

Integrating new neurons into the adult olfactory bulb: joining the network, life–death decisions, and the effects of sensory experience

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In contrast to the situation in the developing brain, neurons born during adulthood must integrate into established neuronal networks characterized by ongoing activity. For sensory systems, this neuronal activity is driven mainly by external stimuli that can lead to experience-dependent morpho-functional changes in adult circuits. Here, we describe new insights into the mechanisms by which sensory experience might govern the targeting of adult-generated neurons to appropriate regions, their differentiation into distinct neuronal subtypes, and finally their survival in the adult olfactory bulb. We propose not only that neurogenesis depends on the degree of sensory experience, but also that new neurons bring unique features to the operational network, allowing a continuous adjustment of information processing in response to an ever-changing external world.

Introduction

Over the past few years it has become clear that newborn neurons continue to be added to some regions of the adult nervous system [1–6]. Understanding the functional meaning of this phenomenon represents a challenging task. Today, it is believed that the generation of new neurons in adult circuits belongs to a large repertoire of neuroadaptive responses [7], with the continuous replacement of old neurons by the newcomers bringing to neuronal networks a degree of circuit adaptation that might depend on neuronal activity. This form of plasticity, however, occurs only in discrete regions of the adult brain, including the olfactory bulb, which receives interneurons issued from the subventricular zone (SVZ) of the forebrain, and the dentate gyrus of the hippocampus. Other areas, such as the substantia nigra [8] and the neocortex [9], also have been thought to incorporate newborn neurons. However, this issue is still highly debated [10,11]. We currently lack confirmation that commonly used markers of neurogenesis (e.g. bromodeoxyuridine, BrdU) do not simply reflect DNA synthesis occurring

during pathological conditions (e.g. trauma and ischemia) in these regions [12–14].

Once adult-generated neurons are produced in the SVZ, they proceed towards the olfactory bulb along an intricate path of migration, up to 5 mm long in rodents, called the rostral migratory stream (RMS) [15,16]. In contrast to the situation in the developing CNS, the newborn neurons in adults are not guided by radial glia but migrate tangentially in chains through tubular structures formed by specialized astrocytes [17] (Figure 1a). When migrating cells have reached the bulb, they turn radially away from the migratory path to invade the overlaying layers, where they differentiate into two local interneuron subtypes: granule cells and periglomerular neurons [2]. In contrast to most parts of the brain, it is noteworthy that the majority of interneurons in the olfactory bulb are generated postnatally [18].

Although the origin of stem cells and the factors controlling proliferation of neuronal precursors in the mature brain have been extensively studied [19,20], very little was known until recently about how neuronal progenitors migrate and integrate into the appropriate target area to become truly functional neurons. We also knew little concerning the factors regulating the recruitment and survival of newborn neurons in already functioning adult neuronal networks. However, new data from the olfactory bulb have begun to address these issues. Here, after brief description of the origin and fate specification of neuronal precursors, we will review new evidence about the role of neuronal activity in pre-existing circuits in controlling the migration, maturation, integration and survival of newborn neurons. We propose that continuous neurogenesis adjusts functioning of the adult bulbar network to new flows of relevant odor information. We also discuss evidence that neurogenesis acts on information processing in a specific and functional manner, and question whether it prepares the bulb for specific behavioral challenges.

Origin and generation of new neurons

In the adult SVZ, periventricular astrocytes (B cells) have been proposed to act as self-renewing neural stem cells

