneurons seems to be favored over remodeling of synaptic connections between existing cells. The dual origin of OB cells in zebrafish, which is also found in other teleosts, is particularly interesting and a similar neurogenic activity has not been reported in mammals. The functional difference between OB- and VZ-derived cells and whether both neurogenic sites generate complementary or identical cell types, however, is currently unknown. Even though relevant signaling molecules have been identified that modulate OB neurogenesis, how these signals communicate between the OB and relevant neurogenic sites and ensure a match between the number of cells that are generated and the number of cells that need to be replaced awaits further experimentation.

While the zebrafish constitutes a tractable and astute model to understand complex phenomena that underlie adult neurogenesis and the molecular mechanisms by which it is regulated, we have only begun to understand some of the more fundamental principles and many important and exiting questions remain:

1. *What is the relationship between progenitor cell populations and OSN subtypes?*

The observation that the zebrafish OE contains at least five morphologically distinct OSN subtypes (ciliated, microvillous, crypt, kappe, and pear cells) raises the question if different, OSN subtype-specific progenitors exist or if a single multipotent progenitor can give rise to all cell lineages. The ILC and SNS are similar but not identical in their output, but the molecular underpinnings of biased generation of microvillous and ciliated cells from these proliferation zones remain currently unknown. The problem is somewhat similar to the situation in the VNO, which comprises V1R- and V2R-expressing microvillous cells that segregate within the apical and basal VNO, respectively (de la Rosa-Prieto et al. 2010). Should different lineage-restricted progenitors exist, they must be intermingled at the ILC and SNS, probably also within the sensory OE, because microvillous and ciliated OSNs are generated from GBCs during constitutive turnover but also from HBCs during regeneration.

2. Can all morphological OSN cell types regenerate equally?

A related question is whether all morphological OSN subtypes can regenerate equally and, if so, whether they are generated by identical HBCs or distinct HBC subpopulations. Ciliated, microvillous, and crypt cells appear to regenerate following their ablation (Iqbal and Byrd-Jacobs 2010), while reconstitution of pear and kappe cells after damage has not been examined in zebrafish. Ciliated cells appear to be more vulnerable to environmental chemicals, but the specificity or selectivity of their restoration has not been addressed systematically. It would be interesting to see if the neurogenic niches can respond selectively if, for instance, only microvillous or ciliated cells were ablated using genetic manipulation and if subtype-specific signaling events exist to bias progenitor activity or output.

3. What is the role of the very high number of adult-born OB interneurons?

Given that the OE undergoes extensive constitutive neurogenesis and OSN turnover, we hypothesize that one of the major functions of OB neurogenesis is to sustain the incorporation of new olfactory axon termini. The bidirectional neuronal turnover would allow for the adjustment of functional OB circuits through formation of new synaptic connections to modulate olfactory processing in response to changing environmental conditions or after injury. Newly generated neurons recruited to the OB develop into granule and periglomerular cells, interneurons that mediate intra- and interglomerular synaptic activity (Shepherd et al. 2007). It is possible that the constant stream of migrating neuroblasts entering the OB allows for a faster and more efficient fine-tuning of olfactory circuits by de novo generation of synaptic connections rather than by recycling existing cells or rewiring synaptic connections.

4. Is there an advantage conferred to zebrafish because of its ability to generate neurons in situ in the OB?

Zebrafish, as many other fish species, rely heavily on olfaction to mediate survival behaviors such as foraging, mating, predator avoidance, and kinship recognition. The olfactory system responds and adapts dynamically to variations in environmental factors and conditions that affect these behaviors, and, thus, local OB neurogenesis could have an important ethological impact. This hypothesis is supported by reports showing that OB neurogenesis can be modulated by olfactory sensory input in zebrafish (Lindsey et al. 2014) and that local OB neurogenesis poses an advantage for short-lived species (Fernandez et al. 2011; Rosillo et al. 2010), or during sensory

modality shifts (Rosillo et al. 2010; Passos et al. 2014) because new cells become more rapidly available. Yet, since the zebrafish brain continues to grow throughout life, it is also likely that a number of newborn OB cells are produced to support growth of the overall structure (Zupanc and Horschke 1996) in addition to their effects on olfactory plasticity.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

- Ables JL, Breunig JJ, Eisch AJ, Rakic P (2011) Not(ch) just development: Notch signalling in the adult brain. *Nat Rev Neurosci* 12:269–283
- Adolf B, Chapouton P, Lam CS, Topp S, Tannhauser B, Strahle U, Gotz M, Bally-Cuif L (2006) Conserved and acquired features of adult neurogenesis in the zebrafish telencephalon. *Dev Biol* 295:278–293
- Aguillon R, Blader P, Batut J (2016) Patterning, morphogenesis, and neurogenesis of zebrafish cranial sensory placodes. *Methods Cell Biol* 134:33–67
- Aguillon R, Batut J, Subramanian A, Madelaine R, Dufourcq P, Schilling TF, Blader P (2018) Cell-type heterogeneity in the early zebrafish olfactory epithelium is generated from progenitors within preplacodal ectoderm. *Elife* 7:e32041
- Ahuja G, Ivandic I, Saltürk M, Oka Y, Nadler W, Korsching SI (2013) Zebrafish crypt neurons project to a single, identified mediodorsal glomerulus. *Sci Rep* 3:2063
- Ahuja G, Bozorg Nia S, Zapilko V, Shiriagin V, Kowatschew D, Oka Y, Korsching SI (2014) Kappe neurons, a novel population of olfactory sensory neurons. *Sci Rep* 4:4037
- Ahuja G, Reichel V, Kowatschew D, Syed AS, Kotagiri AK, Oka Y, Weth F, Korsching SI (2018) Overlapping but distinct topology for zebrafish V2R-like olfactory receptors reminiscent of odorant receptor spatial expression zones. *BMC Genomics* 19:383
- Alfonso J, Penkert H, Duman C, Zuccotti A, Monyer H (2015) Downregulation of sphingosine 1-phosphate receptor 1 promotes the switch from tangential to radial migration in the OB. *J Neurosci* 35:13659–13672
- Alioto TS, Ngai J (2005) The odorant receptor repertoire of teleost fish. *BMC Genomics* 6:173
- Alioto TS, Ngai J (2006) The repertoire of olfactory C family G protein-coupled receptors in zebrafish: candidate chemosensory receptors for amino acids. *BMC Genomics* 7:309

