REVIEW

Mechanisms of Neurogenesis in the Normal and Injured Adult Brain

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Even in the adult brain, new neurons are continuously generated from endogenous neural stem cells that reside in two restricted regions: the subventricular zone (SVZ) of the lateral ventricle and the dentate gyrus of the hippocampus. These new neurons are integrated into the mature neuronal circuitry and become involved in various functions, thereby contributing to structural and functional plasticity in the adult brain. In this review, we summarize our recent findings on the regulatory mechanisms of SVZ neurogenesis under physiological and pathological conditions in various animal models. Some of these findings were presented in the Kitazato Prize Lecture at Keio University School of Medicine in 2011.   (doi: 10.2302/kjm.2012-0005-RE; Keio J Med 62 (1) : 13–28, March 2013)

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Introduction

Until recently, it was commonly believed that the adult brain does not produce new neurons. However, it is now well accepted that neural stem cells continue to reside in the subventricular zone (SVZ) of the lateral ventricle and dentate gyrus (DG) of the hippocampus, and that they produce functional neurons in the adult brain throughout life. In the SVZ, which is the largest neurogenic region in the adult brain, neural stem cells continuously generate new neurons via transit-amplifying neural progenitors. The new neurons form chain-like cell aggregates and migrate toward the olfactory bulb (OB) through the rostral migratory stream (RMS), a specialized route for migrating neurons. After arriving at the OB, the new neurons differentiate into olfactory interneurons, which are implicated in olfactory processing. Recent studies demonstrated that this neurogenic potential in the adult brain is widely conserved from nonmammalian vertebrates to primates, including humans. Interestingly, SVZ neurogenesis can be activated by various injuries and neurological diseases, suggesting that endogenous neural stem cells in the SVZ may be used for brain repair in lower animals, and might be exploited for therapeutic strategies in humans. In this review, we introduce our recent findings on SVZ neurogenesis in the physiological and pathological conditions of various animals.

Neural Stem Cells in the Subventricular Zone

In the adult rodent SVZ, there are four distinct types of cells: ependymal cells (type E cells), astrocytes (type B), transit-amplifying cells (type C), and migrating neuroblasts (type A) (**Fig. 1**).[1,2] Ependymal cells line the wall of lateral ventricles and have multiple motile cilia. The beating of these cilia is involved in controlling the cerebrospinal fluid flow in the lateral ventricles. Glial fibrillary acidic protein-positive (GFAP+) astrocytes in the SVZ generate new neurons and oligodendrocytes.[3] *In vitro*, these cells exhibit the two distinct characteristics of stemness: multipotency and self-renewal. Moreover, a recent study demonstrated that individual radial glia-like GFAP+ cells self-renew and generate neurons and astrocytes in the adult DG, indicating that they have the potential to function as adult neural stem cells *in vivo*.[4] However, differentiative potentials of individual SVZ astrocytes
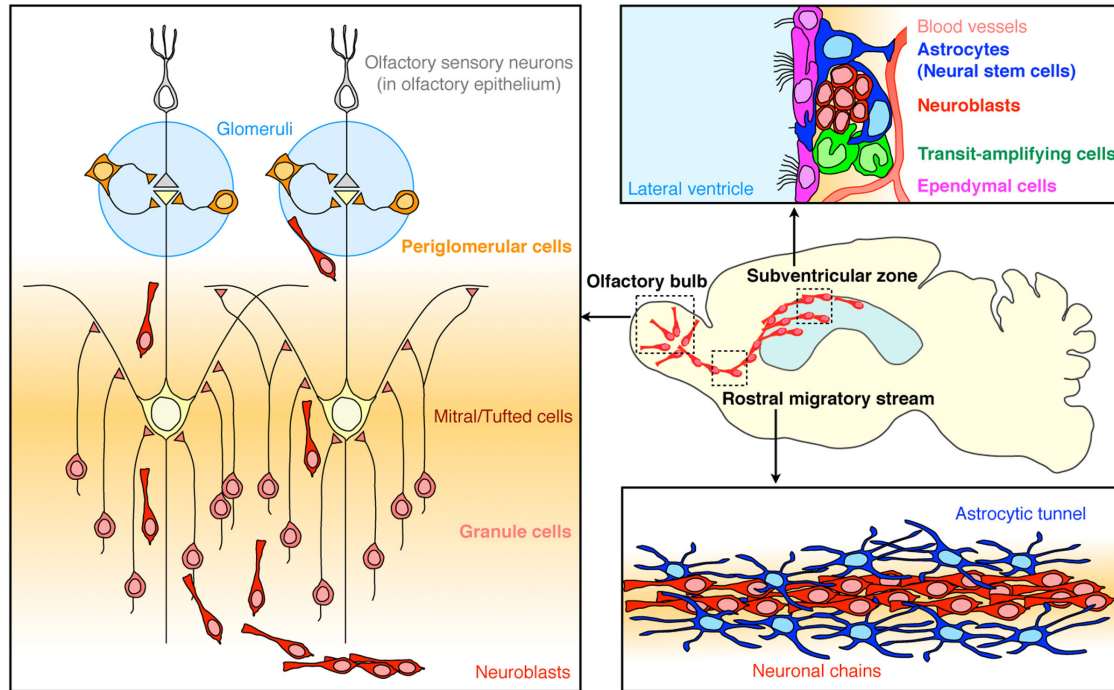

Fig. 1 Neurogenesis in the adult subventricular zone.

In the subventricular zone (SVZ) of the lateral ventricle, there are four distinct types of cells: ependymal cells (purple), astrocytes (blue), transit-amplifying cells (green), and neuroblasts (red). SVZ astrocytes contact the lateral ventricle and act as neural stem cells that generate neural progenitors called transit-amplifying cells. The transit-amplifying cells actively proliferate and generate neuroblasts. Blood vessels surrounding these cells have important roles in regulating neurogenesis in the SVZ. Neuroblasts generated in the SVZ migrate toward the olfactory bulb (OB) through the rostral migratory stream (RMS). These cells form chain aggregates, which are surrounded by tunnels composed of astrocytic processes. After arriving at the OB, the chain-forming neuroblasts are dissociated into individual cells and migrate radially inside the OB. Most of the neuroblasts differentiate into granule cells (pink) and form synapses with mitral/tufted cells (yellow), which are projection neurons in the OB. A small portion of the neuroblasts continue their radial migration to the glomeruli located in the superficial layer of the OB, where they differentiate into periglomerular cells (orange) and form synapses with both olfactory sensory neurons (gray) and the mitral/tufted cells.

in vivo have yet to be clarified. In addition, the precise identification and classification of neural stem cells in the adult SVZ are still difficult because of the lack of an adult neural stem cell-specific marker. Like embryonic neural stem cells, GFAP+ astrocytes in the adult SVZ express neural stem cell markers, including Musashi, LeX/ssea-1, Sox2, Id, and Nestin.[1,5–9] GFAP+ astrocytes in the SVZ proliferate very slowly and generate rapidly dividing transit-amplifying progenitors that generate migrating neuroblasts. In addition, blood vessels in the SVZ that are in contact with these cells play important roles in the control of neurogenesis.[10–13]