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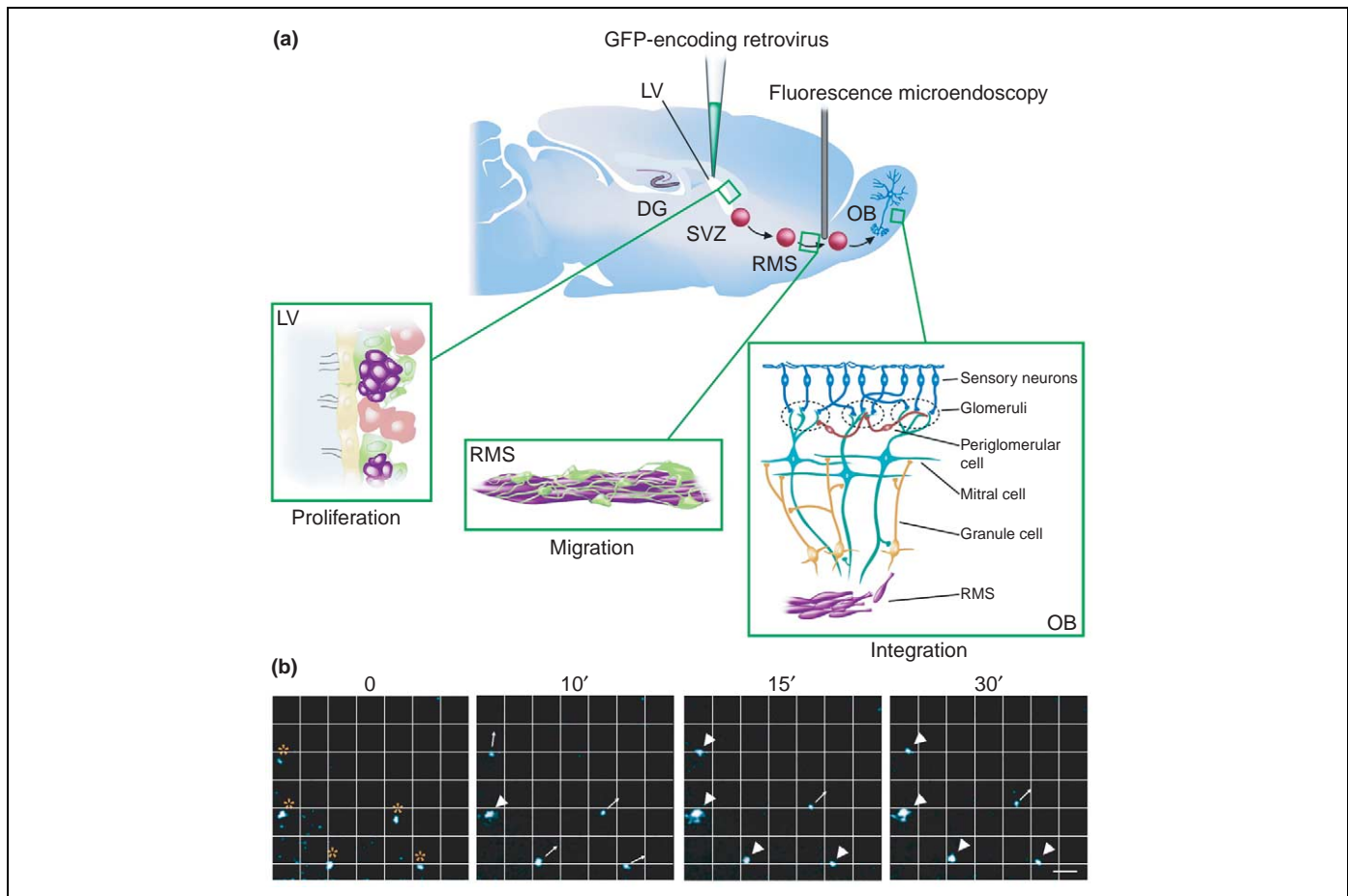


Figure 1. *In vivo* forebrain imaging with fluorescence microendoscopy. (a) Schematic representation of a sagittal view of the brain showing the site of labeling (the subventricular zone, SVZ), the adult-born neuroblasts (red dots) migrating from the SVZ to the olfactory bulb (OB) along the rostral migratory stream (RMS), and the site of imaging with the endoscope probe. (b) GFP-labeled cells migrating along the RMS. All images were acquired at the same recording site and taken at different time points as indicated. Penetration depth: 3 mm. At time 0, stars indicate the initial positions of five newborn neurons. The arrowheads at subsequent times point to non-migrating cells, and the small arrows show moving cells. Scale bar, 60 μ m. Additional abbreviations: DG, dentate gyrus; LV, lateral ventricle.

(NSCs) [19,21,22]. They divide to generate transit amplifying (C) cells, which in turn give rise to neuroblasts (A cells) that migrate in the RMS to their final destination in the olfactory bulb, where they differentiate into functional interneurons [2,19]. Interestingly, it has been suggested that SVZ astrocytes might create an important micro-environmental niche that promotes adult neurogenesis [19,23]. In this scenario, if most SVZ cells are committed to a neuronal lineage and take a rostral migratory route toward the bulb, a subset of SVZ cells remains multipotent. Clonal analyses of progenitors isolated from the postnatal dorsolateral SVZ [24] demonstrate the potential of many of these immature cells to give rise to both neurons and glia *in vitro*.

