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RESEARCH HIGHLIGHT

Adult Neural Stem Cells: Constant Extension from Embryonic Ancestors

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Adult neural stem cells (aNSCs) primarily exist in two regions: the subventricular zone (SVZ) of the lateral ventricle (LV) and the subgranular zone (SGZ) in the hippocampal dentate gyrus (DG) [1]. It has been revealed that aNSCs in the SVZ (called type B cells) originate from embryonic NSCs mainly before embryonic day 15.5 (E15.5), and are set aside for postnatal neurogenesis after diverging [2, 3]. Whether this is the case with aNSCs in the hippocampus remains to be resolved [4]. A prominent new study by Hongjun Song and colleagues showed that dentate NSCs from embryonic to adult stages share a common early origin, suggesting that neurogenesis in the hippocampus is a continuous process throughout development [5].

Dentate aNSCs continuously generate functionally integrated granule cells, which play critical roles in learning and memory, as well as mood regulation [1]. Study of this process will help us better understand the functions of the hippocampus and repair its dysregulation in brain disorders such as Alzheimer's disease and depression [6]. Previous studies indicated that dentate neuroepithelial cells give rise to dentate precursors that migrate and establish the entire structure of the dentate gyrus [7]. A recent study using *Gli-CreER* mice suggested that some dentate aNSCs originate from ventral hippocampal precursors at E17.5 [8]. The developmental trajectory of dentate precursors needs in-depth investigation. Hongjun Song and colleagues set out to define the *bona fide* origin and establishment of dentate aNSCs by using the *Hopx-CreER*^{T2} mouse line. Depending on the dose and injection time of tamoxifen, individual or groups of NSCs at different stages and their progeny were labeled. The clonal lineage tracing results explicitly showed that individual early dentate progenitors continuously generate region-specified neurons during development and convert to quiescent aNSCs mainly in the first two postnatal weeks.

In contrast to progenitors lining the wall of the LV (Fig. 1A) [9], dentate precursors retain the ability to produce the same neuron type until adulthood (Fig. 1B). Single-cell RNA sequencing data demonstrated that immature dentate neurons from E16.5 to postnatal day 132 have conserved transcriptomic characteristics [10]. The molecular coherence of dentate NSCs at different stages remains unknown. To determine the consistency of dentate precursors during development, the authors analyzed the transcriptomic and epigenetic properties of dentate progenitors at different stages using RNA sequencing and ATAC-Seq. Compared with the data-set of the mature granule neuron group, dentate precursors at each stage share many transcriptional and chromatin landscapes. The similar transcriptomic and epigenetic profiles corroborate the above findings that dentate aNSCs evolve from early precursors and extend neurogenesis.

Compared to the rules governing the development of type B cells in the SVZ, the authors suggest a unique "continuous" model: dentate neural epithelial cells drive neurogenesis from its onset to adulthood and the specification of precursors at different stages is constant (Fig. 1). The removal of dentate NSC boundaries highlights the importance of a developmental perspective. The application and manipulation of aNSCs require careful consideration of the legacy of their ancestors. Through quantitative comparative analyses, the authors found that the transition

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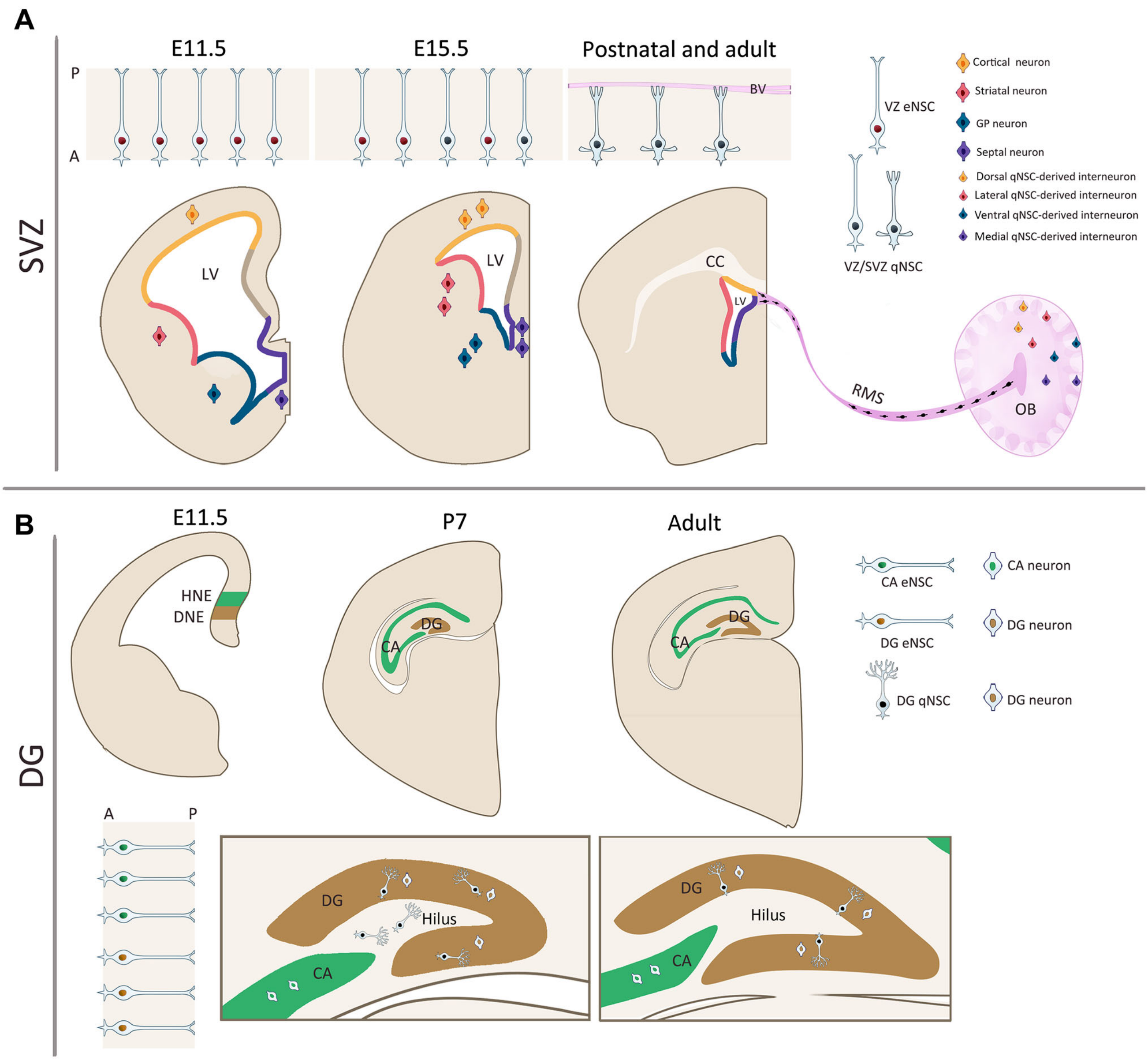