Several extracellular signals and their downstream pathways cooperatively regulate cell proliferation and differentiation in the SVZ. Because SVZ cells are packed into narrow regions lining the lateral ventricles and are in close contact with each other, cell–cell interaction signals could affect their proliferation state. For example, cell-surface carbohydrates could regulate the intercellular

interactions of adult neural stem cells in the SVZ. The carbohydrate-binding protein Galectin-1, a key regulator of various stem cells, is secreted by the majority of GFAP+ astrocytes in the adult SVZ.[14] Cell proliferation in the SVZ is reduced by *galectin-1* deficiency and activated by the infusion of exogenous Galectin-1, indicating that Galectin-1 positively regulates the proliferation of neural stem cells in the SVZ. The Eph-ephrin system is also important for intercellular interaction. The receptor tyrosine kinases EphA/B are expressed in the SVZ and regulate cell proliferation, although their downstream signaling molecules are currently unknown.[15]

Notch signaling is another key factor in many cell–cell interaction systems. During embryonic brain development, Notch is the most critical regulator of neural stem-cell maintenance. Ligand binding to Notch induces cleavage of the Notch intracellular domain, which translocates into the nucleus and induces the expression of transcriptional repressor proteins such as those encoded by the

Hes gene family, which repress the activities of proneural genes. One Notch ligand, Delta-like homologue 1 (Dlk1), is expressed by GFAP+ astrocytes in the postnatal SVZ and is required for the maintenance of neural stem cells.[16] Even in the adult brain, Notch signaling activity is observed in GFAP+ astrocytes in the SVZ. The conditional knockout of *Rbpj*, a Notch-signaling component, in the Nestin-expressing cell lineage causes the complete loss of neural stem cells in the SVZ, indicating that Notch signaling is also important for the maintenance of neural stem cells in the adult SVZ.[17] Interestingly, Notch signaling in neural stem cells in the SVZ is modulated by other extrinsic factors. For example, enhanced epidermal growth factor receptor (EGFR) signaling reduces both Notch1 expression and the number of GFAP+ neural stem cells in the SVZ, and it increases the number of transit-amplifying cells, suggesting that interplay between the Notch and EGFR pathways regulates the balance of the number of neural stem/progenitor cells.[18] In addition, pigment epithelium-derived factor, which is secreted from ependymal cells and blood vessels in the SVZ, enhances the Notch-dependent transcription of target genes, including *Hes1* and *Egfr*, in GLAST+Sox2+ neural stem cells with low Notch activity, suggesting that a vascular modulation of neural stem cells in the adult SVZ is mediated by Notch signaling.[19,20]

Because neural stem cells are widely distributed throughout the SVZ and generate various types of OB neurons, it is possible that they have distinct regional identities. The precise regional labeling of neural stem cells by adenovirus injection revealed that neuronal fates in the OB are pre-determined by the region of the SVZ inhabited by their precursors.[21] Sonic hedgehog (Shh) signaling, which is the determinant for the ventral axis in early neural development, is restricted to the ventral region of the adult SVZ.[22,23] Shh signaling also determines the ventral specification of neural stem cells, which generate specific neuronal progeny in the OB.[24] Bone morphogenic protein (BMP) signaling, which is the determinant of the dorsal axis in the embryonic brain, is also involved in neurogenesis in the adult SVZ,[25] although whether this signaling determines the dorsal specification of neural stem cells is currently unknown. Thus, in addition to Notch signaling, the regional specification by dorsoventral determinants such as Shh and BMP signaling could regulate the proliferation of neural stem cells and contribute to the diversity of neuronal progeny.

Wnt proteins are important soluble regulators of mammalian neural development and have two distinct downstream pathways. The canonical Wnt pathway is mediated by β-catenin, which acts as both a cytoskeletal component and a transcription factor. In the absence of Wnt stimulation, β-catenin is phosphorylated by casein kinase I and GSK3β and is constantly degraded by the ubiquitin–proteasome system. However, Wnt-mediated inhibition of GSK3β blocks this degradation of β-catenin; the unphosphorylated β-catenin then translocates into the nucleus, where it promotes the transcription of developmentally important genes. On the other hand, the non-canonical Wnt pathway is mediated by Wnt/planar cell polarity (PCP) signaling, which mainly regulates cytoskeletal dynamics and cell polarity through c-Jun N-terminal kinase (JNK) and Rho GTPase. However, the roles of these distinct Wnt pathways in the adult SVZ were completely unknown until recently.

Using *Axin2-d2EGFP* mice, in which the activation of β-catenin signaling can be monitored *in vivo*, we found that canonical Wnt/β-catenin signaling is activated in astrocytes and transit-amplifying cells in the adult SVZ.[26] The injection of a retrovirus carrying a constitutively active form of β-catenin or a highly selective GSK3β inhibitor, both of which activate Wnt/β-catenin signaling, increased the proliferation of transit-amplifying cells, which ultimately led to an increased number of new neurons in the OB. These results indicated that Wnt/β-catenin signaling positively regulates the proliferation of neuronal progenitors in the adult SVZ (**Fig. 2**).

Diversin, the mammalian homolog of the *Drosophila* PCP protein Diego, is a component of both canonical and non-canonical Wnt signaling (**Fig. 2**). We found that Diversin is expressed by neuroblasts in the neonatal and adult SVZ and DG.[27] In the adult SVZ, retrovirus-mediated overexpression of full-length Diversin increased the proliferation of neuroblasts. A mutant Diversin lacking the ankyrin repeat domain, which is important for activating the Wnt/PCP pathway, did not have this activity, suggesting that the Wnt/PCP pathway is necessary for the proliferation of neuroblasts. Interestingly, phosphorylated JNK, a downstream component of the Wnt/PCP pathway, could be observed in neuroblasts undergoing mitosis. Taken together, these results suggest that the Wnt/PCP pathway is active in the proliferation of neuroblasts (**Fig. 2**).

Thus, the two Wnt pathways have distinct functions in regulating the proliferation of transit-amplifying cells and neuroblasts in the SVZ (**Fig. 2**). Canonical Wnt/β-catenin signaling controls the proliferation of transit-amplifying cells, whereas the non-canonical Wnt/PCP pathway regulates the proliferation of neuroblasts. Since Diversin is involved in both the canonical and non-canonical Wnt pathways, it could act as a molecular switch for the transition from neuronal progenitors to migrating neuroblasts in the SVZ.

