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Review

Neurogenesis in the aging brain

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ABSTRACT

Adult neurogenesis is the process of producing new neurons from neural stem cells (NSCs) for integration into the brain circuitry. Neurogenesis occurs throughout life in the ventricular-subventricular zone (V-SVZ) of the lateral ventricle and the subgranular zone (SGZ) of the hippocampal dentate gyrus. However, during aging, NSCs and their progenitors exhibit reduced proliferation and neuron production, which is thought to contribute to age-related cognitive impairment and reduced plasticity that is necessary for some types of brain repair. In this review, we describe NSCs and their niches during tissue homeostasis and how they undergo age-associated remodeling and dysfunction. We also discuss some of the functional ramifications in the brain from NSC aging. Finally, we discuss some recent insights from interventions in NSC aging that could eventually translate into therapies for healthy brain aging.

Contents

1. Adult neural stem cells

1.1. Introduction

Neural stem cells (NSCs) are self-renewing cells that reside primarily in two regions: the SGZ of the dentate gyrus, and the V-SVZ, which lines the lateral ventricles. NSCs provide new neurons that are thought to contribute to brain plasticity, learning, memory, and repair. NSCs proliferate throughout life in both brain regions. However, as early as mid-age, NSC function declines, resulting in fewer proliferating cells and reduced neuronal output. In this review, we will describe the characteristics of V-SVZ and SGZ stem cells, their respective niches, and define how aging changes the stem cell niche and function of NSCs. We will also discuss strategies for interventions to curtail age-associated NSC decline.

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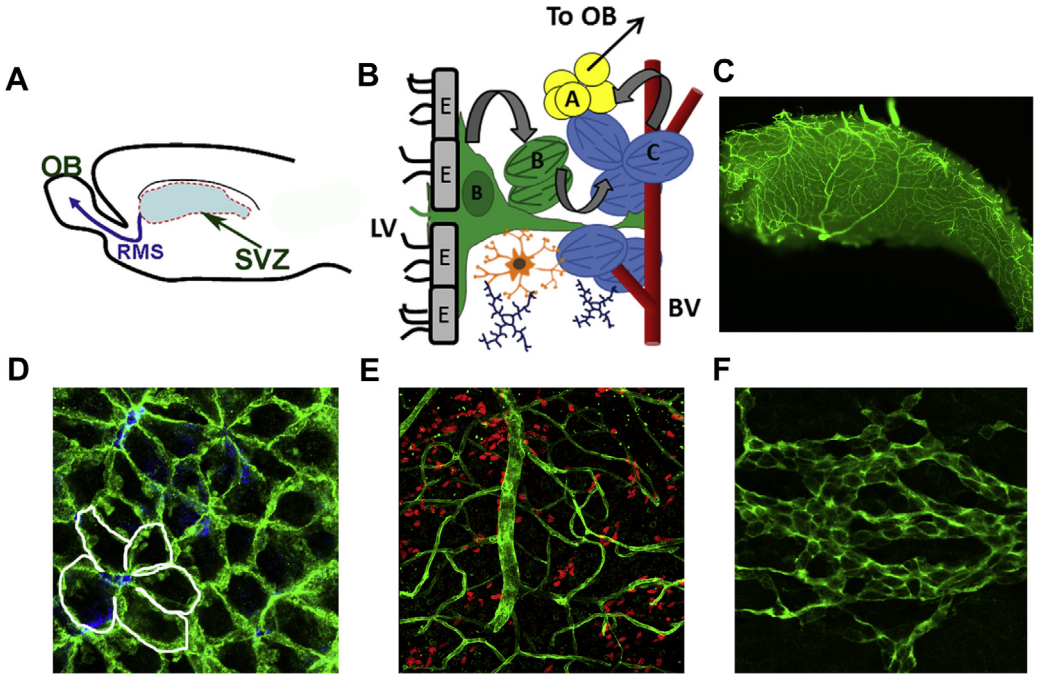

