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The Role of Notch Signaling in Adult Neurogenesis

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Abstract Neurogenesis occurs throughout adulthood in the mammalian brain. Newly born neurons are incorporated into the functional networks of both the olfactory bulb and the hippocampal dentate gyrus, and there is growing evidence that adult neurogenesis is important for various brain functions. Continuous neurogenesis is achieved by the coordinated proliferation and differentiation of adult neural stem cells. In this review, we discuss the recent findings concerning the roles of Notch signaling in adult neural stem cells.

Keywords Notch signaling · Rbpj · Hes1 · Hes5 · Adult neurogenesis · Neural stem cells

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Introduction

Neural stem cells (NSCs) are responsible for generating the complex repertoire of diverse neural cell types in the mature brain [1]. NSCs of the lateral ventricular wall undergo changes in morphology and produce different progeny as the brain development proceeds. NSCs begin as neuroepithelial cells, become radial glial (RG) cells, and then finally have many astrocytic characteristics in the adult brain.

At an early developmental stage, neuroepithelial cells initially undergo symmetric cell division: each neuroepithelial cell divides into two neuroepithelial cells [2–4]. By repeating symmetric cell division, neuroepithelial cells proliferate extensively. Once the progenitor pool has been established and the developing brain epithelium thickens, neuroepithelial cells elongate and convert into RG cells. These cells undergo asymmetric cell division: each RG cell divides into two distinct cell types, one RG cell and one immature neuron or an intermediate progenitor cell [5–7]. Immature neurons migrate outside of the ventricular zone (VZ) into the outer layers, where they become mature neurons, and intermediate progenitor cells migrate into the subventricular zone (SVZ), proliferate further, and give rise to more neurons. By repeating asymmetric cell division, RG cells sequentially give rise to distinct types of neurons or intermediate progenitor cells [8–10]. After producing neurons, RG cells finally differentiate into glial cells, but some of them are maintained as NSCs in the adult brain [1].

In the adult brain, NSCs exist principally in two regions: the SVZ of the lateral ventricle (LV) and the subgranular zone (SGZ) of the hippocampal dentate gyrus (DG) [11–16] where neurogenesis occurs continuously. The SVZ is a layer extending along the lateral wall of the LV and contains many dividing cells. A large number of neurons born in the

SVZ migrate into the olfactory bulb, form a rostral migratory stream, and differentiate into local interneurons (granule cells and periglomerular cells). A subset of glial fibrillary acidic protein (GFAP)-positive cells (type-B cells) function as NSCs in the adult SVZ. Type B cells divide slowly and give rise to rapidly proliferating "transit-amplifying cells" (type-C cells), which then generate migrating neuroblasts (type-A cells) after several cell divisions. Type-B cells have the ultrastructural features of astrocytes and express GFAP, a canonical astrocyte marker protein [17, 18] (Fig. 1a). Thus, NSCs give rise to neurons and glial cells during development and in the adult brain.

In the SGZ of the adult hippocampal DG, Type-1 NSCs have astrocytic features and are marked by GFAP [19–21]. Although these cells have proliferative capacity, they cycle much slower than the type-2 progenitor cells that follow. While Nestin, Sox2, and brain lipid-binding protein are also expressed in type-1 cells, the expression persists into the type-2 cell stages [22]. NeuroD and Doublecortin (Dcx) appear in type-2b, the later stage of type-2 cells, and persist into postmitotic but immature granule cell precursors [23]. Finally, these cells mature into NeuN/calbindin/Prox1-positive granule cell neurons in the DG (Fig. 1b).

The ability of NSCs to continuously generate new neurons over time depends on the coordinated balance of stem cell maintenance and differentiation. Incomplete maintenance and premature neuronal differentiation will deplete the NSC pool and, consequently, reduce the supply of new neurons. Conversely, increased stem cell maintenance at the expense of proper neuronal differentiation will impair the ability of NSCs to generate a sufficient number of new neurons for maintaining the olfactory bulb neural circuit and the hippocampal function [15, 16]. Recent evidence indicates that a Notch-dependent pathway underlies the central molecular mechanism regulating the tight balance between NSC maintenance and differentiation in the adult brain.