Neuronal Migration in the Rostral Migratory Stream

Neuroblasts generated from neural stem cells migrate at high speed from the SVZ toward the OB (**Fig. 1**). These cells form elongated cell aggregates called "chains."[28] In the chains, each neuroblast migrates along its neighbors, indicating that neuroblasts use other neuroblasts as a scaffold for efficient migration. In the lateral wall of the
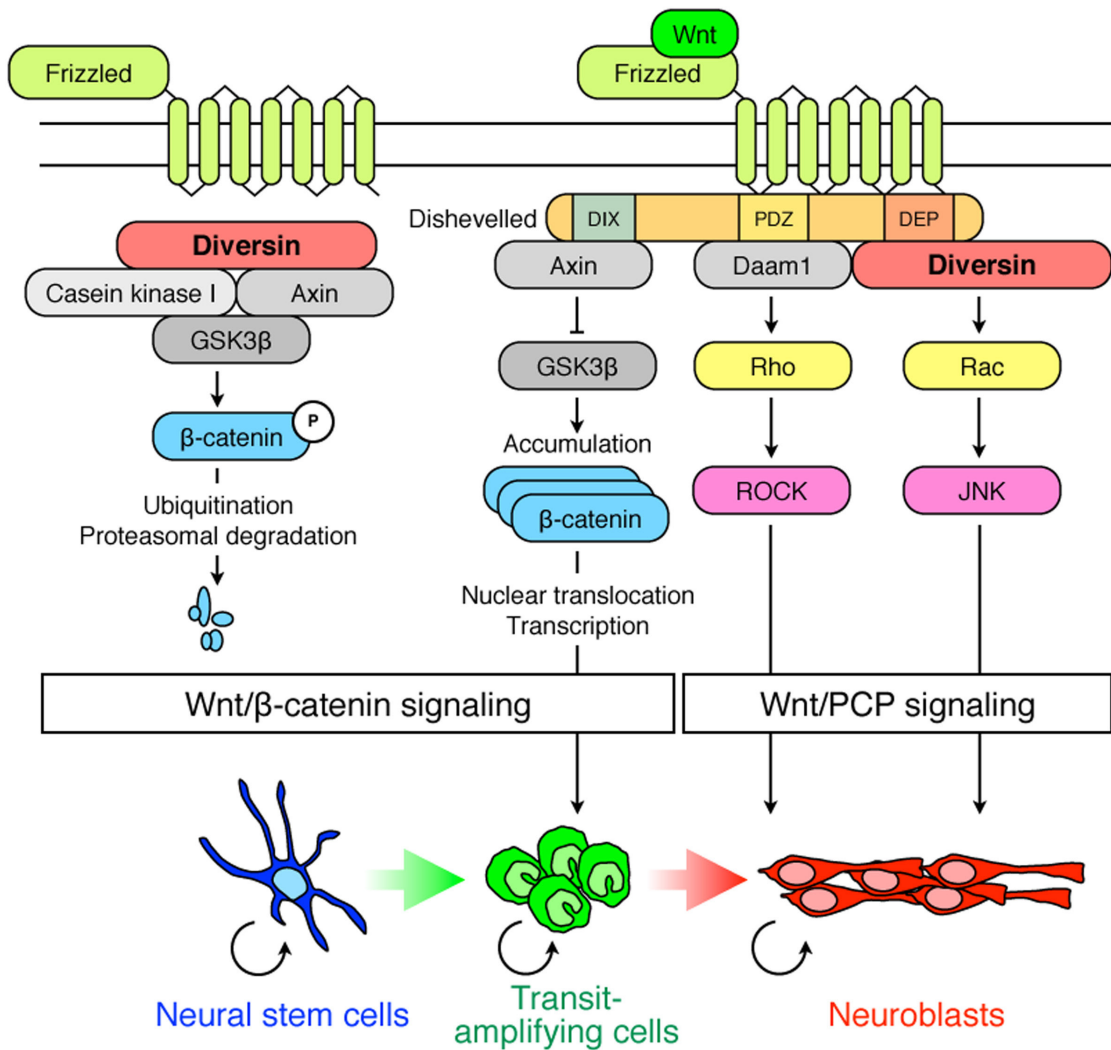
Fig. 2 Regulation of SVZ neurogenesis by Wnt signaling.
Wnt proteins have two distinct downstream signaling pathways. The canonical Wnt pathway is mediated by β-catenin. In the absence of Wnt stimulation, β-catenin is constantly phosphorylated by casein kinase I/GSK3β complex and degraded by the ubiquitin-prote-asome system. This process is inhibited by Wnt-mediated inhibition of GSK3β; the unphosphorylated β-catenin then accumulates in the cytosol and translocates into the nucleus. In the adult SVZ, Wnt/β-catenin signaling is activated in the astrocytes and transit-ampli-fying cells and regulates their proliferation. The non-canonical Wnt pathway is mediated by Wnt/planar cell polarity (PCP) signaling, which regulates cytoskeletal dynamics and cellular polarity through JNK and Rho family small GTPases. Diversin is a component of both the canonical and non-canonical Wnt signaling pathways. The Diversin-mediated Wnt/PCP pathway regulates the proliferation of neuroblasts in the adult SVZ.

lateral ventricle in the adult brain, an extensive network of neuronal chains can be observed, which converge into bundles of chains when entering the RMS, a restricted pathway for migrating neuroblasts.[29] In the RMS, the chain-forming migrating neuroblasts are surrounded by tunnels formed by astrocytic processes. The chain forma-tion of migrating neuroblasts and surrounding glial tubes are two distinct features of the adult RMS (**Fig. 1**).[30]

Several proteins that regulate chain formation have been identified. For example, mice lacking the cell-surface receptors ErbB4 and ApoER2 show defective chain formation and migration in the RMS, resulting in decreased numbers of newly arriving neurons in the OB.[31,32] Extracellular matrix-related molecules such as α6β1-integrin and ADAM2 protease are also involved in neuroblast chain formation.[33–35] These findings raise the possibility that various extracellular stimuli actively regulate the chain formation of neuroblasts.

To migrate at high speed within the neuronal chains, the chain-forming neuroblasts need to slide along each other efficiently. Polysialylated neural cell adhesion molecule (PSA-NCAM), a cell adhesion molecule with a negatively charged polysialic acid (PSA) moiety, is highly expressed on the cell surface of chain-forming neuroblasts in the RMS. *NCAM* gene deletion or enzymatic digestion of the PSA moiety cause migrating neuroblasts to accumulate in the RMS without any defect in chain formation.[36,37] The negative charge of the PSA moiety might increase the cellular motility by decreasing the adhesion between neuroblasts, leading to smooth chain migration in the RMS.[38]

Since chain-forming neuroblasts must migrate over a long distance from the SVZ to the OB, the determination of directionality is important for their appropriate migration. We demonstrated that the direction of migrating neuroblasts in the SVZ is determined by the repulsive factor Slit,[39] which is reported to control axonal guidance in the developing brain by regulating the cytoskeleton.[40,41] Several studies have shown that Slit is secreted from the septum and choroid plexus and can repel migrating neuroblasts generated in the SVZ.[42–44] However, the mechanism by which the Slit proteins reach the migrating neuroblasts in the SVZ was not known.

We found that migrating neuroblasts in the SVZ follow the direction of cerebrospinal fluid (CSF) flow created by the beating of ependymal cilia.[39] Exogenous Slit protein injected into the lateral ventricle formed a concentration gradient within the dorsal SVZ, with the highest signal in the caudal region and the weakest in the rostral area, in parallel with the direction of CSF flow (**Fig. 3A**). The *Tg737^(orpk)* mouse, a mutant strain with cilia-formation defects, showed an impaired Slit gradient and disoriented chain migration in the SVZ (**Fig. 3A**). These results suggest that the concentration gradient of Slit in the SVZ created by the beating of ependymal cilia determines the direction of migrating neuroblasts.