The molecular mechanisms underlying fate specification of adult NSCs have just started to be elucidated. For instance, it is known that adult NSCs express members of the bone morphogenetic protein (BMP) family that instruct them to adopt a glial fate. In the SVZ, it has recently been shown that the BMP inhibitor noggin is secreted by ependymal cells in the lateral ventricle, and blocks the gliogenic effects of BMPs [25]. However, although noggin blocks gliogenic signals, alone it is insufficient to induce the neuronal differentiation of adult NSCs. Wnt signaling is another pathway that

could instruct NSCs to adopt a neuronal fate [26]. In addition to BMP and Wnt signaling, many alternative pathways, depending on other morphogens, transcription factors, growth factors, carbohydrates and neurotransmitters, are involved in controlling NSC renewal, neuroblast proliferation and neuroblast differentiation [2,19]. A balance of competing signaling pathways might therefore represent a general principle by which the micro-environment interacts with NSCs to control their self-renewal, their proliferation and their differentiation, to ensure that new neural cells are generated in a spatially and temporally coordinated fashion.

How adult-generated neuroblasts reach bulbar circuits Tangential migration

In rodents, newborn cells originating in the SVZ migrate for a few days before reaching the developing [15] or the adult [16] olfactory bulb. Although this tangential migration has been demonstrated in most mammals, the presence of a RMS in humans is debated [27,28]. Despite this potential interspecies difference, recent work has continued to elucidate the molecular factors involved in movement along the rodent RMS. Tangential migration requires the presence of polysialated neural cell adhesion molecule (PSA-NCAM) [29–32] and a chemorepulsion

signal that acts through Slit–Robo signaling [33]. Slit1 and Slit2 expressed in the septum and ventricular zone could repel migrating SVZ neuroblasts [33–35]. Members of the ephrin-B family [36], integrins [37,38], astrocyte-derived factors of unknown identity [39] and receptor tyrosine kinase ErbB4 [40] also seem to direct migration through the RMS. Finally, although the bulb has been proposed to participate in tangential migration [41] as a chemoattractant structure, its involvement in proliferation and guidance remains controversial [42,43].

Recently, time-lapse video imaging has enabled direct analysis of cellular migration. Several previous studies have reported fast migration *in vivo* (e.g. $25 \mu\text{m h}^{-1}$ [16]), in explants (e.g. $100 \mu\text{m h}^{-1}$ [44]) and *ex vivo* (e.g. $50 \mu\text{m h}^{-1}$ [45]). Nevertheless, we are still missing detailed analysis of adult neuroblast migration *in vivo* because the adult neurogenic zone (the SVZ), the migratory pathway (the RMS) and the bulbar integration site are deep within the brain, beyond the range of the conventional fluorescence microscopy ($\sim 500 \mu\text{m}$). To resolve this issue, fibered confocal microendoscopy has recently been used to perform long-lasting recordings several millimeters deep in anesthetized animals, enabling, for the first time, visualization of green-fluorescent protein (GFP)-labeled migrating neuronal precursors in the adult brain of living mammals [46]. From this approach, it is clear that nuclear translocation always occurs in the direction of leading process extension, often leaving a thin trailing process behind the cell body. Migratory velocities (ranging from $40 \mu\text{m h}^{-1}$ to $80 \mu\text{m h}^{-1}$) were not constant but rather appeared saltatory, with periods of inactivity interspersed between migratory spurts (Figure 1b). Finally, and remarkably, cells moved bidirectionally, occasionally migrating back in the direction of the SVZ.

Radial migration

After reaching the core of the bulb, neuroblasts detach from their chains and turn radially to reach the outer layers. It is still a mystery how the neuroblasts stop migrating tangentially and begin radial migration. Nevertheless, new insights have been provided by the recent implication of two extracellular matrix molecules in the processes of radial migration. First reelin, a secreted glycoprotein synthesized in the mitral cell layer, was demonstrated to induce neuroblast detachment from chains [47]. Second, tenascin-R was found in the granule cell layer [48] (Figure 2a,c). Tenascin-R not only induces the detachment of neuroblasts, as reported for reelin, but also triggers the radial migration of neuroblasts. Grafting tenascin-R-transfected cells in regions that are not populated by neuroblasts and that do not express tenascin-R de-routes neuronal precursors from their natural migratory pathway to the foreign areas [48] (Figure 2b).