- Alonso JR, Lara J, Vecino E, Covenas R, Aijon J (1989) Cell proliferation in the olfactory bulb of adult freshwater teleosts. *J Anat* 163:155–163
- Alonso JR, Garcia-Ojeda E, Weruaga E, Brinon JG, Arevalo R, Celio MR, Aijon J (1998) McAB 300 antibody against calbindin D-28K is a glial marker in the teleost brain. *Arch Ital Biol* 136:77–81
- Altman J (1969) Autoradiographic and histological studies of postnatal neurogenesis. IV. Cell proliferation and migration in the anterior forebrain, with special reference to persisting neurogenesis in the olfactory bulb. *J Comp Neurol* 137:433–457
- Alunni A, Krecsmarik M, Bosco A, Galant S, Pan L, Moens CB, Bally-Cuif L (2013) Notch3 signaling gates cell cycle entry and limits neural stem cell amplification in the adult pallium. *Development* 140:3335–3347
- Baier H, Korsching S (1994) Olfactory glomeruli in the zebrafish form an invariant pattern and are identifiable across animals. *J Neurosci* 14:219–230
- Baier H, Rotter S, Korsching S (1994) Connectional topography in the zebrafish olfactory system: random positions but regular spacing of sensory neurons projecting to an individual glomerulus. *Proc Natl Acad Sci U S A* 91:11646–11650
- Bailey BJ, Barton S (1975) Olfactory neuroblastoma. Management and prognosis. *Arch Otolaryngol* 101:1–5
- Barth AL, Justice NJ, Ngai J (1996) Asynchronous onset of odorant receptor expression in the developing zebrafish olfactory system. *Neuron* 16:23–34
- Bauer S, Rasika S, Han J, Mauduit C, Raccurt M, Morel G, Jourdan F, Benahmed M, Moyse E, Patterson PH (2003) Leukemia inhibitory factor is a key signal for injury-induced neurogenesis in the adult mouse olfactory epithelium. *J Neurosci* 23:1792–1803
- Baumgart EV, Barbosa JS, Bally-Cuif L, Götz M, Ninkovic J (2012) Stab wound injury of the zebrafish telencephalon: a model for comparative analysis of reactive gliosis. *Glia* 60:343–357
- Bayramli X, Kocagöz Y, Sakizli U, Fuss SH (2017) Patterned arrangements of olfactory receptor gene expression in zebrafish are established by radial movement of specified olfactory sensory neurons. *Sci Rep* 7:5572
- Behrens M, Frank O, Rawel H, Ahuja G, Potting C, Hofmann T, Meyerhof W, Korsching S (2014) ORA1, a zebrafish olfactory receptor ancestral to all mammalian VIR genes, recognizes 4-hydroxyphenylacetic acid, a putative reproductive pheromone. *J Biol Chem* 289:19778–19788
- Beites CL, Kawauchi S, Crocker CE, Calof AL (2005) Identification and molecular regulation of neural stem cells in the olfactory epithelium. *Exp Cell Res* 306:309–316
- Bergström U, Giovanetti A, Piras E, Brittebo EB (2003) Methimazole-induced damage in the olfactory mucosa: effects on ultrastructure and glutathione levels. *Toxicol Pathol* 31:379–387
- Bertmar G (1981) Evolution of vomeronasal organs in vertebrates. *Evolution* 35:359–366
- Bhattarai P, Thomas AK, Cosacak MI, Papadimitriou C, Mashkaryan V, Froc C, Reinhardt S, Kurth T, Dahl A, Zhang Y, Kizil C (2016) IL4/STAT6 Signaling activates neural stem cell proliferation and neurogenesis upon amyloid-beta42 aggregation in adult zebrafish brain. *Cell Rep* 17:941–948
- Bhattarai P, Thomas AK, Cosacak MI, Papadimitriou C, Mashkaryan V, Zhang Y, Kizil C (2017a) Modeling Amyloid- β 42 Toxicity and Neurodegeneration in Adult Zebrafish Brain. *J Vis Exp* 128:56014. <https://doi.org/10.3791/56014>
- Bhattarai P, Thomas AK, Zhang Y, Kizil C (2017b) The effects of aging on amyloid-beta42-induced neurodegeneration and regeneration in adult zebrafish brain. *Neurogenesis* 4:e1322666
- Bhattarai P, Cosacak MI, Mashkaryan V, Demir S, Popova SD, Govindarajan N, Brandt K, Zhang Y, Chang W, Ampatzis K, Kizil C (2020) Neuron-glia interaction through serotonin-BDNF-NGFR axis enables regenerative neurogenesis in Alzheimer's model of adult zebrafish brain. *PLoS Biol* 18:e3000585
- Biechl D, Tietje K, Gerlach G, Wullmann MF (2016) Crypt cells are involved in kin recognition in larval zebrafish. *Sci Rep* 6:24590
- Brann JH, Firestein SJ (2014) A lifetime of neurogenesis in the olfactory system. *Front Neurosci* 8:182
- Braubach OR, Fine A, Croll RP (2012) Distribution and functional organization of glomeruli in the olfactory bulbs of zebrafish (*Danio rerio*). *J Comp Neurol* 520:2317–2339
- Brechbühl J, Klaey M, Broillet MC (2008) Grueneberg ganglion cells mediate alarm pheromone detection in mice. *Science* 321:1092–1095
- Buck L, Axel R (1991) A novel multigene family may encode odorant receptors: a molecular basis for odor recognition. *Cell* 65:175–187
- Buckland ME, Cunningham AM (1998) Alterations in the neurotrophic factors BDNF, GDNF and CNTF in the regenerating olfactory system. *Ann N Y Acad Sci* 855:260–265
- Bumbalo R, Lieber M, Schroeder L, Polat Y, Breer H, Fleischer J (2017) Grueneberg glomeruli in the olfactory bulb are activated by odorants and cool temperature. *Cell Mol Neurobiol* 37:729–742
- Burnstock G (2016a) An introduction to the roles of purinergic signalling in neurodegeneration, neuroprotection and neuroregeneration. *Neuropharmacology* 104:4–17
- Burnstock G (2016b) Short- and long-term (trophic) purinergic signalling. *Philos Trans R Soc Lond Ser B Biol Sci* 371:20150422
- Byrd CA (2000) Deafferentation-induced changes in the olfactory bulb of adult zebrafish. *Brain Res* 866:92–100
- Byrd CA, Brunjes PC (1995) Organization of the olfactory system in the adult zebrafish: histological, immunohistochemical, and quantitative analysis. *J Comp Neurol* 358:247–259
- Byrd CA, Brunjes PC (1998) Addition of new cells to the olfactory bulb of adult zebrafish. *Ann N Y Acad Sci* 855:274–276
- Byrd CA, Brunjes PC (2001) Neurogenesis in the olfactory bulb of adult zebrafish. *Neuroscience* 105:793–801
- Caciali P, D'Angelo L, Kah O, Coumailleau P, Gueguen MM, Pellegrini E, Lucini C (2018a) Neuronal expression of brain derived neurotrophic factor in the injured telencephalon of adult zebrafish. *J Comp Neurol* 526:569–582
- Caciali P, Palladino A, Lucini C (2018b) Role of brain-derived neurotrophic factor during the regenerative response after traumatic brain injury in adult zebrafish. *Neural Regen Res* 13:941–944
- Calvo-Ochoa E, Byrd-Jacobs CA (2019) The olfactory system of zebrafish as a model for the study of neurotoxicity and injury: implications for neuroplasticity and disease. *Int J Mol Sci* 20:1639
- Canalón P (1982) Degeneration and regeneration of olfactory cells induced by ZnSO₄ and other chemicals. *Tissue Cell* 14:717–733
- Canalón P (1983) Influence of a detergent on the catfish olfactory mucosa. *Tissue Cell* 15:245–258
- Cao X, Li LP, Qin XH, Li SJ, Zhang M, Wang Q, Hu HH, Fang YY, Gao YB, Li XW, Sun LR, Xiong WC, Gao TM, Zhu XH (2013) Astrocytic adenosine 5'-triphosphate release regulates the proliferation of neural stem cells in the adult hippocampus. *Stem Cells* 31:1633–1643
- Carr VM, Farbman AI (1992) Ablation of the olfactory bulb up-regulates the rate of neurogenesis and induces precocious cell death in olfactory epithelium. *Exp Neurol* 115:55–59
- Carrillo SA, Anguita-Salinas C, Pena OA, Morales RA, Munoz-Sanchez S, Munoz-Montecinos C, Paredes-Zuniga S, Tapia K, Allende ML (2016) Macrophage recruitment contributes to regeneration of mechanosensory hair cells in the zebrafish lateral line. *J Cell Biochem* 117:1880–1889
- Celik A, Fuss SH, Korsching SI (2002) Selective targeting of zebrafish olfactory receptor neurons by the endogenous OMP promoter. *Eur J Neurosci* 15:798–806