Notch Signaling Pathway

In the developing nervous system, the protein products of proneural genes, such as the basic helix-loop-helix (bHLH) transcriptional activators Mash1 (also called Ascl1) and Neurogenins (Ngn1/2), induce the neuronal differentiation programs [24, 25]. These gene products also activate the expression of Notch receptor ligands such as the transmembrane protein Delta-like1 (Dll1) and Jagged1 (Jag1), which, in turn, activate Notch, another transmembrane protein, in neighboring cells [26]. In addition, the ubiquitin ligase Mind bomb is essential for Dll1-induced activation of Notch signaling [27]. Upon activation of Notch, the Notch intracellular domain (NICD) is released from the

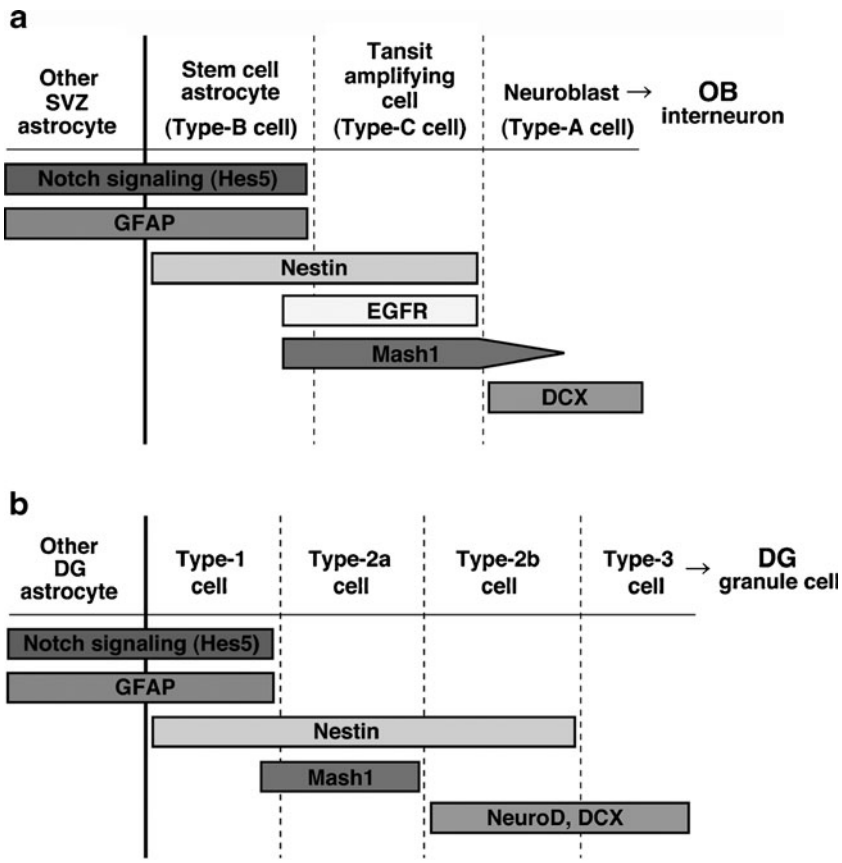

Fig. 1 Current view of the sequence of neurogenesis from NSCs in the adult brain. **a** Generation of new interneurons in the olfactory bulb (*OB*) from NSCs in the subventricular zone of the lateral ventricle (SVZ/LV). **b** Generation of new granular neurons in the dentate gyrus (*DG*) of the hippocampus from NSCs in the subgranular zone (SGZ). Notch signaling is highly activated in type-B cells of the SVZ/LV and type-1 cells of the SGZ/DG