Fig. 1. Organization of the V-SVZ niche. A) Cartoon of the V-SVZ location in a sagittal view of the mouse brain. B) Diagram of the V-SVZ niche. Quiescent type B NSCs (green) send an apical process through the ependymal layer and a basal process to make contact with the blood vessels of the vascular plexus. Activated type B NSCs divide to give rise to type C transit amplifying cells (blue). TACs rapidly divide adjacent to blood vessel before differentiating to type C neuroblasts (yellow). Neuroblasts migrate out of the V-SVZ to the olfactory bulb. Microglia and astrocytes are also depicted as blue and orange cells, respectively. C) Low magnification (0.5×) of the V-SVZ dissected out of the mouse brain as a wholemount immunostained for laminin to show the vascular plexus (green) (scale bar = 500 μm). D) Germinal Pinwheels are made up of ependymal cell junctions visualized with immunohistochemistry for β-catenin (green) and type B NSC apical processes immunostained for GFAP (blue) (magnification = 63×; scale bar = 10 μm). E) Proliferating cells labeled with EdU (red) are positioned adjacent to blood vessels immunostained for laminin (green) (magnification = 25×; scale bar = 50 μm). F) Doublecortin immunolabeled neuroblasts (green) exhibit chain migration as they migrate out to the rostral migratory stream and olfactory bulb (magnification = 40×; scale bar = 20 μm). LV = lateral ventricle E = ependymal cell BV = blood vessel OB = olfactory bulb.

1.2. V-SVZ stem cell characterization and microenvironment

V-SVZ NSCs are located adjacent to the ependymal cells that line the lateral ventricle (Fig. 1). These putative NSCs are astrocyte-like quiescent cells that express glial fibrillary acidic protein (GFAP) and CD133 and are called type B cells. Type B cells become activated, upregulate the mitogen receptor epidermal growth factor receptor (EGFR) and the pan stem cell marker nestin, and undergo division [1,2]. The balance between NSC quiescence and activation is critical as loss of NSC quiescence results in depletion of the stem cell pool and insufficient neurogenesis. Activated type B NSCs divide to give rise to a transit amplifying cell (TAC), also known as a type C cell. TACs rapidly divide to expand the progenitor pool but have a limited capacity for self-renewal. TACs eventually give rise to neuroblasts, which form chains and migrate out of the V-SVZ into the rostral migratory stream until they ultimately reach the olfactory bulb (Fig. 1). Once these neuroblasts reach the olfactory bulb, a limited number will integrate into the existing circuitry and mature into GABAergic and dopaminergic interneurons [3,4].

NSCs and progenitors are regulated by their niche, which is a specialized microenvironment that supports NSC and progenitor function. If NSCs are transplanted outside of the neurogenic niche, they lose their ability to self-renew and give rise to neurons [5]. This loss of self-renewal potential is thought to occur due to the absence of niche signals. This idea is supported by studies that show transplantation of NSCs back into a neurogenic niche results in integration of NSCs and their progeny within the niche and promotes neurogenesis [1,5,6]. Structurally, the V-SVZ niche is highly organized, with NSCs and their progeny sandwiched between the ciliated ependymal cells and a vast vascular plexus that separates the V-SVZ from the underlying striatum (Fig. 1). Quiescent and activated Type B NSCs have a radial morphology with an apical process that projects into the ependymal cell layer and a basal process that extends toward the striatum, making contact with the vascular plexus (Fig. 1B & C). The NSC's apical process has a single non-motile cilium that makes direct contact with cerebral spinal fluid. These apical processes are bundled between the ependymal cells in flower-like structures termed germinal pinwheels [7–9] (Fig. 1D). The apical process of quiescent NSCs is capped by vascular cell adhesion molecule (VCAM1), which anchors NSCs in the niche and regulates quiescence by maintaining the correct balance of reactive oxygen species for downstream signaling [10]. Quiescence has also been shown to be maintained by Neurotrophin-Factor 3 (NT3), which is secreted by the endothelial cells in the nearby choroid plexus and V-SVZ vascular plexus. NT3 is taken up by NSCs which express the NT-3 receptor TrkC, resulting in synthesis of nitric oxide, which inhibits NSC proliferation [11]. Reductions in either VCAM1 or NT3 signaling results in an initial increase in NSC proliferation, followed by exhaustion of the stem cell pool and loss of neurogenesis [10,11]. This supports the notion that the CSF/ependymal compartment supports NSC quiescence [12]. In contrast, proliferating Type B NSCs and TACs have been shown to preferentially divide near the vasculature [8,13] (Fig. 1E). This is mediated by endothelial cell secreted factors such as the chemokine stromal cell-derived factor 1 (SDF1) [6] and the neurotrophic protein pigment epithelium-derived factor (PEDF), which induce activation of NSCs and TACs to proliferate [14]. Located between these two major compartments are also neuroblasts, which proliferate within the V-SVZ before undergoing chain migration out of the V-SVZ to the olfactory bulb (Fig. 1F).