- Chang I, Parrilla M (2016) Expression patterns of homeobox genes in the mouse vomeronasal organ at postnatal stages. *Gene Expr Patterns* 21:69–80
- Chao YC, Fleischer J, Yang RB (2018) Guanylyl cyclase-G is an alarm pheromone receptor in mice. *EMBO J* 37:39–49
- Chapouton P, Jagasia R, Bally-Cuif L (2007) Adult neurogenesis in non-mammalian vertebrates. *Bioessays* 29:745–757
- Chapouton P, Skupien P, Hesl B, Coolen M, Moore JC, Madelaine R, Kremmer E, Faus-Kessler T, Blader P, Lawson ND, Bally-Cuif L (2010) Notch activity levels control the balance between quiescence and recruitment of adult neural stem cells. *J Neurosci* 30:7961–7974
- Chapouton P, Webb KJ, Stigloher C, Alunni A, Adolf B, Hesl B, Topp S, Kremmer E, Bally-Cuif L (2011) Expression of hairy/enhancer of split genes in neural progenitors and neurogenesis domains of the adult zebrafish brain. *J Comp Neurol* 519:1748–1769
- Chen M, Tian S, Yang X, Lane AP, Reed RR, Liu H (2014) Wnt-responsive *Lgr5*⁺ globose basal cells function as multipotent olfactory epithelium progenitor cells. *J Neurosci* 34:8268–8276
- Clint SC, Zupanc GK (2001) Neuronal regeneration in the cerebellum of adult teleost fish, *Apteronotus leptorhynchus*: guidance of migrating young cells by radial glia. *Brain Res Dev Brain Res* 130:15–23
- Coleman JH, Lin B, Louie JD, Peterson J, Lane RP, Schwob JE (2019) Spatial determination of neuronal diversification in the olfactory epithelium. *J Neurosci* 39:814–832
- Cong X, Zheng Q, Ren W, Chéron JB, Fiorucci S, Wen T, Zhang C, Yu H, Golebiowski J, Yu Y (2019) Zebrafish olfactory receptors ORAs differentially detect bile acids and bile salts. *J Biol Chem* 294:6762–6771
- Coppola DM, Waggenger CT, Radwani SM, Brooks DA (2013) An electroolfactogram study of odor response patterns from the mouse olfactory epithelium with reference to receptor zones and odor sorptiveness. *J Neurophysiol* 109:2179–2191
- Cosacak MI, Bhattarai P, Reinhardt S, Petzold A, Dahl A, Zhang Y, Kizil C (2019) Single-cell transcriptomics analyses of neural stem cell heterogeneity and contextual plasticity in a zebrafish brain model of amyloid toxicity. *Cell Rep* 27:1307–1318.e3
- Costanzo RM, Graziadei PP (1983) A quantitative analysis of changes in the olfactory epithelium following bulbectomy in hamster. *J Comp Neurol* 215:370–381
- Cowan CM, Roskams AJ (2002) Apoptosis in the mature and developing olfactory neuroepithelium. *Microsc Res Tech* 58:204–215
- Crespo C, Liberia T, Blasco-Ibáñez JM, Nacher J, Varela E (2013) The circuits of the olfactory bulb. The exception as a rule. *Anat Rec (Hoboken)* 296:1401–1412
- Cuoghi B, Mola L (2009) Macroglial cells of the teleost central nervous system: a survey of the main types. *Cell Tissue Res* 338:319–332
- Dalton VS, Borich SM, Murphy P, Roberts BL (2009) Brain-derived neurotrophic factor mRNA expression in the brain of the teleost fish, *Anguilla anguilla*, the European Eel. *Brain Behav Evol* 73:43–58
- Dang P, Fisher SA, Stefanik DJ, Kim J, Raper JA (2018) Coordination of olfactory receptor choice with guidance receptor expression and function in olfactory sensory neurons. *PLoS Genet* 14:e1007164
- de la Rosa-Prieto C, Saiz-Sánchez D, Ubeda-Bañón I, Argandoña-Palacios L, García-Muñozguren S, Martínez-Marcos A (2010) Neurogenesis in subclasses of vomeronasal sensory neurons in adult mice. *Dev Neurobiol* 70:961–970
- de Oliveira-Carlos V, Ganz J, Hans S, Kaslin J, Brand M (2013) Notch receptor expression in neurogenic regions of the adult zebrafish brain. *PLoS One* 8:e73384
- Demir MC, Sakizli U, Bali B, Kocagöz Y, Eski SE, Ergönen A, Alkiraz AS, Bayramli X, Hassenklöver T, Manzini I, Fuss SH (2020) Purinergic signalling selectively modulates maintenance but not repair neurogenesis in the zebrafish olfactory epithelium. *FEBS J* 287:2699–2722
- Dieris M, Ahuja G, Krishna V, Korsching SI (2017) A single identified glomerulus in the zebrafish olfactory bulb carries the high-affinity response to death-associated odor cadaverine. *Sci Rep* 7:40892
- Diotel N, Servili A, Gueguen MM, Mironov S, Pellegrini E, Vaillant C, Zhu Y, Kah O, Anglade I (2011) Nuclear progesterone receptors are up-regulated by estrogens in neurons and radial glial progenitors in the brain of zebrafish. *PLoS One* 6:e28375
- Diotel N, Vaillant C, Gabbero C, Mironov S, Fostier A, Gueguen MM, Anglade I, Kah O, Pellegrini E (2013) Effects of estradiol in adult neurogenesis and brain repair in zebrafish. *Horm Behav* 63:193–207
- Diotel N, Rodriguez Viales R, Armant O, Marz M, Ferg M, Rastegar S, Strahle U (2015) Comprehensive expression map of transcription regulators in the adult zebrafish telencephalon reveals distinct neurogenic niches. *J Comp Neurol* 523:1202–1221
- Diotel N, Vaillant C, Kah O, Pellegrini E (2016) Mapping of brain lipid binding protein (Blbp) in the brain of adult zebrafish, co-expression with aromatase B and links with proliferation. *Gene Expr Patterns* 20:42–54
- Doetsch F, Alvarez-Buylla A (1996) Network of tangential pathways for neuronal migration in adult mammalian brain. *Proc Natl Acad Sci U S A* 93:14895–14900
- Doetsch F, Caille I, Lim DA, Garcia-Verdugo JM, Alvarez-Buylla A (1999) Subventricular zone astrocytes are neural stem cells in the adult mammalian brain. *Cell* 97:703–716
- Dorsemans AC, Soule S, Weger M, Bourdon E, Lefebvre d'Helencourt C, Meilhac O, Diotel N (2017) Impaired constitutive and regenerative neurogenesis in adult hyperglycemic zebrafish. *J Comp Neurol* 525:442–458
- Dunlap KD, Castellano JF, Prendaj E (2006) Social interaction and cortisol treatment increase cell addition and radial glia fiber density in the diencephalic periventricular zone of adult electric fish, *Apteronotus leptorhynchus*. *Horm Behav* 50:10–17
- Edelmann K, Glashauser L, Sprungala S, Hesl B, Fritschle M, Ninkovic J, Godinho L, Chapouton P (2013) Increased radial glia quiescence, decreased reactivation upon injury and unaltered neuroblast behavior underlie decreased neurogenesis in the aging zebrafish telencephalon. *J Comp Neurol* 521:3099–3115
- Edwards JG, Michel WC (2003) Pharmacological characterization of ionotropic glutamate receptors in the zebrafish olfactory bulb. *Neuroscience* 122:1037–1047
- Eisthen HL (1992) Phylogeny of the vomeronasal system and of receptor cell types in the olfactory and vomeronasal epithelia of vertebrates. *Microsc Res Tech* 23:1–21
- Farbman AI, Brunjes PC, Rentfro L, Michas J, Ritz S (1988) The effect of unilateral naris occlusion on cell dynamics in the developing rat olfactory epithelium. *J Neurosci* 8:3290–3295
- Fernandez AS, Rosillo JC, Casanova G, Olivera-Bravo S (2011) Proliferation zones in the brain of adult fish *Austrolebias (Cyprinodontiform: Rivulidae)*: a comparative study. *Neuroscience* 189:12–24
- Feron F, Vincent A, Mackay-Sim A (1999) Dopamine promotes differentiation of olfactory neuron in vitro. *Brain Res* 845:252–259
- Ferretti P (2011) Is there a relationship between adult neurogenesis and neuron generation following injury across evolution? *Eur J Neurosci* 34:951–962
- Figueres-Onate M, Sánchez-Villalón M, Sánchez-González R, López-Mascaraque L (2019) Lineage tracing and cell potential of postnatal single progenitor cells in vivo. *Stem Cell Rep* 13:700–712
- Fletcher RB, Prasol MS, Estrada J, Baudhuin A, Vranizan K, Choi YG, Ngai J (2011) p63 regulates olfactory stem cell self-renewal and differentiation. *Neuron* 72:748–759
- Folgueira M, Bayley P, Navratilova P, Becker TS, Wilson SW, Clarke JD (2012) Morphogenesis underlying the development of the everted teleost telencephalon. *Neural Dev* 7:212
- Francois A, Laziz I, Rimbaud S, Grebert D, Durieux D, Pajot-Augy E, Meunier N (2013) Early survival factor deprivation in the olfactory