Our findings indicated that the beating of ependymal cilia plays an important role in neuronal migration in the SVZ. During the early postnatal stage, the developing ependymal cells acquire two types of cellular polarity, translational and rotational polarity.[45,46] The anterior migration of basal bodies (translational polarity) and coordinated ciliary beating (rotational polarity) in the ependymal cells are both important for appropriate ciliary beating and the formation of CSF flow. We showed that non-muscle myosin II and the Wnt/PCP pathway distinctly regulate the processes responsible for generating translational and rotational polarity, respectively.[47,48] These results suggest that the distribution and orientation of basal bodies are regulated by distinct mechanisms, and that both contribute to the control of CSF flow.

Although repulsive mechanisms could be crucial for neuroblast movement from the SVZ toward the RMS, such mechanisms seemed less effective for cells migrating in the RMS toward the OB because of the long distances involved. Instead, attractant factors released from the OB could be involved in directionality in the RMS. The secreted protein prokineticin 2 (PK2) is expressed in the granule and glomerular layer of the OB, whereas PK2 receptor (Prokr2) is expressed in the neuroblasts migrating in the RMS.[49,50] PK2 knockout and Prokr2 mutant mice show an accumulation of migrating neuroblasts in the rostral RMS, indicating that PK2 is a possible attractant for neuroblasts toward the OB.[49,50] Other growth/trophic factors such as hepatocyte growth factor, brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor, and Netrin-1 also show attractant activity for neuroblasts *in vitro*, although *in vivo* evidence for their involvement remains to be demonstrated.[51–54]

In the RMS, neuroblasts move inside the glial tube, which is reported to support their long-distance cell migration through intercellular molecular interactions. For example, the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) secreted by migrating neuroblasts is taken up by the RMS astrocytes, leading to negative regulation of the migration speed.[55] Conversely, glutamate released by RMS astrocytes activates *N*-methyl-d-aspartate receptor in the migrating neuroblasts, which promotes their survival before they enter the synaptic network in the OB.[56] RMS astrocytes also interact with blood vessels inside the glial tube and capture BDNF secreted from endothelial cells, which leads to the vasculature-associated migration of neuroblasts in the RMS.[57,58] It was reported that Slit1 and its receptors Robo2/3, which mediate the repellant properties of Slit1, are expressed by migrating neuroblasts in the RMS, suggesting that Slit1 has a cell-autonomous role in the RMS.[59] We showed that Robo2 is strongly expressed by tunnel-forming astrocytes in the RMS. Slit1-secreting migrating neuroblasts repel the Robo-expressing astrocytes to actively regulate the astrocytes' morphology, leading to efficient neuroblast migration.[60] In the RMS of Slit1^(-/-) mice, cellular organization and neuronal migration are disturbed (**Fig. 3B**). To examine whether neuroblasts regulate the formation of the glial tube, we eliminated migrating neuroblasts pharmacologically by Ara-C treatment. After the elimination of migrating neuroblasts, the glial-tube structure became disorganized (**Fig. 3B**). These results indicated that Slit–Robo-mediated repulsive signaling is required for both the efficient migration of neuroblasts and the formation of the glial tube in the RMS.

Extracellular cues, such as Slit proteins, dynamically reorganize the cytoskeleton of each migrating neuroblast through various intracellular pathways. Migrating neuroblasts have a bipolar shape with a long leading process and a short trailing process. Because neuroblasts migrate in a saltatory manner, with repeated steps of leading-process extension followed by movement of the cell soma, it is necessary to maintain the cell polarity and cooperatively regulate the cytoskeleton of each neuroblast. For
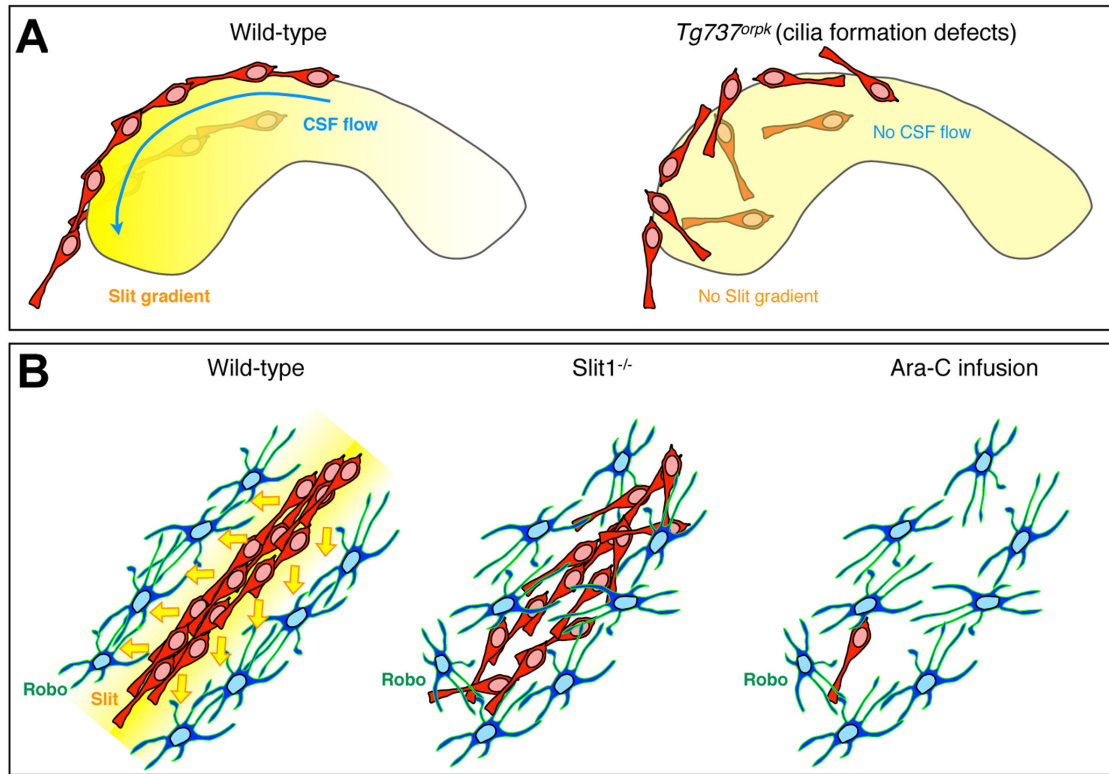
Fig. 3 Slit-mediated regulation of neuronal migration in the SVZ and RMS.
(A) In the lateral ventricles of wild-type mice, the beating of ependymal cilia generates the flow of cerebrospinal fluid (CSF) (blue arrow). This flow forms a concentration gradient of Slit proteins within the dorsal SVZ (yellow), leading to the repulsion of neuroblasts (red) from the SVZ toward the RMS. *Tg737^{orpk}*, a mutant mouse strain with cilia-formation defects, showed an impaired Slit gradient and disoriented chain migration in the SVZ. (B) Migrating neuroblasts (red) express Slit proteins (yellow), whereas the surrounding astrocytes (blue) express Robo receptors (green) in the RMS of wild-type mice. Slit secreted from neuroblasts actively repels astrocytes, leading to efficient neuronal migration and the formation of glial tubes. In Slit1^{-/-} mice, this cellular organization and neuronal migration are disturbed. Pharmacological elimination (Ara-C infusion) of the migrating neuroblasts also causes disorganization of the glial-tube structure.