These observations raise the question of how dispersed radially migrating cells converge onto specific bulbar neurons. What are the relative contributions of innate guidance factors and activity-dependent processes in specifying the connections? The genetic experiments mentioned here have demonstrated essential

determinants in the recruitment of newborn bulbar neurons, but it is also likely that the formation, maintenance and refinement of synaptic connections between newborn neurons and their target cells are under the control of activity-dependent processes.

Maturation of newborn neurons: a substrate for experience-dependent plasticity

Once in the bulb, newborn cells differentiate mainly into neurons that grow dendritic trees. Most of the SVZ-derived cells ($\sim 95\%$) differentiate into GABA-containing granule cells, whereas the rest differentiate into periglomerular cells expressing GABA and/or the dopamine-synthesizing enzyme tyrosine hydroxylase [49–55]. Successive maturation steps during this differentiation have been studied using a GFP-encoding retrovirus injected into the adult SVZ [52]. Five different classes of newborn neurons were established according to their morphology and location in the bulb. Consecutive electrophysiological stages through which the neuroblast passes before becoming a fully mature neuron have also been described [54,55]. As early as six days after their birth, some new neurons reach the bulb and start radial migration to their final positions. Fourteen days after virus injection, they display dendritic spines, suggesting they might already receive synaptic inputs. Indeed, patch-clamp recordings detect spontaneous synaptic currents soon after migration is complete. However, at this stage of differentiation newborn neurons remain unable to fire action potentials [55]. Surprisingly, in contrast to events during developmental neurogenesis, spiking activity is the last characteristic acquired by maturing neurons [5]. Thus, the maturation of synaptic inputs in the adult bulb does not recapitulate events during embryogenesis, perhaps in part because of the high neuronal activity already occurring in mature circuitry. The lack of spiking ability could protect adult circuits from uncontrolled neurotransmitter release that might otherwise adversely alter network activity. Future studies should be aimed at determining whether this late spiking phenomenon also occurs in other adult-generated neurons.

It also remains to be examined whether newborn bulbar interneurons make functional synapses with their downstream target neurons and release appropriate neurotransmitters. This would unequivocally demonstrate their integration into adult circuitry. Interestingly, the multiple stages in the maturation of newborn neurons might serve as a substrate for structural and physiological plasticity, as recently shown in the hippocampus [56]. They could provide the bulb with a large repository of plastic cells to enable better responses to changes in the environment. For instance, the late onset of NMDA receptor expression, and the maturation sequence of glutamatergic synapses reported in adult-generated granule [55] and periglomerular [54] cells, could indicate unique developmental sequences adapted for experience-dependent maturation of adult neural circuits. We also do not yet know whether adult-generated bulbar interneurons differ from older cells. Functionally, are there two distinct types of granule cell – a larger population generated during development and early postnatal life,