- epithelium enhances activity-driven survival. *Front Cell Neurosci* 7: 271
- Friedrich RW, Korsching SI (1997) Combinatorial and chemotopic odorant coding in the zebrafish olfactory bulb visualized by optical imaging. *Neuron* 18:737–752
- Friedrich RW, Genoud C, Wanner AA (2013) Analyzing the structure and function of neuronal circuits in zebrafish. *Front Neur Circuits* 7: 71
- Fuentealba LC, Rompani SB, Parraguez JI, Obernier K, Romero R, Cepko CL, Alvarez-Buylla A (2015) Embryonic origin of postnatal neural stem cells. *Cell* 161:1644–1655
- Fukuda Y, Katsunuma S, Uranagase A, Nota J, Nibu KI (2018) Effect of intranasal administration of neurotrophic factors on regeneration of chemically degenerated olfactory epithelium in aging mice. *Neuroreport* 29:1400–1404
- Fuller CL, Villanueva R, Byrd CA (2005) Changes in glutamate receptor subunit 4 expression in the deafferented olfactory bulb of zebrafish. *Brain Res* 1044:251–261
- Fuller CL, Yettaw HK, Byrd CA (2006) Mitral cells in the olfactory bulb of adult zebrafish (*Danio rerio*): morphology and distribution. *J Comp Neurol* 499:218–230
- Fuss SH, Omura M, Mombaerts P (2005) The Grueneberg ganglion of the mouse projects axons to glomeruli in the olfactory bulb. *Eur J Neurosci* 22:2649–2654
- Gage FH (2000) Mammalian neural stem cells. *Science* 287:1433–1438
- Galvaio RP, Garcia-Verdugo JM, Alvarez-Buylla A (2008) Brain-derived neurotrophic factor signaling does not stimulate subventricular zone neurogenesis in adult mice and rats. *J Neurosci* 28:13368–13383
- Ganz J, Kaslin J, Hochmann S, Freudenreich D, Brand M (2010) Heterogeneity and Fgf dependence of adult neural progenitors in the zebrafish telencephalon. *Glia* 58:1345–1363
- Gayoso J, Castro A, Anadon R, Manso MJ (2012) Crypt cells of the zebrafish *Danio rerio* mainly project to the dorsomedial glomerular field of the olfactory bulb. *Chem Senses* 37:357–369
- Gerhard GS, Kauffman EJ, Wang X, Stewart R, Moore JL, Kasales CJ, Demidenko E, Cheng KC (2002) Life spans and senescent phenotypes in two strains of Zebrafish (*Danio rerio*). *Exp Gerontol* 37: 1055–1068
- Ghosh S, Prakash Hui S (2016) Regeneration of zebrafish CNS: Adult neurogenesis. *Neural Plast* 2016:5815439
- Giacobini P, Benedetto A, Tirindelli R, Fasolo A (2000) Proliferation and migration of receptor neurons in the vomeronasal organ of the adult mouse. *Brain Res Dev Brain Res* 123:33–40
- Gould AC, Haulena M, Pawlik M, LePage V, Mareschal A, Manalang MRM, Snyman H (2020) Rare neural crest tumor in teleost species: olfactory neuroblastoma in a spotted pike-characin *Boulengerella maculata*. *Dis Aquat Org* 138:29–33
- Grandel H, Kaslin J, Ganz J, Wenzel I, Brand M (2006) Neural stem cells and neurogenesis in the adult zebrafish brain: origin, proliferation dynamics, migration and cell fate. *Dev Biol* 295:263–277
- Graziadei PPC, Monti Graziadei GA (1978) Continuous nerve cell renewal in the olfactory system. In: Jacobson M (ed) *Handbook of sensory physiology, Development of sensory systems*, vol 9. Springer, Berlin, pp 55–83
- Graziadei PP, Levine RR, Graziadei GA (1978) Regeneration of olfactory axons and synapse formation in the forebrain after bulbectomy in neonatal mice. *Proc Natl Acad Sci U S A* 75:5230–5234
- Graziadei PP, Karlan MS, Graziadei GA, Bernstein JJ (1980) Neurogenesis of sensory neurons in the primate olfactory system after section of the fila olfactoria. *Brain Res* 186:289–300
- Green PA, Van Valkenburgh B, Pang B, Bird D, Rowe T, Curtis A (2012) Respiratory and olfactory turbinal size in canid and artoid camivorans. *J Anat* 221:609–621
- Grüneberg H (1973) A ganglion probably belonging to the *N. terminalis* system in the nasal mucosa of the mouse. *Z Anat Entwicklungsgesch* 140:39–52
- Grupp L, Wolburg H, Mack AF (2010) Astroglial structures in the zebrafish brain. *J Comp Neurol* 518:4277–4287
- Grus WE, Zhang J (2006) Origin and evolution of the vertebrate vomeronasal system viewed through system-specific genes. *Bioessays* 28:709–718
- Guo Z, Packard A, Krolewski RC, Harris MT, Manglapus GL, Schwob JE (2010) Expression of pax6 and sox2 in adult olfactory epithelium. *J Comp Neurol* 518:4395–4418
- Hansen A, Finger TE (2000) Phyletic distribution of crypt-type olfactory receptor neurons in fishes. *Brain Behav Evol* 55:100–110
- Hansen A, Zeiske E (1998) The peripheral olfactory organ of the zebrafish, *Danio rerio*: an ultrastructural study. *Chem Senses* 23: 39–48
- Hansen A, Zielinski BS (2005) Diversity in the olfactory epithelium of bony fishes: development, lamellar arrangement, sensory neuron cell types and transduction components. *J Neurocytol* 34:183–208
- Hansen A, Anderson KT, Finger TE (2004) Differential distribution of olfactory receptor neurons in goldfish: structural and molecular correlates. *J Comp Neurol* 477:347–359
- Hassenklöver T, Kurtanska S, Bartoszek I, Junek S, Schild D, Manzini I (2008) Nucleotide-induced Ca²⁺ signaling in sustentacular supporting cells of the olfactory epithelium. *Glia* 56:1614–1624
- Hassenklöver T, Schwartz P, Schild D, Manzini I (2009) Purinergic signaling regulates cell proliferation of olfactory epithelium progenitors. *Stem Cells* 27:2022–2031
- Haughey NJ, Nath A, Chan SL, Borchard AC, Rao MS, Mattson MP (2002) Disruption of neurogenesis by amyloid beta-peptide, and perturbed neural progenitor cell homeostasis, in models of Alzheimer's disease. *J Neurochem* 83:1509–1524
- Hayoz S, Jia C, Hegg C (2012) Mechanisms of constitutive and ATP-evoked ATP release in neonatal mouse olfactory epithelium. *BMC Neurosci* 13:53
- Hegg CC, Irwin M, Lucero MT (2009) Calcium store-mediated signaling in sustentacular cells of the mouse olfactory epithelium. *Glia* 57: 634–644
- Hentig JT, Byrd-Jacobs CA (2016) Exposure to zinc sulfate results in differential effects on olfactory sensory neuron subtypes in adult zebrafish. *Int J Mol Sci* 17:1445
- Hernandez-Ontiveros DG, Tajiri N, Acosta S, Giunta B, Tan J, Borlongan CV (2013) Microglia activation as a biomarker for traumatic brain injury. *Front Neurol* 4:30
- Herrick DB, Lin B, Peterson J, Schnitke N, Schwob JE (2017) Notch1 maintains dormancy of olfactory horizontal basal cells, a reserve neural stem cell. *Proc Natl Acad Sci U S A* 114:E5589–E5598
- Herzog C, Pons Garcia L, Keatinge M, Greenald D, Moritz C, Peri F, Herrgen L (2019) Rapid clearance of cellular debris by microglia limits secondary neuronal cell death after brain injury in vivo. *Development* 146:dev174698
- Hinds JW, Hinds PL, McNelly NA (1984) An autoradiographic study of the mouse olfactory epithelium: evidence for long-lived receptors. *Anat Rec* 210:375–383
- Hinsch K, Zupanc GK (2007) Generation and long-term persistence of new neurons in the adult zebrafish brain: a quantitative analysis. *Neuroscience* 146:679–696
- Hodos W, Butler AB (1997) Evolution of sensory pathways in vertebrates. *Brain Behav Evol* 50:189–197
- Holl AM (2018) Survival of mature mouse olfactory sensory neurons labeled genetically perinatally. *Mol Cell Neurosci* 88:258–269
- Hurt ME, Thomas DA, Working PK, Monticello TM, Morgan KT (1988) Degeneration and regeneration of the olfactory epithelium following inhalation exposure to methyl bromide: pathology, cell kinetics, and olfactory function. *Toxicol Appl Pharmacol* 94:311–328
- Hussain A, Saraiva LR, Korsching SI (2009) Positive Darwinian selection and the birth of an olfactory receptor clade in teleosts. *Proc Natl Acad Sci U S A* 106:4313–4318