example, PKCζ and GSK3β orchestrate neuronal polarity by controlling the centrosomal positioning, leading to dynamic reorganization of the cytoskeleton, including changes in microtubules and actin filaments.[61] The actin-binding Akt substrate Girdin is necessary for the chain migration of neuroblasts, suggesting that regulation of the actin cytoskeleton is important for chain migration.[62] Consistent with this idea, mDia, a downstream effector of Rho GTPase, is involved in centrosomal movement and nuclear translocation in neuroblast migration by regulating F-actin dynamics.[63] Nuclear translocation is disturbed in the neuroblast migration of doublecortin mutant mice, suggesting a role of microtubule-related factors.[64] We found that CDK5, a microtubule regulator for neuronal migration in the developing brain, also has an essential role in neuroblast migration in the postnatal RMS. Conditional knockout CDK5 mice showed defects in the chain formation, migration speed, and polarity of neuro-

blasts in the RMS, suggesting that CDK5 is required for chain formation and efficient migration of neuroblasts.[65]

These studies demonstrated the mechanisms regulating the directional control and chain formation of migrating neuroblasts as well as the formation of glial tubes. However, how the activation and dynamics of intracellular cytoskeletal regulators are integrated during chain migration remains unknown. Unlike the processes involved in other types of cell migration, chain-forming neuroblasts in the RMS migrate along their neighbors by constantly changing their adhesive properties. It is possible that neuronal chains provide not only a simple migratory scaffold but also actively instructive cues for the efficient migration in chains. More detailed analyses of chain migration are still needed to gain further insight into neuroblast migration in the adult brain.

Neuronal Maturation and Turnover in the Olfactory Bulb

After arriving at the OB, the chain-forming migrating neuroblasts dissociate into individual cells and start to migrate radially within the OB (**Fig. 1**). In the transition from chain migration to radial migration, the neurons must detach from the neuronal chains at the core of the OB. PK2 has a role in the detachment of cells from the chains within the OB in addition to its role in the attraction of neuroblasts in the RMS toward the OB.[49] Reelin, which is important for neuronal positioning in the developing brain, is secreted by mitral cells in the adult OB and promotes chain dissociation.[66] Interestingly, the expression of Tenascin-R, another detachment signaling molecule, is regulated by olfactory input, suggesting that activity-dependent detachment from the neuronal chains occurs.[67]

Most new neurons differentiate into granule cells in the granule cell layer (**Fig. 1**). In addition, a small portion of the new neurons continue their radial migration and reach olfactory glomeruli located in the superficial layer of the OB, where they differentiate into periglomerular cells (**Fig. 1**). These two types of adult-born neurons are GABAergic interneurons and are constantly replaced throughout life.[68–70] These neurons are reported to have various olfactory functions, such as in olfactory learning and odor discrimination.[71–75]

The maturation process of new neurons in the OB is dynamically regulated by both intrinsic and extrinsic factors. Several studies using knockout mice suggest that transcriptional factors such as Pax6 and Sp8 are required for the genesis of distinct subtypes of olfactory interneurons.[76–79] On the other hand, extrinsic factors including olfactory input from olfactory sensory neurons and centrifugal inputs from higher brain centers are also important for the maturation of new neurons in the OB.

Since the OB is a primary processing center for olfactory stimulations, it directly receives olfactory input transmitted by olfactory sensory neurons in the olfactory epithelium. Olfactory input is a critical factor for the survival of new neurons in the OB. Several studies using anosmic mice,[80] olfactory deprivation,[81–83] and various odorants[84,85] revealed that olfactory input promotes the survival of newly arrived neurons in the OB. A recent study revealed that new granule cells are eliminated during the postprandial period, and this elimination is enhanced by olfactory deprivation.[86] Thus, olfactory input regulates the integration process of newly arrived neurons in the OB.

In addition, the OB receives various kinds of centrifugal input from higher brain centers. Several neurotransmitter systems such as noradrenergic input and serotonergic input are reported to innervate within the OB.[87] Acetylcholine (ACh) is an important neurotransmitter in learning and memory formation. The granule cell layer and glomerular layer of the OB are extensively innervated with basal forebrain cholinergic neurons, suggesting that cholinergic input may affect mature or immature interneurons in the OB. We found that both PSA-NCAM-expressing migrating neuroblasts and mature granule cells express multiple types of ACh receptors and often make contact with cholinergic fibers in the OB.[88] Inhibiting the cholinergic system by injecting the acetylcholinesterase inhibitor Donepezil increased the survival of new neurons in the OB without affecting cell proliferation in the SVZ. These results suggested that the survival of new neurons in the OB is partly regulated by the activity of the centrifugal cholinergic system, which can be affected by various physiological and pathological aspects of an animal. Thus, the survival of new neurons is regulated by the combination of peripheral and centrifugal inputs, which can be dynamically affected by the conditions, behaviors, and environment of an animal.

The surviving new neurons are functionally integrated into mature circuits in the adult OB. During this process, the new neurons show high synaptic and dendritic plasticity, which is promoted by olfactory input.[89,90] A recent study demonstrated that the synaptic plasticity of new neurons lasts for several months, contributing to the plasticity of OB circuits.[91] At the same time, older interneurons in the OB are eliminated by apoptotic cell death. Thus, olfactory interneurons are continuously replaced throughout life, and this process can be regulated by olfactory input. Although this neuronal turnover was thought to underlie plasticity and stability in the adult OB, the relationship between lost and replaced cells was not fully understood, largely due to the difficulty of monitoring individual neurons over time in live adult animals.

