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Regulation of neurogenesis in the adult and aging brain

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Neural stem cells (NSCs) represent a remarkable developmental unit, necessary for the proper functioning of neurogenesis, by retaining their plasticity to self-renew and give rise to progeny throughout life in specific regions of the adult brain. Although NSCs were thought to merely represent a stem cell type in the brain, recent advances have demonstrated the incredible complexity of NSC identity and functions. Ranging between quiescence, activation and intermediary subtypes, NSCs choose their fate through their developmental inheritance, regional positioning within the niche, as well as dynamic transcriptional and metabolic states. The plasticity of their developmental program is reflected in the tremendous changes they undergo upon external environmental cues and extrinsic manipulations, and harnessing these potentials can open new avenues to fight against brain injury, neurodegenerative and age-related diseases.

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Introduction

The process of adult mammalian neurogenesis, the birth of new neurons in the brain, was discovered over 50 years ago [1], and during these last decades enormous progress has been made in deciphering the mechanistic aspects of adult neurogenesis, regulation of intrinsic NSC machinery, as well as systemic regulation of the niche in animal models; yet this field of research still remains fruitful. Identification of pathways involved in adult neurogenesis and exploration of the mechanistic regulation of NSCs can increase our understanding of this process and give us further insight into the relationship of adult neurogenesis and neurological and psychiatric disorders, as well as brain injury. For this, open questions about the biology of NSCs, and the way their activity could be regulated, need to be addressed. Recently, in addition to the study of the overall process of neurogenesis, much effort has focused on deciphering the intrinsic regulation of stem cells in the brain, both in the hippocampus as well as the subventricular zone (SVZ) niche. In this review we discuss recent advances and new insights into *in vivo* NSC heterogeneity, the balance between quiescence and activation, the role of cell metabolism, as well as transcriptomic and metabolomic analyses that have pushed the field forward into the exploration of the multiple facets of the adult NSC as a cell type that can dynamically transit between different states upon external cues.

Human adult neurogenesis

The main reason behind the continuing interest in understanding the process of mammalian adult neurogenesis is the notion that similar processes might be involved in the human brain. Whether neurogenesis in humans exists has been investigated using several and distinct approaches that brought compelling evidence about the presence of adult hippocampal neurogenesis in human brains. Because of the difficulty in accessing human adult tissue and measuring the incorporation of thymidine analogs to label proliferating cells in humans *in vivo*, several studies were based on the analysis of postmortem human brains, which had been labeled for different purposes. For example, the remarkable study by Eriksson *et al.* provided strong evidence for the birth of newborn neurons and incorporation of BrdU in cycling progenitor cells in brains of cancer patients [2], whereas Spalding *et al.* took advantage of the concentration of nuclear bomb test-derived ^{14}C in genomic DNA to demonstrate the existence and to calculate the turnover rate of newborn neurons throughout adult life in humans [3]. Interestingly, two very recent -but opposing-publications brought back the debate concerning the existence of human adult neurogenesis. Sorrells *et al.*, using postmortem and fresh tissue, reported that there was no evidence of neurogenesis in humans after adolescence whatsoever [4•], while the study by Boldrini *et al.* demonstrated the exact opposite by showing that adult neurogenesis persists during life in humans, albeit with a small decrease with aging, while the volume of the dentate gyrus remains the same [5•]. Further exploration of this complex question is necessary in order to conclude on the processes underlying the timeline and the mechanisms of neurogenesis in humans.

Neural stem cell heterogeneity: not all NSCs are born equal

In the adult mammalian brain, NSCs reside mainly in two areas of the adult brain, the SVZ and the dentate gyrus of