transmembrane portion and transferred to the nucleus, where it forms a complex with the DNA-binding protein RBPj. The NICD-RBPj complex is a transcriptional activator and induces the expression of bHLH transcriptional repressors, such as *Hes1* and *Hes5*. Hes1 and Hes5 then repress the expression of proneural genes and Dll1, thereby inhibiting neuronal differentiation and maintenance of NSCs [28]. Thus, via this lateral inhibition, a differentiating neuron prevents neighboring NSCs from differentiating, thereby promoting asymmetric division into one NSC and one differentiating daughter neuron. It has been shown that a loss of function for Notch receptors [29], Dll1 [30], Mind bomb [27], RBPj [31], and Hes transcriptional factors [32, 33] resulted in the premature neuronal differentiation and rapid depletion of NSCs, indicating that Notch signaling plays an essential role in the maintenance of embryonic NSCs.

Functional Analysis of Notch-Pathway Genes in Adult NSCs

The roles of Notch signaling in NSCs were studied mainly during embryonic developmental periods, but there is growing evidence that Notch signaling also plays essential roles in maintenance and differentiation of adult NSCs [34]. Notch pathway components are expressed in the germinal zone of the early postnatal and adult brain [35–37], supporting the possibility that Notch signaling might regulate postnatal NSCs. Precise Notch signaling activity in adult NSCs has been recently determined using transgenic mouse reporters for Notch signaling. Transgenic mice containing either the *Hes5* promoter or RBPj-binding sites revealed that Notch signaling is highly activated in type-B cells of the SVZ/LV [31] and type-1 cells of the SGZ/DG [38, 39]. Under normal conditions, Notch-activated NSCs are largely quiescent, and only restricted subsets seem to be proliferating and generating new neurons through transit-amplifying cells.

Conditional inactivation of RBPj revealed a definitive role for canonical Notch signaling in the long-term maintenance of NSCs in the adult SVZ/LV [31]. Using the tamoxifen-inducible Cre transgenic driver mouse strain (Nes-CreER^{T2}), the authors found that deleting RBPj in adult NSCs resulted in a transient burst in proliferation at the SVZ, increased neurogenesis, and then depletion of NSCs. This phenotype was caused by premature conversion of slowly dividing NSCs (type-B cells) into transit-amplifying cells. Because transit-amplifying cells have limited self-renewal capacity, after the transient increased proliferation, they all eventually differentiated into neurons. The same study also showed that Notch signaling is required for regeneration in the AraC-treated brain. Following deletion of the RBPj gene, the SVZ could not recover from treatment with the antimitotic drug AraC, indicating that slowly dividing or quiescent NSCs were depleted without Notch signaling. This study demonstrated that RBPj-mediated canonical Notch signaling is an essential component of the regulatory network in adult NSCs, controlling the tight balance between NSC quiescence and active neurogenesis [31].

It was recently reported that inactivation of Notch1 or RBPj in NSCs of the postnatal SGZ/DG also results in a neurogenesis phenotype, that is highly similar to the SVZ/LV neurogenesis. Conditional inactivation of RBPj in hippocampal NSCs led to increased neuronal differentiation of NSCs at an early time point, depletion of the Sox2-positive NSC pool, and suppression of hippocampal neurogenesis [39]. The loss of Notch1 in adult NSCs also resulted in loss of the radial glia-like stem cell (type-1 cell) population [40], and the loss of Notch1 in early postnatal hippocampus promoted the cell cycle exit of NSCs [41]. Moreover, sustained expression of NICD strongly enhanced the proliferation of NSCs in the postnatal hippocampus [41]. However, inactivation of RBPj and of Notch1 did not produce completely the same phenotypes. Lack of Notch1 leads to dramatic decrease of NSCs without a transient burst in proliferation [40]. It is most likely that the phenotypic differences are due to the fact that Notch signaling was inhibited at different levels. In addition to Notch1, other Notch receptors are expressed in NSCs of the SGZ/DG [39, 41]. Signaling of other Notch receptors mediated by RBPj in the Notch1 conditional knockout mice might contribute to the phenotypic differences. RBPj-independent Notch signaling regulates the number of NSCs through JAK-STAT signaling and Hes3 [42], raising another possibility that phenotypic differences could also be derived from different activity of non-canonical Notch signaling in NSCs (see above for discussion of Ehm et al. [39]). While more work will be needed to fully understand Notch signaling in adult neurogenesis, especially in the downstream mechanism, these studies provide strong evidence that Notch signaling plays essential roles in maintenance and differentiation of adult NSCs. Taken together, these studies also indicate that both the SVZ/LV and the SGZ/DG share the same principal mechanism of NSC maintenance.