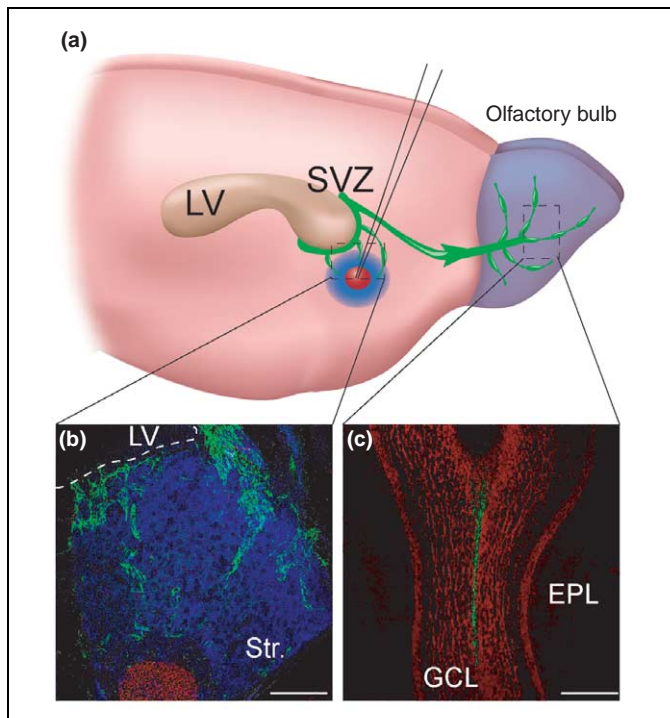


Figure 2. The extracellular matrix molecule, tenascin-R, re-directs migrating neuroblasts. **(a)** Schematic representation of mouse brain with tenascin-R-rich areas in blue and migrating neuroblasts in green. Note that ectopic expression of tenascin-R in the striatum re-routes migrating neuroblasts. **(b)** Tenascin-R-secreting grafted cells pre-labeled with a fluorescent dye (PKH26; red) were placed into the striatum (Str.) neighboring the SVZ. Neuroblasts migrating towards the tenascin-R-immunopositive area (blue) are visualized using PSA-NCAM staining (green). **(c)** Coronal section of the olfactory bulb, showing the pattern of tenascin-R expression (red). Migrating neuroblasts are labeled with PSA-NCAM antibodies (green). Note the absence of tenascin-R from the RMS of the olfactory bulb (i.e. core of the olfactory bulb). Scale bar in (b), 100 μ m; scale bar in (c), 400 μ m. Abbreviations: GCL, granule cell layer; EPL, external plexiform layer.

and a smaller one generated during adulthood? Answering this question will clearly influence our interpretation of the functional role of adult neurogenesis. Finally, it should be noted that only about half of the newly generated bulbar interneurons survive more than several days after reaching their mature state [52,53]. We do not yet know whether this survival time is sufficient for these cells to have a significant role in bulbar function. Understanding the role of neuronal replacement in the adult brain will require recognition of the fact that half of newborn neurons are transient and are replaced through a process that has yet to be discovered.

New granule cells not only might possess unique functions themselves but also might introduce new functions to the pre-existing neuronal circuitry. In line with this, sensory deprivation drastically decreases the number, the dendritic length and the spine density of newborn granule cells (Figure 3). These effects are coupled with a reduced frequency of miniature inhibitory postsynaptic responses impinging onto principal (mitral) cells. However, at the same time, a compensatory increase in the excitability of newborn granule cells preserves the overall inhibitory drive to the principal cells. Bulbar network functions thus remain grossly unaltered [57]. These results show that the level of neuronal activity in the host circuit regulates not only the development and maturation of newborn cells, but also their

electrophysiological properties. Thus, a cohort of newborn granule cells brings to the olfactory bulb circuit unique adaptive properties that enable experience-induced alterations, and also uphold the overall function of the neuronal network in response to the ever-changing olfactory world.

Neuronal activity also regulates the recruitment of newborn neurons, even before they start their maturation. As already discussed here, the transition from tangential to radial migration requires the presence of tenascin-R (Figure 2). Interestingly, expression of tenascin-R depends on the degree of bulbar activity, because odor deprivation dramatically decreased both mRNA and protein levels of bulb tenascin-R. This was associated with impaired ascending migration of neuroblasts into different bulbar layers [48]. If activity-dependent recruitment of neurons is related to odor stimulation, the question is then whether alteration in the number of newborn interneurons might relate to changes in odor information processing and olfactory behavioral function. This hypothesis has been tested in several studies aimed at challenging adult neurogenesis. In all cases, a clear relationship was established between the quantity of newborn neurons and olfactory performance [58–60] (reviewed in Ref. [4]). These results have led to proposals for a specific role for newborn interneurons in coding of olfactory information. Because >90% of SVZ-generated interneurons are GABAergic [49], a critical level of GABA-receptor-mediated inhibition might be crucial for correct olfactory processing, at least at the first relay of the system [61,62]. Additionally, because bulbar neurogenesis is sensitive to the degree of sensory input activity, we propose that the production of newborn neurons might adjust neuronal network activity to optimize processing of sensory information in the olfactory bulb. It could therefore represent an adaptive response necessary for the fine-tuning of olfactory abilities.