the hippocampus [6,7], and they represent a pool of self-renewing cells that can differentiate into neurons upon different stimuli [8]. Despite the preconceived notion that adult NSCs are merely stem cells residing in the brain, increasing evidence suggests that NSCs constitute an extremely diverse population of cells. NSCs exhibit different characteristics and functions depending on their proliferative state, as well as their regional identity. In the SVZ, NSC have restricted positional information depending on the specific location where they reside, which will determine the neuronal type into which they will terminally differentiate and mature in the olfactory bulb [9]. Depending on the respective microdomain in the SVZ niche, patterned by specific transcription factors such as *Nkx6.2*, *Zic* [10], *Gsx2* [11], *Nkx2.1* [12] or *Pax6* [13,14], NSCs generate several different subtypes of interneurons that regulate the olfactory bulb [15], revealing the complexity and inter-regulation between cell types in the neurogenic niche [16,17]. In addition, adult NSCs and their embryonic counterparts generate functionally distinct subpopulations of dopaminergic neurons [18], while exposure to reward-associated odors specifically increases the activity of adult-born neurons but not preexisting neurons [19]. The remarkable plasticity of NSCs is also demonstrated by the capacity of SVZ NSCs to convert to reactive astrocytes and contribute to the astrocyte scar following brain injury, and these SVZ-derived reactive astrocytes can also be converted to neurons by Mash1 [20]. Interestingly, it was recently reported that a subset of CD133+ ependymal cells throughout the central nervous system (CNS) can be reactivated into neuronal differentiation upon specific cues, such as VEGF and bFGF, suggesting that these cells are dormant ependymal NSCs [21], lending more credence to the stem cell identity of ependymal cells [16,22–24].

The above findings show that regional and developmental identity plays a pivotal role for NSC lineage progression.

The dynamic state of a neural stem cell

Although adult stem cells in brain niches are broadly referred to as NSCs, we can distinguish different subtypes of NSCs, mainly based on their state of quiescence or activation. NSCs in the adult SVZ niche originate from a subpopulation of embryonic radial glia cells, which become specified during development and maintain their quiescent state until reactivation in adulthood [25]. Specifically, most adult SVZ NSCs originate from a distinct population of slowly dividing neural progenitors in the ganglionic eminence of the embryonic brain [26]. Single-cell transcriptomic analyses confirmed that adult NSCs share a core transcriptional phenotype with their radial glial progenitors and that the transition to the adult NSC state occurs during late neurogenesis [27]. Interestingly, the number of the embryonic stem cells that will become adult NSCs is regulated by the type of cell division during embryonic development [28••]. Modification of the embryonic program, such as deletion of VCAM1, a molecule necessary for the maintenance of adult quiescence [29], results in a reduction of the adult quiescent NSC (qNSC) pool, showing that maintenance of NSC properties is a continuous developmental process, operating in a temporal-dependent and region-dependent mechanism [30]. Chronic live imaging of the hippocampus showed that NSCs divide within a limited time window and that their division patterns are associated with each NSC's cell division history [31]. Lineage tracing techniques in the SVZ showed that a small subset of adult dividing NSCs go through symmetric self-renewing divisions, whereas the majority, around 75%, undergoes lineage progression to generate neural progenitors, which rapidly differentiate into neuroblasts at the expense of NSCs [32•]. While some activated NSCs (aNSCs) rapidly cease their neurogenic activity, other NSCs are re-activated from their quiescent state to take over lineage progression and thus safeguard the continuation of neurogenesis [33]. Simultaneously, a small fraction of NSCs can revert back to a transient quiescent state through degradation of proactivation factor Ascl1 in order to maintain life-long hippocampal neurogenesis and avoid stem cell pool exhaustion [34]. However, the majority of NSCs, once activated they divide until they become exhausted, which could explain NSC depletion with aging. The advance of single-cell transcriptomics has provided extremely useful information about the different states of a NSC, from quiescence to activation, suggesting a high degree of transcriptional dynamics throughout these states. Purification of acutely isolated SVZ NSCs revealed four types: dormant NSCs, qNSCs, aNSCs and progenitor cells (Figure 1a). NSCs present a heterogeneous molecular profile and multiple states of activation in the adult SVZ niche [35]. Most NSCs are ciliated, quiescent, express GFAP and CD133, and they give rise to cycling, activated EGFR + NSCs, which in turn differentiate into progenitors and finally neuroblasts [36,37]. Activated NSCs retain the ability to from spheres *in vitro*, unlike qNSCs [38]. However, additional NSC subpopulations in intermediate states have recently been discovered. Pseudotemporal ordering of single-cell transcriptomic analyses revealed three subpopulations of aNSCs (early, mid and late activation states), which exhibit variations in cell cycle timing and progression, together with differential expression of specific genes, placing these subpopulations in a continuum between quiescence and activation [39•]. In these cells, activation is associated with protein synthesis and differentiation priming, while dormancy is coupled to high glycolytic and lipid metabolism [35]. Interestingly, single-cell RNA-Seq in the dentate gyrus revealed that hippocampal NSCs also exhibit a molecular heterogeneity and take part in a progressive continuum of transcriptional dynamics from quiescence to neuronal differentiation [40,41•].

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