Fig. 1 Different models for VZ/SVZ NSCs and DG NSCs. **A** "Set-aside" model for VZ/SVZ NSCs (colored lines around the LV). From the onset of neurogenesis (embryonic day 11.5, E11.5), VZ eNSCs lining the dorsal (yellow line), dorsal lateral (red line), ventral lateral (blue line), and ventral medial (purple line) walls of the LV produce cortical (yellow cell), striatal (red cell), GP (blue cell), and septal (yellow cell) neurons. NSCs diverge during the mid-neurogenesis stage. At E15.5, some VZ NSCs (red nuclei) continue to generate local neuronal progeny, while others (black nuclei) remain dormant until postnatal and adult stages. Upon reactivation, SVZ qNSCs in different regions give rise to specific sets of OB interneurons migrating along the RMS. **B** "Continuous" model for DG NSCs. During embryonic development, eNSCs in the HNE (green) and DNE (brown) regions generate CA (green) and DG (brown) neurons. In the early postnatal stage, dentate NSCs gradually transition to qNSCs (black nuclei) that disperse in the DG and hilus. All the qNSCs relocate to the SGZ in adulthood in rodents. Dentate neurogenesis continues without interruption and lasts for 1-2 years. NSC, neural stem cell; eNSC, embryonic NSC; qNSC, quiescent NSC; P, pial surface; A, apical surface; BV, blood vessel; LV, lateral ventricle; VZ, ventricular zone; SVZ, subventricular zone; GP, globus pallidus; CC, corpus callosum; RMS, rostral migration stream; OB, olfactory bulb; HNE, hippocampal neuroepithelium; DNE, dentate neuroepithelium; CA, cornu ammonis; DG, dentate gyrus; P7, postnatal day 7; SGZ, subgranular zone.

of dentate NSCs involves the gradual and continuous regulation of gene expression, meeting the various needs of different stages. Efforts are needed to address the key intrinsic determinants and external signals that control the transition and maintenance of precursors. How is the intrinsic machinery coupled to niche signals to influence the development of precursors? The two properties of gradual shifting and constant specification of dentate aNSCs raise questions about their physiological significance. It is noteworthy that clonal tracing data still do not exclude the possible diversity and multiplicity of sources of aNSCs. Another interesting question to consider is the general and differential regulatory mechanisms in different regions of adult neurogenesis. The interpretation of these issues will be fruitful.

The self-renewal feature of dentate aNSCs in rodents has led to the belief that the recruitment of new neurons also occurs in the adult hippocampus of primates, including humans [11]. Recently, the debate over whether dentate neurogenesis exists in adult humans has been reignited [12]. Breakthroughs in new tracking and imaging technologies will facilitate the settlement of these disputes [13]. In rodents, type B cells give rise to interneurons by depletion, while dentate aNSCs produce granule neurons by self-renewal [3, 5]. In humans, NSCs in the SVZ are maintained longer than dentate progenitor cells [12]. The underlying mechanisms and functions in these species differences await to be uncovered. The solution of these problems will set the stage for the treatment of brain diseases. In conclusion, this study reveals the origin and developmental dynamics of dentate aNSCs, providing novel insights into a general principle of adult neurogenesis and the plastic nature of the adult brain [5].

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