- Hussain A, Saraiva LR, Ferrero DM, Ahuja G, Krishna VS, Liberles SD, Korsching SI (2013) High-affinity olfactory receptor for the death-associated odor cadaverine. *Proc Natl Acad Sci U S A* 110:19579–19584
- Iqbal T, Byrd-Jacobs C (2010) Rapid degeneration and regeneration of the zebrafish olfactory epithelium after triton X-100 application. *Chem Senses* 35:351–361
- Iwai N, Zhou Z, Roop DR, Behringer RR (2008) Horizontal basal cells are multipotent progenitors in normal and injured adult olfactory epithelium. *Stem Cells* 26:1298–1306
- Iwema CL, Schwob JE (2003) Odorant receptor expression as a function of neuronal maturity in the adult rodent olfactory system. *J Comp Neurol* 459:209–222
- Jang W, Chen X, Flis D, Harris M, Schwob JE (2014) Label-retaining, quiescent globose basal cells are found in the olfactory epithelium. *J Comp Neurol* 522:731–749
- Jia C, Hegg CC (2010) NPY mediates ATP-induced neuroproliferation in adult mouse olfactory epithelium. *Neurobiol Dis* 38:405–413
- Jia C, Hegg CC (2012) Neuropeptide Y and extracellular signal-regulated kinase mediate injury-induced neuroregeneration in mouse olfactory epithelium. *Mol Cell Neurosci* 49:158–170
- Jia C, Doherty JP, Crudginton S, Hegg CC (2009) Activation of purinergic receptors induces proliferation and neuronal differentiation in Swiss Webster mouse olfactory epithelium. *Neuroscience* 163:120–128
- Jia C, Cussen AR, Hegg CC (2011) ATP differentially upregulates fibroblast growth factor 2 and transforming growth factor α in neonatal and adult mice: effect on neuroproliferation. *Neuroscience* 177:335–346
- Jin K, Sun Y, Xie L, Bateur S, Mao XO, Smelick C, Logvinova A, Greenberg DA (2003) Neurogenesis and aging: FGF-2 and HB-EGF restore neurogenesis in hippocampus and subventricular zone of aged mice. *Aging Cell* 2:175–183
- Johansen IB, Sorensen C, Sandvik GK, Nilsson GE, Hoglund E, Bakken M, Overli O (2012) Neural plasticity is affected by stress and heritable variation in stress coping style. *Comp Biochem Physiol Part D Genomics Proteomics* 7:161–171
- Johnson VE, Stewart W, Smith DH (2013) Axonal pathology in traumatic brain injury. *Exp Neurol* 246:35–43
- Jurisch-Yaksi N, Yaksi E, Kizil C (2020) Radial glia in the zebrafish brain: functional, structural, and physiological comparison with the mammalian glia. *Glia*. <https://doi.org/10.1002/glia.23849>
- Karve IP, Taylor JM, Crack PJ (2016) The contribution of astrocytes and microglia to traumatic brain injury. *Br J Pharmacol* 173:692–702
- Kaslin J, Ganz J, Brand M (2008) Proliferation, neurogenesis and regeneration in the non-mammalian vertebrate brain. *Philos Trans R Soc Lond Ser B Biol Sci* 363:101–122
- Keightley MC, Wang CH, Pazhakh V, Lieschke GJ (2014) Delineating the roles of neutrophils and macrophages in zebrafish regeneration models. *Int J Biochem Cell Biol* 56:92–106
- Kermen F, Franco LM, Wyatt C, Yaksi E (2013) Neural circuits mediating olfactory-driven behavior in fish. *Front Neur Circuits* 7:62
- Kim EJ, Simpson PJ, Park DJ, Liu BQ, Ronnett GV, Moon C (2005) Leukemia inhibitory factor is a proliferative factor for olfactory sensory neurons. *Neuroreport* 16:25–28
- Kishimoto N, Alfaro-Cervello C, Shimizu K, Asakawa K, Urasaki A, Nonaka S, Kawakami K, Garcia-Verdugo JM, Sawamoto K (2011) Migration of neuronal precursors from the telencephalic ventricular zone into the olfactory bulb in adult zebrafish. *J Comp Neurol* 519:3549–3565
- Kizil C, Kaslin J, Kroehne V, Brand M (2012) Adult neurogenesis and brain regeneration in zebrafish. *Dev Neurobiol* 72:429–461
- Kizil C, Kyritsis N, Brand M (2015) Effects of inflammation on stem cells: together they strive? *EMBO Rep* 16:416–426
- Klein R, Nanduri V, Jing SA, Lamballe F, Tapley P, Bryant S, Cordon-Cardo C, Jones KR, Reichardt LF, Barbacid M (1991) The trkB tyrosine protein kinase is a receptor for brain-derived neurotrophic factor and neurotrophin-3. *Cell* 66:395–403
- Koide T, Miyasaka N, Morimoto K, Asakawa K, Urasaki A, Kawakami K, Yoshihara Y (2009) Olfactory neural circuitry for attraction to amino acids revealed by transposon-mediated gene trap approach in zebrafish. *Proc Natl Acad Sci U S A* 106:9884–9889
- Kondo K, Suzukawa K, Sakamoto T, Watanabe K, Kanaya K, Ushio M, Yamaguchi T, Nibu K, Kaga K, Yamasoba T (2010) Age-related changes in cell dynamics of the postnatal mouse olfactory neuroepithelium: cell proliferation, neuronal differentiation, and cell death. *J Comp Neurol* 518:1962–1975
- Konzelmann S, Saucier D, Strotmann J, Breer H, Astic L (1998) Decline and recovery of olfactory receptor expression following unilateral bulbectomy. *Cell Tissue Res* 294:421–430
- Koos DS, Fraser SE (2005) The Grueneberg ganglion projects to the olfactory bulb. *Neuroreport* 16:1929–1932
- Korsching SI, Argo S, Campenhausen H, Friedrich RW, Rummrich A, Weth F (1997) Olfaction in zebrafish: what does a tiny teleost tell us? *Semin Cell Dev Biol* 8:181–187
- Kriegstein A, Alvarez-Buylla A (2009) The glial nature of embryonic and adult neural stem cells. *Annu Rev Neurosci* 32:149–184
- Kroehne V, Freudenreich D, Hans S, Kaslin J, Brand M (2011) Regeneration of the adult zebrafish brain from neurogenic radial glia-type progenitors. *Development* 138:4831–4841
- Kyritsis N, Kizil C, Zocher S, Kroehne V, Kaslin J, Freudenreich D, Iltzsche A, Brand M (2012) Acute inflammation initiates the regenerative response in the adult zebrafish brain. *Science* 338:1353–1356
- Labusch M, Mancini L, Morizet D, Bally-Cuif L (2020) Conserved and divergent features of adult neurogenesis in zebrafish. *Front Cell Dev Biol* 8:525
- Lam CS, Marz M, Strahle U (2009) Gfap and nestin reporter lines reveal characteristics of neural progenitors in the adult zebrafish brain. *Dev Dyn* 238:475–486
- Lazzari M, Bettini S, Franceschini V (2014) Immunocytochemical characterisation of olfactory ensheathing cells of zebrafish. *J Anat* 224:192–206
- Leung CT, Coulombe PA, Reed RR (2007) Contribution of olfactory neural stem cells to tissue maintenance and regeneration. *Nat Neurosci* 10:720–726
- Li Q, Tachie-Baffour Y, Liu Z, Baldwin MW, Kruse AC, Liberles SD (2015) Non-classical amine recognition evolved in a large clade of olfactory receptors. *Elife* 4:e10441
- Lim DA, Alvarez-Buylla A (2016) The adult ventricular-subventricular zone (V-SVZ) and olfactory bulb (OB) neurogenesis. *Cold Spring Harb Perspect Biol* 8:a018820
- Lindsey BW, Darabie A, Tropepe V (2012) The cellular composition of neurogenic periventricular zones in the adult zebrafish forebrain. *J Comp Neurol* 520:2275–2316
- Lindsey BW, Di Donato S, Kaslin J, Tropepe V (2014) Sensory-specific modulation of adult neurogenesis in sensory structures is associated with the type of stem cell present in the neurogenic niche of the zebrafish brain. *Eur J Neurosci* 40:3591–3607
- Lipschitz DL, Michel WC (2002) Amino acid odorants stimulate microvillar sensory neurons. *Chem Senses* 27:277–286
- Lledo PM, Valley M (2016) Adult olfactory bulb neurogenesis. *Cold Spring Harb Perspect Biol* 8:a018945
- Lois C, Alvarez-Buylla A (1994) Long-distance neuronal migration in the adult mammalian brain. *Science* 264:1145–1148
- Lois C, Garcia-Verdugo JM, Alvarez-Buylla A (1996) Chain migration of neuronal precursors. *Science* 271:978–981
- Luo J, Daniels SB, Lenington JB, Notti RQ, Conover JC (2006) The aging neurogenic subventricular zone. *Aging Cell* 5:139–152
- Luskin MB (1993) Restricted proliferation and migration of postnatally generated neurons derived from the forebrain subventricular zone. *Neuron* 11:173–189