That experience shapes the maturation of newborn neurons in the adult olfactory bulb suggests that this process might share common features with the early development of sensory systems. In the developing brain, it is well established that activity-dependent processes are crucial for the correct wiring of neuronal circuits [63]. It follows that some of the important issues concerning activity-dependent neuronal development might also need to be addressed in the field of adult neurogenesis. For example, to what extent do activity-dependent versus activity-independent processes govern the maturation of adult-generated bulbar neurons? Within activity-dependent mechanisms, what are the respective contributions of spontaneous and experience-evoked activity [63]? And, finally, is the role of activity in adult neurogenesis permissive or instructive [64]? Odor stimuli might simply allow changes in a circuit or they might actively direct establishment and reorganization of neural connections.

Born to survive or to die?

A subset of newly-generated interneurons is integrated into bulbar circuits while the remaining newborn cells are eliminated. Quantitative studies have demonstrated that nearly half of newborn interneurons are eliminated

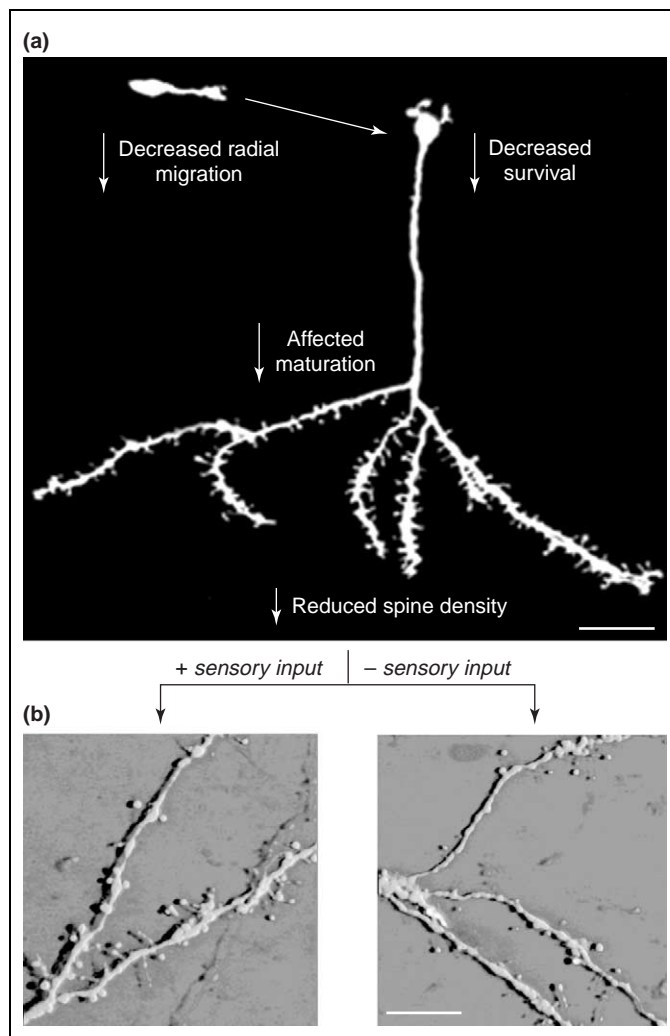


Figure 3. Role of sensory activity in shaping adult neurogenesis. **(a)** Two-photon imaging of GFP-labeled newborn granule cells, illustrating the effects of reduced sensory activity. Using a sensory deprivation paradigm, it has been demonstrated that odor-induced activity is required for normal radial migration of neuroblasts, as well as for their survival and maturation in the olfactory bulb [57]. **(b)** High-magnification images of the dendritic trees of newborn granule cells in control (left) and odor-deprived (right) bulbs. Note reduced spine density for newborn granule cells in the odor-deprived bulb. Scale bar in (a), 20 μ m; scale bar in (b), 10 μ m.

between two and eight weeks after their birth [52,53]. This elimination mechanism is more prominent in the bulb than in the RMS and SVZ [52,61] and it might maintain a constant bulbar cell number by continuous cell turnover. Using a retroviral vector to label SVZ precursors, it was shown that most dying cells were mature, harboring dendritic arborizations, and probably receiving synaptic connections [52]. Indeed, several studies have shown that the survival of newborn granule cells depends on sensory input [52,59,65,66], suggesting a role for these connections in determining cell survival. However, once a cell is fated to survive, it does so for a long period: the 50% of newly generated neurons that survive the initial period of cell elimination survive for at least 19 more months [53].