It was recently reported that the turnover of periglomerular cells can be visualized in live animals using *in vivo* two-photon laser-scanning microscopy.[92,93] Since this methodology enables the same region of olfactory glomeruli to be observed over time, it can be used to detect new additions and eliminations of neurons in addition to stably existing neurons. Using this method and a naris occlusion plug that can reversibly regulate olfactory input (**Fig. 4A**), we showed that, in live animals, the addition and elimination of periglomerular cells are dynamically controlled by olfactory input in a neuronal subtype-specific manner.[94] To examine the spatiotemporal relationship between lost and replaced neurons, we developed a method for *in vivo* two-photon laser-ablation of periglomerular cells (**Fig. 4B**), by which we could selectively eliminate targeted neurons in live animals. Interestingly, the positions of neurons ablated by the two-photon laser were filled by neurons of the same subtype in an olfactory-input-dependent manner. These results suggested that neuronal turnover is spatiotemporally regulated by olfactory input in a neuronal subtype-specific manner, which could contribute to the structural stability of olfactory glomeruli. Another notable finding was that the dendritic
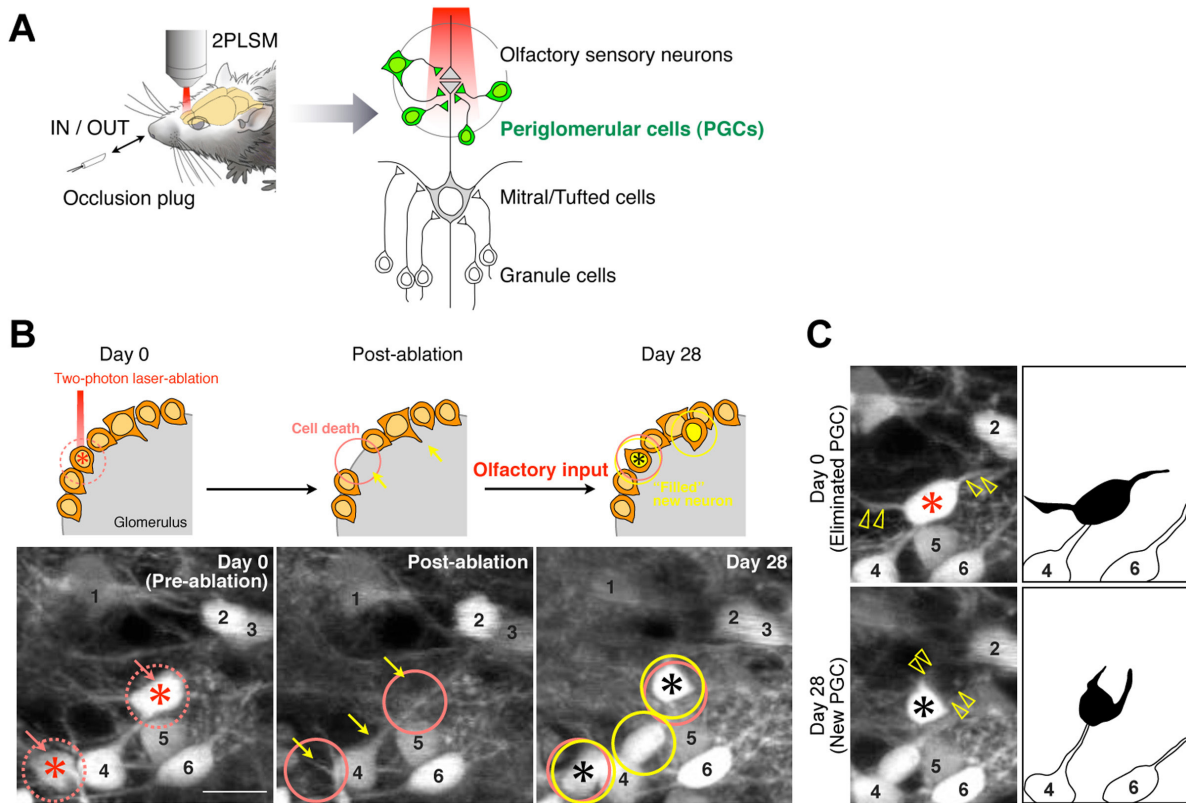
Fig. 4 Olfactory input-dependent spatial regulation of neuronal turnover in the adult olfactory bulb (modified from Sawada et al., *J. Neurosci.*, 2011).[94]
(A) Fluorescent protein-labeled periglomerular cells (PGCs, green) could be observed over time in live animals under two-photon laser-scanning microscopy (2PLSM). To reversibly regulate the olfactory input, a naris occlusion plug was used. (B) Two-photon laser-ablation enables the selective elimination of targeted PGCs (red asterisks). Twenty-eight days after laser-ablation, newly added PGCs could be observed (yellow arrows and circles). The positions that lost PGCs (pink circles) by laser-ablation were filled by new PGCs (black asterisks) in an olfactory input-dependent manner. (C) Maximum projection images of lost and replaced PGCs shown in (B). In the replaced positions, the dendritic directions (yellow open arrowheads) of lost and replaced PGCs were different. Numbers indicate PGCs whose positions were stable during the imaging period. Scale bar: 10 μm.

directions of the lost and replaced neurons at the same positions were different, indicating that these neurons maintain their dendritic plasticity (**Fig. 4C**). Taken together, we propose that the activity-dependent reiterated use of the same positions by new neurons enables both active remodeling of neuronal circuits by cellular turnover and maintenance of the glomerular structure.

Several studies have shown that the survival of new neurons in the OB is regulated by olfactory input; however, the mechanisms regulating neuronal turnover are just beginning to be clarified. A recent study showed that depleted granule cells are compensated for by new cells of the same neuronal subtype in a local area of the granule cell layer.[95] Thus, it is possible that adult-born olfactory interneurons show subtype-specific turnover patterns.[94] The turnover of olfactory interneurons is thought to be important for both the maintenance and the plasticity of

olfactory functions. Further analysis of the spatiotemporal regulation of neuronal turnover will be needed to understand how neuronal turnover contributes to structural and functional plasticity and/or stability in the adult OB.

Neurogenesis in the Adult Injured Brain

Recent studies suggest that neurogenesis in the adult brain can be affected by various pathological conditions. Experimental models of brain injury (such as trauma, hypoxia, and ischemia) and of neurodegenerative diseases (including Alzheimer's disease, Parkinson's disease, and Huntington's disease) are reported to stimulate neurogenesis in the SVZ of the adult rodent brain.[96] Of these disease models, middle cerebral artery occlusion (MCAO) is widely used for investigating neurogenesis in the SVZ of the injured brain. In the MCAO model, the striatum
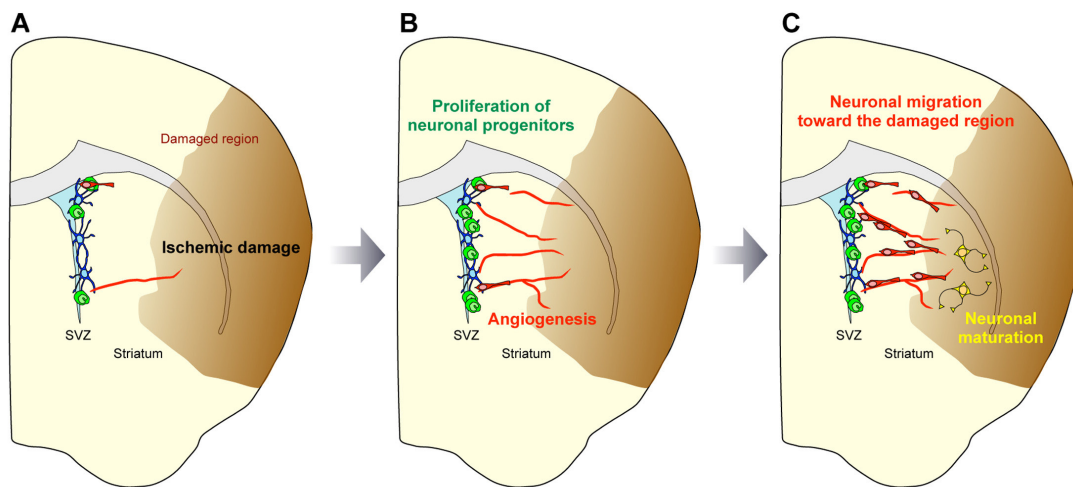
Fig. 5 Neurogenesis in the injured adult brain.
(A) Experimental ischemic model in which middle cerebral artery occlusion (MCAO) causes infarction in the striatum and cerebral cortex (brown). (B) After MCAO, the proliferation of SVZ cells (green) is activated. Angiogenesis also occurs surrounding the damaged region (red). (C) Dcx+ neuroblasts (red) derived from SVZ astrocytes migrate along both newly formed and preexisting blood vessels toward the damaged region. In some cases, these migrating neuroblasts form chains in the striatum. Despite the appearance of many migrating neuroblasts in the damaged striatum, only a small number of them survive and differentiate into mature neurons (yellow).