- Luu P, Acher F, Bertrand HO, Fan J, Ngai J (2004) Molecular determinants of ligand selectivity in a vertebrate odorant receptor. *J Neurosci* 24:10128–10137
- Lyons DA, Talbot WS (2014) Glial cell development and function in zebrafish. *Cold Spring Harb Perspect Biol* 7:a020586
- Ma L, Wu Y, Qiu Q, Scheerer H, Moran A, Yu CR (2014) A developmental switch of axon targeting in the continuously regenerating mouse olfactory system. *Science* 344:194–197
- Mackay-Sim A, Kittel PW (1991) On the life span of olfactory receptor neurons. *Eur J Neurosci* 3:209–215
- Makantasi P, Demmon CR (2014) Estradiol treatment decreases cell proliferation in the neurogenic zones of adult female zebrafish (*Danio rerio*) brain. *Neuroscience* 277:306–320
- Malik SZ, Lewis M, Isaacs A, Haskins M, Van Winkle T, Vite CH, Watson DJ (2012) Identification of the rostral migratory stream in the canine and feline brain. *PLoS One* 7:e36016
- Martinez-Marcos A, Jia C, Quan W, Halpern M (2005) Neurogenesis, migration, and apoptosis in the vomeronasal epithelium of adult mice. *J Neurobiol* 63:173–187
- Marz M, Chapouton P, Diot N, Vaillant C, Hesl B, Takamiya M, Lam CS, Kah O, Bally-Cuif L, Strahle U (2010) Heterogeneity in progenitor cell subtypes in the ventricular zone of the zebrafish adult telencephalon. *Glia* 58:870–888
- Matulionis DH (1975) Ultrastructural study of mouse olfactory epithelium following destruction by ZnSO₄ and its subsequent regeneration. *Am J Anat* 142:67–89
- Mazaheri F, Breus O, Durdu S, Haas P, Wittbrodt J, Gilmour D, Peri F (2014) Distinct roles for BAI1 and TIM-4 in the engulfment of dying neurons by microglia. *Nat Commun* 5:4046
- McIntyre JC, Bose SC, Stromberg AJ, McClintock TS (2008) Emx2 stimulates odorant receptor gene expression. *Chem Senses* 33:825–837
- Meyers JR (2018) Zebrafish: Development of a vertebrate model organism. *Curr Protocols Essen Lab Techniques Microsc Res Tech* 23:49–61
- Miyamichi K, Serizawa S, Kimura HM, Sakano H (2005) Continuous and overlapping expression domains of odorant receptor genes in the olfactory epithelium determine the dorsal/ventral positioning of glomeruli in the olfactory bulb. *J Neurosci* 25:3586–3592
- Miyasaka N, Wanner AA, Li J, Mack-Bucher J, Genoud C, Yoshihara Y, Friedrich RW (2013) Functional development of the olfactory system in zebrafish. *Mech Dev* 130:336–346
- Miyasaka N, Arganda-Carreras I, Wakisaka N, Masuda M, Sumbul U, Seung HS, Yoshihara Y (2014) Olfactory projectome in the zebrafish forebrain revealed by genetic single-neuron labelling. *Nat Commun* 5:3639
- Moine F, Brechbühl J, Nenniger Tosato M, Beaumann M, Broillet MC (2018) Alarm pheromone and kairomone detection via bitter taste receptors in the mouse Grueneberg ganglion. *BMC Biol* 16:12
- Mombaerts P (2004) Odorant receptor gene choice in olfactory sensory neurons: the one receptor-one neuron hypothesis revisited. *Curr Opin Neurobiol* 14:31–36
- Mombaerts P (2006) Axonal wiring in the mouse olfactory system. *Annu Rev Cell Dev Biol* 22:713–737
- Mombaerts P, Wang F, Dulac C, Chao SK, Nemes A, Mendelsohn M, Edmondson J, Axel R (1996) Visualizing an olfactory sensory map. *Cell* 87:675–686
- Moody SA, LaMantia AS (2015) Transcriptional regulation of cranial sensory placode development. *Curr Top Dev Biol* 111:301–350
- Mori K, von Campenhouse H, Yoshihara Y (2000) Zonal organization of the mammalian main and accessory olfactory systems. *Philos Trans R Soc Lond B* 355:1801–1812
- Morrison EE, Costanzo RM (1992) Morphology of olfactory epithelium in humans and other vertebrates. *Microsc Res Tech* 23:49–61
- Moulton DG (1974) Dynamics of cell populations in the olfactory epithelium. *Ann N Y Acad Sci* 237:52–61
- Moulton DG (1975) Cell renewal in the olfactory epithelium of the mouse. In: Denton DA, Coughlan JP (eds) *Olfaction and taste*. vol. V. Academic Press, New York, pp 111–114
- Mulvaney BD, Heist HE (1971) Regeneration of rabbit olfactory epithelium. *Am J Anat* 131:241–251
- Nguyen-Chi M, Laplace-Builhe B, Travnickova J, Luz-Crawford P, Tejedor G, Phan QT, Duroux-Richard I, Levraud JP, Kissa K, Lutfalla G, Djouad F (2015) Identification of polarized macrophage subsets in zebrafish. *Elife* 4:e07288
- Niimura Y (2009) On the origin and evolution of vertebrate olfactory receptor genes: comparative genome analysis among 23 chordate species. *Genome Biol Evol* 1:34–44
- Niimura Y, Nei M (2005) Evolutionary dynamics of olfactory receptor genes in fishes and tetrapods. *Proc Natl Acad Sci U S A* 102:6039–6044
- Nikaido M, Suzuki H, Toyoda A, Fujiyama A, Hagino-Yamagishi K, Kocher TD, Carleton K, Okada N (2013) Lineage-specific expansion of vomeronasal type 2 receptor-like (OlfC) genes in cichlids may contribute to diversification of amino acid detection systems. *Genome Biol Evol* 5:711–722
- Nottebohm F, O'Loughlin B, Gould K, Yohay K, Alvarez-Buylla A (1994) The life span of new neurons in a song control nucleus of the adult canary brain depends on time of year when these cells are born. *Proc Natl Acad Sci U S A* 91:7849–7853
- Oehlmann VD, Berger S, Sterner C, Korsching SI (2004) Zebrafish beta tubulin 1 expression is limited to the nervous system throughout development, and in the adult brain is restricted to a subset of proliferative regions. *Gene Expr Patterns* 4:191–198
- Oka Y, Korsching SI (2011) Shared and unique G alpha proteins in the zebrafish versus mammalian senses of taste and smell. *Chem Senses* 36:357–365
- Oka Y, Saraiva LR, Korsching SI (2012) Crypt neurons express a single V1R-related ora gene. *Chem Senses* 37:219–227
- Olivera-Pasilio V, Peterson DA, Castelló ME (2014) Spatial distribution and cellular composition of adult brain proliferative zones in the teleost, *Gymnotus omarorum*. *Front Neuroanat* 8:88. <https://doi.org/10.3389/fnana.2014.00088>
- Olivera-Pasilio V, Lasserre M, Castello ME (2017) Cell proliferation, migration, and neurogenesis in the adult brain of the pulse type weakly electric fish, *Gymnotus omarorum*. *Front Neurosci* 11:437
- Orechio D, Andrade Aguiar B, Baroni Diniz G, Cioni Bittencourt J, Haemmerle CAS, Watanabe IS, Miglino MA, Castelucci P (2018) Morphological and cellular characterization of the fetal canine (*Canis lupus familiaris*) subventricular zone, rostral migratory stream, and olfactory bulb. *Anat Rec (Hoboken)* 301:1570–1584
- Packard A, Schnittke N, Romano RA, Sinha S, Schwob JE (2011) DeltaNp63 regulates stem cell dynamics in the mammalian olfactory epithelium. *J Neurosci* 31:8748–8759
- Paredes MF, Sorrells SF, Cebrian-Silla A, Sandoval K, Qi D, Kelley KW, James D, Mayer S, Chang J, Auguste KI, Chang EF, Gutierrez Martin AJ, Kriegstein AR, Mathern GW, Oldham MC, Huang EJ, Garcia-Verdugo JM, Yang Z, Alvarez-Buylla A (2018) Does adult neurogenesis persist in the human hippocampus? *Cell Stem Cell* 23:780–781
- Parker VJ, Morrison JA, Yaeger MJ (2010) Olfactory neuroblastoma in a cat. *J Feline Med Surg* 12:867–871
- Paskin TR, Byrd-Jacobs CA (2012) Reversible deafferentation of the adult zebrafish olfactory bulb affects glomerular distribution and olfactory-mediated behavior. *Behav Brain Res* 235:293–301
- Paskin TR, Iqbal TR, Byrd-Jacobs CA (2011) Olfactory bulb recovery following reversible deafferentation with repeated detergent application in the adult zebrafish. *Neuroscience* 196:276–284
- Passos C, Tassinio B, Reyes F, Rosenthal GG (2014) Seasonal variation in female mate choice and operational sex ratio in wild populations of an annual fish, *Austrolebias reicherti*. *PLoS One* 9:e101649