Additional information is required before we can know how adult bulbar neurogenesis is regulated by physiological and pharmacological factors. A growing effort has already provided a list of factors that affect neurogenesis within the adult dentate gyrus [67]. Neurotransmitters,

hormonal status, growth factors and injuries are known to influence the rate of proliferation and/or survival of neuroblasts in the hippocampus [68]. At present, the regulation of adult bulbar neurogenesis by such factors is only starting to receive such attention. Several neurotransmitters might have a substantial role in controlling bulbar neurogenesis because massive centrifugal projections, mediating actions of ACh, 5-hydroxytryptamine and catecholamines, converge on the bulb. To test this 'top-down' hypothesis, a mouse model lacking the predominant population of brain nicotinic receptors has been recently analyzed. The animals showed increased survival of newborn granule cells, but not of newborn periglomerular neurons [69]. Such a role for cholinergic inputs in adult bulbar neurogenesis has received further support from studies employing immunotoxic lesions: removing cholinergic neurons in the basal forebrain leads to decreased adult neurogenesis [70]. Together, this strongly indicates that the survival of newborn neurons depends not only on the degree of sensory inputs but also on top-down, context-dependent processes.

Concluding remarks

The representation of odors in the brain is dynamic and highly complex, and might therefore require a unique mechanism of plasticity. The production, migration and maturation of bulbar interneurons are likely to form part of this adaptive mechanism. It takes a few weeks for a new SVZ neuron to become part of the existing circuit in the olfactory bulb – implying that neuronal production during adulthood might enable only slow adaptive responses – and during this time it undergoes a series of unique maturational stages. The presence of young neurons at different stages of differentiation in the adult bulb could allow the preparation of all necessary morphological and physiological structures from which new cells and connections will be selected according to particular patterns of neuronal activity. Such a mechanism could act in parallel with experience-induced changes in synaptic weights to give the adult bulb a wide range of adaptive properties.

It is also worth noting that bulbar neurogenesis occurs in a neuronal network in which sensory inputs are continuously replaced. Mature olfactory sensory neurons have only a limited life span – ~90 days in rodents – and this is tightly regulated by environmental factors [7]. It is thus tempting to propose that bulbar neurogenesis represents a mechanism by which processing of sensory information in the brain could be adjusted in response to ever-changing sensory inputs. Are these two levels of neurogenesis tightly correlated, and does the generation of new olfactory sensory neurons influence changes in bulbar circuits? These questions remain yet unanswered.

A fuller understanding of the role of adult neurogenesis in neuronal plasticity depends not only on gathering more and better data showing the dynamics, spatial extent and longevity of experience-dependent structural changes in adult circuits. It also depends: (i) on a fuller description of the integrative properties of individual newborn neurons; (ii) on better models of the representational redundancies that exist among the neurons within neuronal networks

(e.g. do newborn and pre-existing neurons share similar response properties?); and (iii) on a more complete description of the guidance and selection mechanisms that act on the new neurons. Identification of the physical change(s) encoding long-term information remains a central issue in neuroscience. In approaching this, and other questions related to the physical substrate for long-term adaptation in the adult brain, an interdisciplinary approach combining molecular, anatomical, physiological, theoretical and behavioral methods is the most likely to succeed.

Finally, the remarkable developmental potential and the capacity for continuous self-renewal of NSCs make them a promising donor source for cell-replacement strategies for brain repair. This is particularly exciting because utilizing adult-generated NSCs would overcome ethical and scientific problems concerning the use of embryonic stem cells in similar brain repair approaches. The prerequisites for the development of successful brain repair strategies are: (i) in-depth understanding of the molecular mechanisms of proliferation, migration, cell fate and survival of NSCs, and of how changes in gene expression levels and the molecular environment of precursors can affect their destiny; (ii) targeted manipulation of NSCs to express survival-promoting and/or differentiation-promoting genes to generate cells with enhanced survival and/or differentiation properties; and (iii) knowledge of the host tissue conditions, including molecular factors and neuronal activity, that are required for the survival and function of newly-generated neurons. These important questions remain unanswered, but the recent work discussed in this review might one day lead, however indirectly, to the development of successful therapeutic strategies.

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