and dorsolateral cerebral cortex are damaged, and mature neurons in these regions undergo cell death (**Fig. 5A**). After MCAO, neurogenesis in the adult SVZ is upregulated, followed by the appearance of many neuroblasts expressing Dcx in the vicinity of the injured area, called the ischemic penumbra (**Fig. 5B, C**). However, only a small portion of these cells differentiate into mature neurons in the striatum.[97,98] We have focused on this experimental model and investigated the regenerative potential of SVZ cells after injury.

The first reactive response after MCAO is an increased proliferation of SVZ cells (**Fig. 5B**). Several reports suggest that various chemokines and growth factors, including EGF, are upregulated in the damaged striatum[99] and vascular endothelial cells,[100] which could stimulate the proliferation of SVZ cells after MCAO. However, it was unknown what kind of cells could respond to EGF in the SVZ. We determined that EGFR is expressed by transit-amplifying type C cells in the SVZ after MCAO.[101] In addition, these cells dynamically expand their number in response to EGF infusion. EGF infusion increased the number of neuroblasts in the damaged area, suggesting that neuronal replacement in the injured striatum might be enhanced by the EGF-induced expansion of transit-amplifying cells in the SVZ.

The second reactive response is the appearance of Dcx+ cells in the ischemic penumbra (**Fig. 5C**). These Dcx+ cells show a migratory morphology, suggesting

that they are migrating from somewhere toward the damaged area.[97] Several angiogenic and inflammatory factors such as angiopoietin-1 and SDF-1 are involved in this migration.[102–104] However, the origin of these Dcx+ cells remained unknown. We demonstrated using a virus infection-mediated fate-mapping technique that these Dcx+ cells are derived from GFAP+ astrocytes in the SVZ and migrate toward the damaged regions.[105] In addition, some of the migrating Dcx+ neuroblasts form chains and closely associate with blood vessels and astrocytic processes. These results raised the possibility that in the injured striatum, migrating cells use the blood vessels as a scaffold for their efficient migration. Using time-lapse recording in slice culture, we demonstrated that SVZ-derived neuroblasts migrate along blood vessels toward the damaged striatum.[106] Furthermore, the migration speed of these neuroblasts was decreased by the pharmacological inhibition of CXCR4, suggesting that chemokine signaling is involved in this vasophilic migration.

In contrast to the adult RMS, which provides a specialized, permissive environment for cell migration, neuroblasts in the damaged striatum must migrate through complex neuronal circuits. Furthermore, the activation of reactive astrocytes and microglia, and the subsequent formation of a glial scar, could worsen the conditions for migrating neuroblasts to reach the damaged area. Moreover, many questions remain to be answered. Why do neuroblasts form chains and migrate along the blood ves-
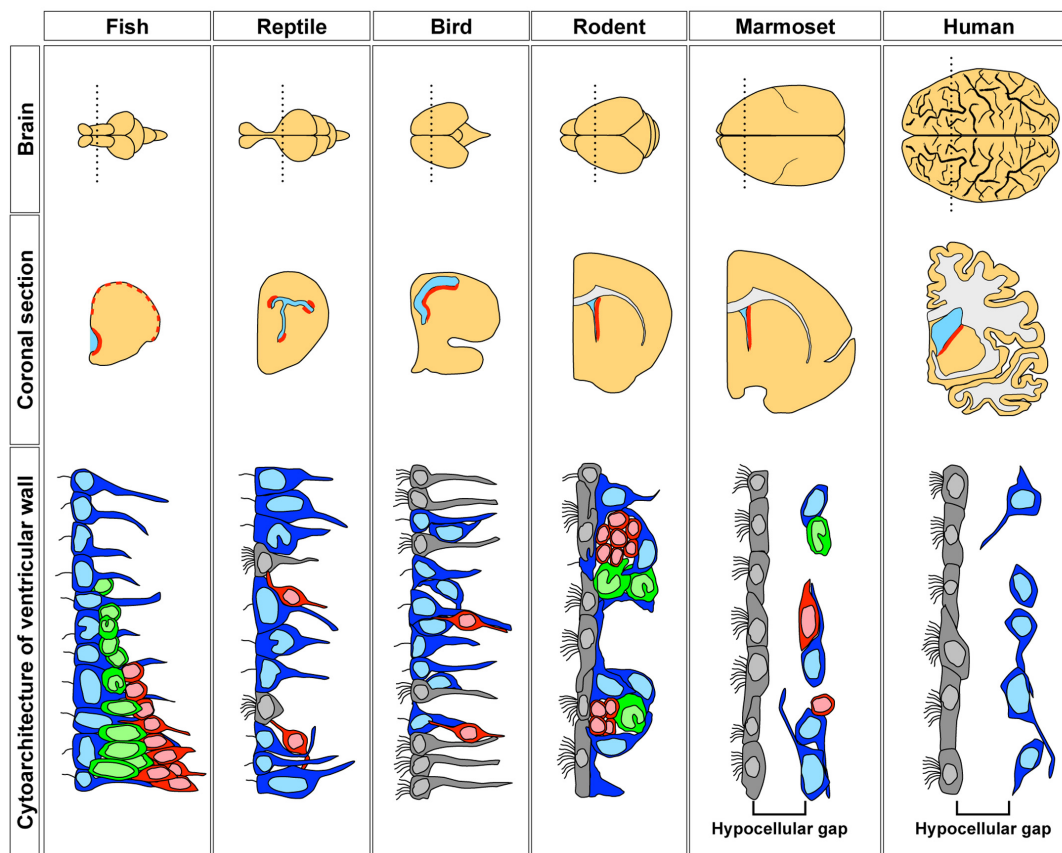
Fig. 6 Adult neurogenesis in various vertebrates (modified from Garcia-Verdugo et al., *Brain Res. Bull.*, 2002).[111]
Illustrations of the fish, reptile, bird, rodent, marmoset, and human brain are shown in the upper row. Coronal sections of the brain hemispheres at the location of the dotted lines in the illustrations are shown in the middle row. Red lines indicate the neurogenic regions. The neural stem cell niche in the adult brain is widely conserved at the ventricular wall (blue). The cytoarchitecture of the ventricular wall in various vertebrates is shown in the bottom row. In fish, the ventricular wall is covered with radial glia (blue). The ratio of ependymal cells (gray) to radial glia or astrocytes in lower species is smaller than in higher species. In primates (marmosets and humans), the ventricular wall is fully covered with ependymal cells. Moreover, the hypocellular gap layer is a typical feature of the primate ventricular wall. In all species except for adult human, neuroblasts (red) are observed beneath the ventricular wall. In the neonatal human SVZ, many neuroblasts are observed at birth, but disappear by 18 months of age.[113] In fish, rodents, and marmosets, transit-amplifying neuronal progenitors (green) are also observed.