- Pellegrini E, Menuet A, Lethimonier C, Adrio F, Gueguen MM, Tascon C, Anglade I, Pakdel F, Kah O (2005) Relationships between aromatase and estrogen receptors in the brain of teleost fish. *Gen Comp Endocrinol* 142:60–66
- Pellegrini E, Mouriec K, Anglade I, Menuet A, Le Page Y, Gueguen MM, Marmignon MH, Brion F, Pakdel F, Kah O (2007) Identification of aromatase-positive radial glial cells as progenitor cells in the ventricular layer of the forebrain in zebrafish. *J Comp Neurol* 501(1):150–167
- Perez-Gomez A, Stein B, Leinders-Zufall T, Chamero P (2014) Signaling mechanisms and behavioral function of the mouse basal vomeronasal neuroepithelium. *Front Neuroanat* 8:135
- Petraneau L, Alvarez-Buylla A (2002) Maturation and death of adult-born olfactory granule neurons: role of olfaction. *J Neurosci* 22: 6106–6113
- Pinto L, Götz M (2007) Radial glial cell heterogeneity—the source of diverse progeny in the CNS. *Prog Neurobiol* 83:2–23
- Plendl J, Stierstorfer B, Sinowatz F (1999) Growth factors and their receptors in the olfactory system. *Anat Histol Embryol* 28:73–79
- Pozzuto JM, Fuller CL, Byrd-Jacobs CA (2019) Deafferentation-induced alterations in mitral cell dendritic morphology in the adult zebrafish olfactory bulb. *J Bioenerg Biomembr* 51:29–40
- Rakic P (1998) Young neurons for old brains? *Nat Neurosci* 1:645–647
- Reiten I, Uslu FE, Fore S, Pelgrims R, Ringers C, Diaz Verdugo C, Hoffman M, Lal P, Kawakami K, Pekkan K, Yaksi E, Jurisch-Yaksi N (2017) Motile-cilia-mediated flow improves sensitivity and temporal resolution of olfactory computations. *Curr Biol* 27: 166–174
- Ressler KJ, Sullivan SL, Buck LB (1993) A zonal organization of odorant receptor gene expression in the olfactory epithelium. *Cell* 73:597–609
- Rieger A, Deitmer JW, Lohr C (2007) Axon-glia communication evokes calcium signaling in olfactory ensheathing cells of the developing olfactory bulb. *Glia* 55:352–359
- Rosillo JC, Casanova G, Olivera S, Fernandez A (2010) Cell heterogeneity of the telencephalic ventricular zone: a neurogenic brain region of *Austrolebias charrua*. *Acta Microsc* 19:152–159
- Rothenaigner I, Krecsmarik M, Hayes JA, Bahn B, Lepier A, Fortin G, Gotz M, Jagasia R, Bally-Cuif L (2011) Clonal analysis by distinct viral vectors identifies bona fide neural stem cells in the adult zebrafish telencephalon and characterizes their division properties and fate. *Development* 138:1459–1469
- Royet JP, Souchier C, Jourdan F, Ploye H (1988) Morphometric study of the glomerular population in the mouse olfactory bulb: numerical density and size distribution along the rostrocaudal axis. *J Comp Neurol* 270:559–568
- Rupp B, Wullmann MF, Reichert H (1996) The zebrafish brain: a neuroanatomical comparison with the goldfish. *Anat Embryol (Berl)* 194:187–203
- Santoro SW, Dulac C (2012) The activity-dependent histone variant H2BE modulates the life span of olfactory neurons. *Elife* 1:e00070
- Saraiva LR, Korsching SI (2007) A novel olfactory receptor gene family in teleost fish. *Genome Res* 17:1448–1457
- Saraiva LR, Ahuja G, Ivandic I, Syed AS, Marioni JC, Korsching SI, Logan DW (2015) Molecular and neuronal homology between the olfactory systems of zebrafish and mouse. *Sci Rep* 5:11487
- Sato Y, Miyasaka N, Yoshihara Y (2005) Mutually exclusive glomerular innervation by two distinct types of olfactory sensory neurons revealed in transgenic zebrafish. *J Neurosci* 25:4889–4897
- Sato Y, Miyasaka N, Yoshihara Y (2007) Hierarchical regulation of odorant receptor gene choice and subsequent axonal projection of olfactory sensory neurons in zebrafish. *J Neurosci* 27:1606–1615
- Saxena A, Peng BN, Bronner ME (2013) Sox10-dependent neural crest origin of olfactory microvillous neurons in zebrafish. *Elife* 19(2): e00336
- Scheib J, Byrd-Jacobs C (2020) Zebrafish astroglial morphology in the olfactory bulb is altered with repetitive peripheral damage. *Front Neuroanat* 14:4
- Scheib JJ, Pozzuto JM, Byrd-Jacobs CA (2019) Reversible deafferentation of the zebrafish olfactory bulb with wax plug insertion. *J Neurosci Methods* 311:47–56
- Schmidt R, Strähle U, Scholpp S (2013) Neurogenesis in zebrafish - from embryo to adult. *Neural Dev* 8:3
- Schnitke N, Herrick DB, Lin B, Peterson J, Coleman JH, Packard AI, Jang W, Schwob JE (2015) Transcription factor p63 controls the reserve status but not the stemness of horizontal basal cells in the olfactory epithelium. *Proc Natl Acad Sci U S A* 112:E5068–E5077
- Schwob JE (2002) Neural regeneration and the peripheral olfactory system. *Anat Rec* 269:33–49
- Schwob JE, Szumowski KE, Stasky AA (1992) Olfactory sensory neurons are trophically dependent on the olfactory bulb for their prolonged survival. *J Neurosci* 12:3896–3919
- Schwob JE, Youngentob SL, Mezza RC (1995) Reconstitution of the rat olfactory epithelium after methyl bromide-induced lesion. *J Comp Neurol* 359:15–37
- Schwob JE, Jang W, Holbrook EH, Lin B, Herrick DB, Peterson JN, Hewitt Coleman J (2017) Stem and progenitor cells of the mammalian olfactory epithelium: taking poietic license. *J Comp Neurol* 525: 1034–1054
- Scopa C, Marrocco F, Latina V, Ruggeri F, Corvaglia V, La Regina F, Ammassari-Teule M, Middei S, Amadoro G, Meli G, Cattaneo A (2020) Impaired adult neurogenesis is an early event in Alzheimer's disease neurodegeneration, mediated by intracellular Abeta oligomers. *Cell Death Differ* 27:934–948
- Shepherd GM (1972) Synaptic organization of the mammalian olfactory bulb. *Physiol Rev* 52:864–917
- Shepherd GM, Chen WR, Willhite D, Migliore M, Greer CA (2007) The olfactory granule cell: from classical enigma to central role in olfactory processing. *Brain Res Rev* 55:373–382
- Shohayeb B, Diab M, Ahmed M, Ng DCH (2018) Factors that influence adult neurogenesis as potential therapy. *Transl Neurodegener* 7:4. <https://doi.org/10.1186/s40035-018-0109-9>
- Shook BA, Manz DH, Peters JJ, Kang S, Conover JC (2012) Spatiotemporal changes to the subventricular zone stem cell pool through aging. *J Neurosci* 32:6947–6956
- Silva L, Antunes A (2017) Vomeronasal receptors in vertebrates and the evolution of pheromone detection. *Annu Rev Anim Biosci* 5:353–370
- Silvotti L, Moiani A, Gatti R, Tirindelli R (2007) Combinatorial co-expression of pheromone receptors, V2Rs. *J Neurochem* 103: 1753–1763
- Simpson PJ, Wang E, Moon C, Matarazzo V, Cohen DR, Liebl DJ, Ronnett GV (2003) Neurotrophin-3 signaling maintains maturational homeostasis between neuronal populations in the olfactory epithelium. *Mol Cell Neurosci* 24:858–874
- Skaggs K, Goldman D, Parent JM (2014) Excitotoxic brain injury in adult zebrafish stimulates neurogenesis and long-distance neuronal integration. *Glia* 62:2061–2079
- Smith CG (1951) Regeneration of sensory olfactory epithelium and nerves in adult frogs. *Anat Rec* 109:661–671
- Sokpor G, Abbas E, Rosenbusch J, Staiger JF, Tuoc T (2018) Transcriptional and epigenetic control of mammalian olfactory epithelium development. *Mol Neurobiol* 55:8306–8327
- Sorensen C, Bohlin LC, Overli O, Nilsson GE (2011) Cortisol reduces cell proliferation in the telencephalon of rainbow trout (*Oncorhynchus mykiss*). *Physiol Behav* 102:518–523
- Sorensen C, Nilsson GE, Summers CH, Overli O (2012) Social stress reduces forebrain cell proliferation in rainbow trout (*Oncorhynchus mykiss*). *Behav Brain Res* 227:311–318