Carlen et al. reported that Notch signaling plays a role in maintaining the quiescent state of ependymal cells in the adult mouse brain [43]. In addition, in the adult zebrafish brain, where NSCs seem to transit back and forth between the quiescent and dividing state, it was shown that Notch activity levels control the balance between quiescence and recruitment of NSCs [44]. Notch induction drives NSCs into quiescence, whereas blocking Notch massively re-initiates NSC division and subsequent differentiation toward post-mitotic neurons [44].

Currently, little is known about how Notch signaling activity is regulated in the adult NSC niches. In the SVZ/LV, Jag1 is expressed and required for NSC maintenance in the early postnatal brain [45]. Another Notch ligand, Dll1, is also expressed in the SVZ/LV [36], but it has not been clearly determined which cell type is the main Notch ligand-presenting cell in the adult neurogenic niches. It has been shown that NSCs are closely associated with blood vessels, and there is an emerging understanding of the importance of the vascular system within the NSC niches [46–50]. Two Notch ligands, Jag1 and Dll4, are prominently expressed in the vasculature [51], and it is possible that these vasculature-derived Notch-ligands might regulate Notch signaling activity in NSCs.

A recent study revealed that interaction between NSCs and transit-amplifying cells is important for maintaining a homeostatic balance between the sizes of these cell populations [52]. In transgenic mice in which the EGF receptor (EGFR) was over-expressed in transit-amplifying (type-C) cells and NG2+ cells, the number of transit-amplifying cells was increased in the SVZ/LV. Interestingly, this transgenic mouse strain had a reduced number of NSC (type-B) cells. It was also shown that enhanced EGFR signaling in transit-amplifying cells "non-cell-autonomously" suppresses Notch signaling in NSCs by regulating the level of Numb expression. Although the exact mechanism by which EGFR signaling in transit-amplifying cells modulates Notch signaling in NSCs is not clear, this study revealed that neurogenic niche cells can modulate the behavior of NSCs by regulating Notch signaling.

In the SGZ/DG, Jag1 is specifically expressed in transit-amplifying cells [41, 53]. Conditional inactivation of Prox1 led to the loss of Jag1-expressing transit-amplifying cells and resulted in attenuated Notch signaling in NSCs in the SGZ [53].

The roles of Notch signaling in maturating newly born neurons have been reported. Recent study showed that Notch signaling regulates the dendritic morphology and complexity of newly born neurons in the postnatal and adult DG [40, 41]. Inhibition of Notch1 in newly born neurons led to simpler dendritic trees, whereas in NICD-over-expressed mice, a greater amount of dendritic complexity in newly born neurons was observed. Another study raised a possibility that physical exercise increases survival and cell cycle exit of immature newly born neurons via Notch signaling in the DG [54].

Closing Remarks

Newly born neurons are incorporated into the functional networks of both the olfactory bulb and the hippocampal dentate gyrus, and there is growing evidence that adult neurogenesis intensely contributes to neural circuit plasticity [16, 55, 56], and various brain functions, including learning and memory [21, 57], and that impaired neurogenesis may contribute to various neuropsychiatric diseases [58].

As Notch signaling is essential for NSC maintenance in the adult brain and for prolonged neurogenesis throughout life, these observations raise the possibility that dysregulation of Notch signaling might contribute to stem cell loss, attenuated neurogenesis, and impaired olfactory bulb and hippocampal function during aging. The further analysis of Notch signaling function will add to our understanding of the basic mechanisms of adult neurogenesis, which may lead to the development of novel therapies for functional recovery after disease, trauma, or pathological aging.

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