sels in the damaged brain? What mechanisms direct the migrating neuroblasts toward the damaged area? How do neurons migrate through the complex, disadvantageous environment? Understanding the mechanisms regulating the interactions between migrating neuroblasts and their surrounding microenvironment may provide new insights for novel therapies involving the regeneration of lost neuronal circuits using endogenous neural stem cells in the adult brain.[96,107–110]

Adult Neurogenesis in Various Species

Most of the studies on adult neurogenesis cited above used rodents. However, neurogenesis is observed in the adult brain of many vertebrates, from fish to humans.

A comparable neural stem cell niche in the adult brain is widely conserved at the ventricular wall[1,111–115] (**Fig. 6**), where embryonic neural stem cells are located in the developing brain. Neural stem cells in the adult human brain are a promising endogenous cell source for brain regeneration after various injuries and diseases. Thus, comparative studies of neurogenesis in the adult brain among different species are needed to better understand the features and regulatory mechanisms of adult neural stem cells.

We have focused on zebrafish as a nonmammalian vertebrate model in which genetic and pharmacological manipulations are available. Recent studies suggested that, as in rodents, neuronal progenitors are generated in the telencephalic ventricular zone (VZ) and migrate toward

the OB in the adult zebrafish.[116–119] However, the cytoarchitecture of the VZ–OB pathway was unknown. We demonstrated that the telencephalic VZ of the zebrafish consists of three types of cells: GFAP+ radial glial cells, PCNA+ proliferative cells, and PSA-NCAM+ neuroblasts (**Fig. 6**).[112] Moreover, a continuous migratory stream of PSA-NCAM+ neuronal progenitors extends from the VZ to the OB, but the neurons do not move through glial tunnels. Time-lapse imaging using Tg(*ngn1:gfp*) fish demonstrated that neuronal progenitors migrate rostrally along blood vessels in the RMS toward the OB, indicating that the PSA-NCAM+ stream is the functional route for the migration of neuronal progenitors in the adult zebrafish brain. In the rodent RMS, the chain-forming new neurons also migrate along blood vessels,[57,58] suggesting the existence of common mechanisms for vasophilic migration. Thus, these results reveal similarities and differences in the ventricular neurogenic niche between zebrafish and rodent brains.

Compared with rodents, zebrafish have a higher regenerative potential after brain injury. We established a traumatic brain injury (TBI) model in the adult zebrafish and demonstrated that the glutamatergic neurons lost from the dorsolateral telencephalon after TBI are regenerated from VZ-derived neuronal progenitors.[120] This process was abolished by the pharmacological inhibition of Notch signaling, indicating that Notch signaling is required for neuronal repair. Thus, the zebrafish is a useful and powerful model for genetic and pharmacological screening to investigate the mechanisms regulating adult neurogenesis under physiological and pathological conditions.

To understand evolutionarily conserved neurogenesis in the adult brain, we need to examine the primate brain in addition to that of nonmammalian vertebrates and rodents. The SVZ–OB pathway has been reported in the Old World primates *Macaca mulatta* and *Macaca fascicularis*.[121–123] However, there are several limitations associated with the use of these macaque monkeys for studying adult neurogenesis, including their low availability, slow sexual maturation, and large body size. In contrast, the common marmoset, *Callithrix jacchus*, a New World primate, has advantages in terms of its small size (300–500 g at maturity) and stable supply because of its availability from breeding colonies. In addition, several neurological disease models and transgenic animals are already available ,[124,125] indicating that the common marmoset is useful for studying adult neurogenesis.

We recently reported the cellular composition and organization of the SVZ and RMS in the common marmoset.[115] Interestingly, the SVZ–OB pathway in the marmoset is more similar to that of humans than to that of rodents. Like the adult human SVZ,[114] the adult marmoset SVZ consists of three distinct layers: the ependymal, hypocellular gap, and astrocytic ribbon layers (**Fig. 6**).[115] Moreover, although an extensive network of PSA-NCAM+ elongated cell aggregates can be observed in the

SVZ, only individually migrating neuroblasts are found in the olfactory tract and OB. These findings indicate that the SVZ–OB pathway in the adult marmoset has several characteristics in common with that in humans. However, the anterior SVZ contains some putative progenitors similar to the transit-amplifying cells in rodents, but this feature is not conserved in the human brain (**Fig. 6**). Notably, in the neonatal (postnatal day 0–1) marmoset, the SVZ contains chains of migrating neuroblasts that continue toward the OB.[115] This active neonatal neurogenesis and rodent-like chain migration was also recently reported in the neonatal human SVZ, in which many Dcx+ neuroblasts exist in the layer corresponding to the hypocellular gap of the adult stage.[113] Thus, again, the SVZ–OB pathway in marmosets is very similar to that in humans.

The neurogenic potential of the SVZ–OB pathway differs among animal species, probably because of differences in how much the animal depends on olfaction for its survival. In primates such as humans and marmosets, which depend on the visual system more than the olfactory system, new neurons generated in the SVZ may migrate to different locations and have different functions. Indeed, the human brain has an additional migratory stream of neurons that branches off from the RMS and ends in the ventromedial prefrontal cortex, raising the possibility that new neurons derived from SVZ neural stem cells are involved in functions other than olfaction in higher primates.[113] Further characterization of the fates of the neural stem/progenitor cells in the primate SVZ using marmoset models of neurological disorders should contribute to novel strategies for brain repair using endogenous neural stem cells.

Conclusion

Since the discovery of neural stem cells in the adult brain, many features of adult neurogenesis have been described.[2,96,126–129] We now know that neurogenesis in the adult brain consists of complex biological events including the genesis, migration, differentiation, and maintenance of new neurons (**Fig. 1**). Although a variety of molecular and cellular mechanisms have been shown to regulate each aspect of adult neurogenesis, it is important to integrate these findings to obtain a comprehensive understanding of this complex system. Adult neurogenesis could enable the dynamic remodeling of mature neuronal circuits by adding new neurons, contributing to structural and functional plasticity in the adult brain. Adult neurogenesis could also have an important role in the injured brain, in regenerating the lost neurons from adult neural stem cells. This endogenous potential needs to be further investigated in future studies. Importantly, adult neurogenesis is regulated not only by developmental genetic programs but also by environmental and internal changes in animals. Thus, adult neurogenesis could be a fundamental mechanism for experience-dependent plas-

ticity, which is the most important feature of the adult brain. We hope that future studies on the physiological and pathological conditions of various animals will improve our understanding of the biological functions and significance of neurogenesis in the adult brain.

Acknowledgments

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