- Sorenson PW, Hara TJ, Stacey NE (1991) Sex pheromones selectively stimulate the medial olfactory tracts of male goldfish. *Brain Res* 558: 343–347
- Soustiel JF, Palzur E, Nevo O, Thaler I, Vlodavsky E (2005) Neuroprotective anti-apoptosis effect of estrogens in traumatic brain injury. *J Neurotrauma* 22:345–352
- Strobl-Mazzulla PH, Nunez A, Pellegrini E, Gueguen MM, Kah O, Somoza GM (2010) Progenitor radial cells and neurogenesis in pejerrey fish forebrain. *Brain Behav Evol* 76:20–31
- Sultan-Styne K, Toledo R, Walker C, Kallkopf A, Ribak CE, Guthrie KM (2009) Long-term survival of olfactory sensory neurons after target depletion. *J Comp Neurol* 515:696–710
- Sülz L, Astorga G, Bellette B, Iturriaga R, Mackay-Sim A, Bacigalupo J (2009) Nitric oxide regulates neurogenesis in adult olfactory epithelium in vitro. *Nitric Oxide* 20:238–252
- Suyama S, Sunabori T, Kanki H, Sawamoto K, Gachet C, Koizumi S, Okano H (2012) Purinergic signaling promotes proliferation of adult mouse subventricular zone cells. *J Neurosci* 32:9238–9247
- Suzuki J, Osumi N (2015) Neural crest and placode contributions to olfactory development. *Curr Top Dev Biol* 111:351–374
- Suzuki Y, Takeda M, Obara N, Suzuki N (1998) Bulbectomy of neonatal mice induces migration of basal cells from the olfactory epithelium. *Brain Res Dev Brain Res* 108:295–298
- Suzuki S, Gerhold LM, Bottner M, Rau SW, Dela Cruz C, Yang E, Zhu H, Yu J, Cashion AB, Kindy MS, Wise PM (2007) Estradiol enhances neurogenesis following ischemic stroke through estrogen receptors alpha and beta. *J Comp Neurol* 500:1064–1075
- Suzuki H, Nikaido M, Hagino-Yamagishi K, Okada N (2015) Distinct functions of two olfactory marker protein genes derived from teleost-specific whole genome duplication. *BMC Evol Biol* 15:245
- Takahashi H, Ogawa Y, Yoshihara S, Asahina R, Kinoshita M, Kitano T, Kitsuki M, Tatsumi K, Okuda M, Tatsumi K, Wanaka A, Hirai H, Stern PL, Tsuboi A (2016) A subtype of olfactory bulb interneurons is required for odor detection and discrimination behaviors. *J Neurosci* 36:8210–8227
- Takahashi H, Yoshihara S, Tsuboi A (2018) The functional role of olfactory bulb granule cell subtypes derived from embryonic and postnatal neurogenesis. *Front Mol Neurosci* 11:229
- Tea J, Alderman SL, Gilmour KM (2019) Social stress increases plasma cortisol and reduces forebrain cell proliferation in subordinate male zebrafish (*Danio rerio*). *J Exp Biol* 222:jeb194894
- Teles MC, Sirbulescu RF, Wellbrock UM, Oliveira RF, Zupanc GK (2012) Adult neurogenesis in the brain of the Mozambique tilapia, *Oreochromis mossambicus*. *J Comp Physiol A Neuroethol Sens Neural Behav Physiol* 198:427–449
- Terzibasi E, Valenzano DR, Cellerino A (2007) The short-lived fish *Nothobranchius furzeri* as a new model system for aging studies. *Exp Gerontol* 42:81–89
- Than-Trong E, Ortica-Gatti S, Mella S, Nepal C, Alunni A, Bally-Cuif L (2018) Neural stem cell quiescence and stemness are molecularly distinct outputs of the Notch3 signalling cascade in the vertebrate adult brain. *Development* 145:dev161034
- Tong SK, Mouriec K, Kuo MW, Pellegrini E, Gueguen MM, Brion F, Kah O, Chung BC (2009) A cyp19a1b-gfp (aromatase B) transgenic zebrafish line that expresses GFP in radial glial cells. *Genesis* 47:67–73
- Tonnus W, Meyer C, Paliege A, Belavgeni A, von Mässenhausen A, Bornstein SR, Hugo C, Becker JU, Linkermann A (2019) The pathological features of regulated necrosis. *J Pathol* 247:697–707
- Torikata C, Mukai M, Kageyama K (1989) Spontaneous olfactory neuroepithelioma in a domestic medaka (*Oryzias latipes*). *Cancer Res* 49:2994–2998
- Torres-Paz J, Whitlock KE (2014) Olfactory sensory system develops from coordinated movements within the neural plate. *Dev Dyn* 243:1619–1631
- Traniello IM, Sirbulescu RF, Ilies I, Zupanc GK (2014) Age-related changes in stem cell dynamics, neurogenesis, apoptosis, and gliosis in the adult brain: a novel teleost fish model of negligible senescence. *Dev Neurobiol* 74:514–530
- Trimpe DM, Byrd-Jacobs CA (2016) Patterns of olfactory bulb neurogenesis in the adult zebrafish are altered following reversible deafferentation. *Neuroscience* 331:134–147
- Tsai L, Barnea G (2014) A critical period defined by axon-targeting mechanisms in the murine olfactory bulb. *Science* 344:197–200
- Vankirk AM, Byrd CA (2003) Apoptosis following peripheral sensory deafferentation in the olfactory bulb of adult zebrafish. *J Comp Neurol* 455:488–498
- Var SR, Byrd-Jacobs CA (2019) Microglial response patterns following damage to the zebrafish olfactory bulb. *IBRO Rep* 7:70–79
- Var SR, Byrd-Jacobs CA (2020) Role of macrophages and microglia in zebrafish regeneration. *Int J Mol Sci* 21(13):4768
- Vassalli A, Rothman A, Feinstein P, Zapotocky M, Mombaerts P (2002) Minigenes impart odorant receptor-specific axon guidance in the olfactory bulb. *Neuron* 35:681–696
- Vassar R, Ngai J, Axel R (1993) Spatial segregation of odorant receptor expression in the mammalian olfactory epithelium. *Cell* 74:309–318
- Venereau E, Ceriotti C, Bianchi ME (2015) DAMPs from cell death to new life. *Front Immunol* 6:422
- Vigliano FA, Marcaccini AJ, Sarradell J, Bermúdez R, Quiroga MI (2011) First description of an olfactory neuroblastoma in goldfish *Carassius auratus*: a case report. *Dis Aquat Org* 96:61–68
- Villani A, Benjaminsen J, Moritz C, Henke K, Hartmann J, Norlin N, Richter K, Schieber NL, Franke T, Schwab Y, Peri F (2019) Clearance by microglia depends on packaging of phagosomes into a unique cellular compartment. *Dev Cell* 49:77–88.e7
- Villanueva R, Byrd-Jacobs CA (2009) Peripheral sensory deafferentation affects olfactory bulb neurogenesis in zebrafish. *Brain Res* 1269:31–39
- Von Rekowski C, Zippel HP (1993) In goldfish the qualitative discriminative ability for odors rapidly returns after bilateral nerve axotomy and lateral olfactory tract transection. *Brain Res* 618:338–340
- Wakisaka N, Miyasaka N, Koide T, Masuda M, Hiraki-Kajiyama T, Yoshihara Y (2017) An adenosine receptor for olfaction in fish. *Curr Biol* 27:1437–1447.e4
- Watt WC, Sakano H, Lee ZY, Reusch JE, Trinh K, Storm DR (2004) Odorant stimulation enhances survival of olfactory sensory neurons via MAPK and CREB. *Neuron* 41:955–967
- Weiler E, Farbman AI (1997) Proliferation in the rat olfactory epithelium: age-dependent changes. *J Neurosci* 17:3610–3622
- Weth F, Nadler W, Korsching S (1996) Nested expression domains for odorant receptors in zebrafish olfactory epithelium. *Proc Natl Acad Sci U S A* 93:13321–13326
- White EJ, Kounelis SK, Byrd-Jacobs CA (2015) Plasticity of glomeruli and olfactory-mediated behavior in zebrafish following detergent lesioning of the olfactory epithelium. *Neuroscience* 284:622–631
- Whitlock KE (2008) Developing a sense of scents: plasticity in olfactory placode formation. *Brain Res Bull* 75:340–347
- Whitlock KE, Westerfield M (2000) The olfactory placodes of the zebrafish form by convergence of cellular fields at the edge of the neural plate. *Development* 127:3645–3653
- Wu HH, Ivkovic S, Murray RC, Jaramillo S, Lyons KM, Johnson JE, Calof AL (2003) Autoregulation of neurogenesis by GDF11. *Neuron* 37:197–207
- Wullmann MF, Mueller T (2004) Teleostean and mammalian forebrains contrasted: evidence from genes to behavior. *J Comp Neurol* 475: 143–162
- Yabuki Y, Koide T, Miyasaka N, Wakisaka N, Masuda M, Ohkura M, Nakai J, Tsuge K, Tsuchiya S, Sugimoto Y, Yoshihara Y (2016) Olfactory receptor for prostaglandin F2 α mediates male fish courtship behavior. *Nat Neurosci* 19:897–904

- Yamate J, Izawa T, Ogata K, Kobayashi O, Okajima R, Kuwamura M, Kotani T, Aoki M (2006) Olfactory neuroblastoma in a horse. *J Vet Med Sci* 68:495–498
- Yoshihara Y (2009) Molecular genetic dissection of the zebrafish olfactory system. *Results Probl Cell Differ* 47:97–120
- You MS, Wang WP, Wang JY, Jiang YJ, Chi YH (2019) *Sun1* mediates interkinetic nuclear migration and notch signaling in the neurogenesis of zebrafish. *Stem Cells Dev* 28:1116–1127
- Zambusi A, Ninkovic J (2020) Regeneration of the central nervous system-principles from brain regeneration in adult zebrafish. *World J Stem Cells* 12(1):8–24
- Zapiec B, Mombaerts P (2020) The zonal organization of odorant receptor gene choice in the main olfactory epithelium of the mouse. *Cell Rep* 30:4220–4234
- Zapiec B, Dieriks BV, Tan S, Faull RLM, Mombaerts P, Curtis MA (2017) A ventral glomerular deficit in Parkinson's disease revealed by whole olfactory bulb reconstruction. *Brain* 140:2722–2736
- Zhang X, Firestein S (2009) Genomics of olfactory receptors. *Results Probl Cell Differ* 47:25–36
- Zhang G, Ferg M, Lubke L, Takamiya M, Beil T, Gourain V, Diotel N, Strahle U, Rastegar S (2020) Bone morphogenetic protein signaling regulates *Id1*-mediated neural stem cell quiescence in the adult zebrafish brain via a phylogenetically conserved enhancer module. *Stem Cells* 36:875–889
- Zhao S, Tian H, Ma L, Yuan Y, Yu CR, Ma M (2013) Activity-dependent modulation of odorant receptor gene expression in the mouse olfactory epithelium. *PLoS One* 8:e69862
- Zupanc GK, Clint SC (2003) Potential role of radial glia in adult neurogenesis of teleost fish. *Glia* 43(1):77–86
- Zupanc GK, Horschke I (1996) Salvage pathway of pyrimidine synthesis: divergence of substrate specificity in two related species of teleostean fish. *Comp Biochem Physiol B Biochem Mol Biol* 114:269–274
- Zupanc GK, Sirbulescu RF (2011) Adult neurogenesis and neuronal regeneration in the central nervous system of teleost fish. *Eur J Neurosci* 34:917–929
- Zupanc GK, Zupanc MM (2006) New neurons for the injured brain: mechanisms of neuronal regeneration in adult teleost fish. *Regen Med* 1:207–216
- Zupanc GK, Hinsch K, Gage FH (2005) Proliferation, migration, neuronal differentiation, and long-term survival of new cells in the adult zebrafish brain. *J Comp Neurol* 488:290–319

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