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Review

New neurons in adult brain: distribution, molecular mechanisms and therapies

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ABSTRACT

"Are new neurons added in the adult mammalian brain?" "Do neural stem cells activate following CNS diseases?" "How can we modulate their activation to promote recovery?" Recent findings in the field provide novel insights for addressing these questions from a new perspective. In this review, we will summarize the current knowledge about adult neurogenesis and neural stem cell niches in healthy and pathological conditions. We will first overview the milestones that have led to the discovery of the classical ventricular and hippocampal neural stem cell niches. In adult brain, new neurons originate from proliferating neural precursors located in the subventricular zone of the lateral ventricles and in the subgranular zone of the hippocampus. However, recent findings suggest that new neuronal cells can be added to the adult brain by direct differentiation (*e.g.,* without cell proliferation) from either quiescent neural precursors or non-neuronal cells undergoing conversion or reprogramming to neuronal fate. Accordingly, in this review we will also address critical aspects of the newly described mechanisms of quiescence and direct conversion as well as the more canonical activation of the neurogenic niches and neuroblast reservoirs in pathological conditions. Finally, we will outline the critical elements involved in neural progenitor proliferation, neuroblast migration and differentiation and discuss their potential as targets for the development of novel therapeutic drugs for neurodegenerative diseases.

Contents

Abbreviations: AD, Alzheimer's disease; AEBSF, 4-(2-aminoethyl benzenesulfonyl fluoride); Ara-C, cytosine-D-arabinofuranoside; BDNF, brain-derived neurotrophic factor; BIO, 6-bromoindirubin 3-oxine; BMP, bone morphogenic protein; BP, basal progenitor; BrdU, bromodeoxyuridine; CNS, central nervous system; CNTF, ciliary neurotrophic factor; CREB, cAMP response element binding; DCX, doublecortin; DG, dentate gyrus; DHEA, dehydroespiandrosterone; ECM, extracellular matrix; EGF, epithelial growth factor; FAO, fatty acid oxidation; FASN, fatty acid synthase; FGF, fibroblast growth factor; GDNF, glial-cell derived neurotrophic factor; GFAP, glial fibrillary acidic protein; GRP17, G protein-coupled receptor 17; GSK3β, glycogen synthase kinase 3β; HD, Huntington's disease; HGF, hepatocyte growth factor; IGF, insulin growth factor; IP, intermediate progenitor; iPSCs, induced pluripotent stem cells; KO, knock-out; LTP, long-term potentiation; MAPK, mitogen activated protein kinase; MDS, Miller-Dieker syndrome; Mfn2, mitofusin 2; NGF, nerve growth factor; NK, natural killer cells; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; NP, neural precursor; NSC, neural stem cell; OB, olfactory bulb; OPC, oligodendrocytes progenitor cell; ORGC, outer radial glia cells; PAR1, protease activated receptor 1; PD, Parkinson's disease; PDE, phosphodiesterase; PDGFR β, platelet-derived growth factor receptor β; PI3-K, Phosphatidylinositol 3-kinase; RG, Radial glia; RSM, Rostral migratory stream; SCI, Spinal cord injury; SDF1, Stromal-derived factor 1; SGZ, Subgranular zone; SHH, Sonic hedgehog; SVZ, Subventricular zone; TGFβ1, Transforming growth factor- β1; TBI, Traumatic brain injury; TubIII, Tubulin III; VEGF, Vascular endothelial growth factor.

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1. Introduction

Mammalian neurogenesis is defined as the process that leads to the generation of functional neurons from neural stem cells (NSCs). This process occurs in four different steps that are: 1) cell proliferation by asymmetric division; 2) cell fate specification; 3) cell migration; 4) cell differentiation, maturation and synaptic integration in the circuitry [1–3]. Throughout this review, we will refer to NSCs as the self-renewal, multipotent cells able to differentiate through different neural lineages (*i.e.* glial and neuronal). Radial glia (RG) cells represent the population of NSCs with radial morphology and glial features present in the developing brain and persisting in subventricular zone (SVZ) and subgranular zone (SGZ) of postnatal and adult brains [4]; progenitors are proliferating cells

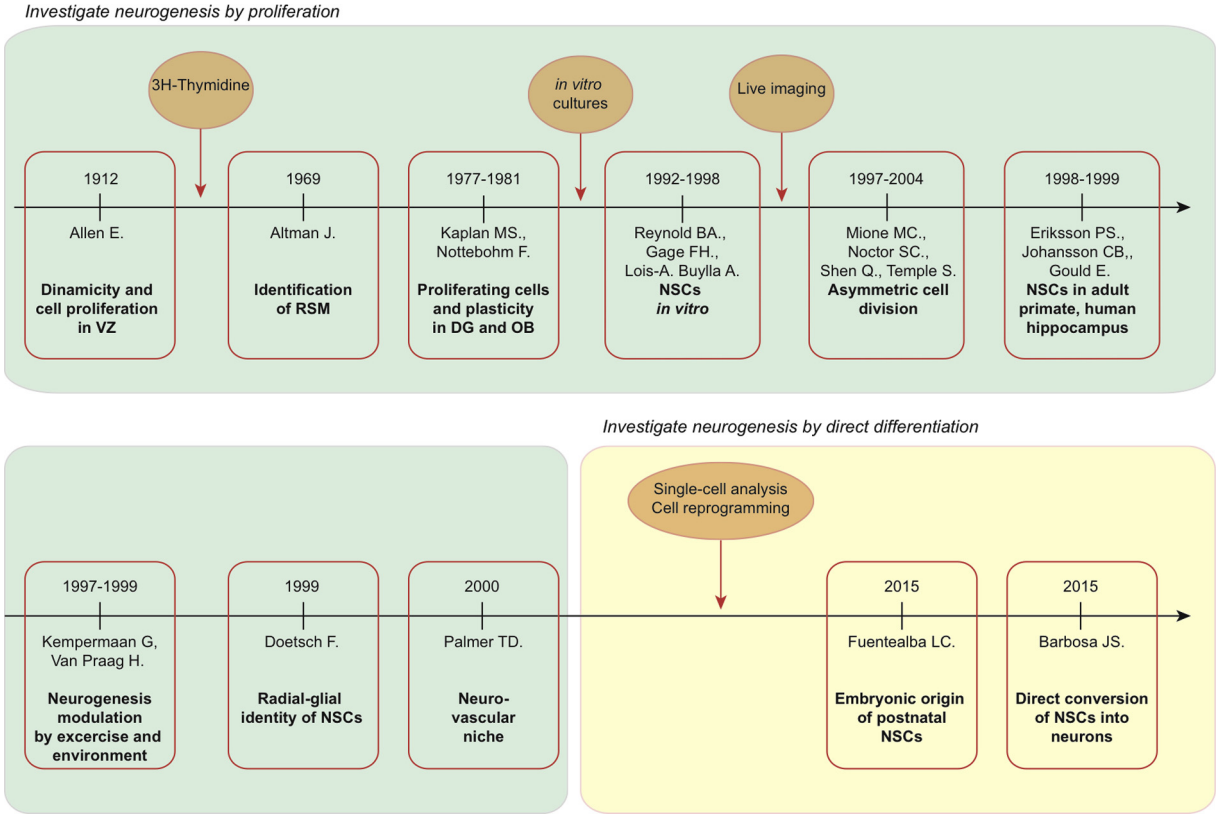

Fig. 1. Graphical representation of the timeline of the most important studies and discoveries on adult neurogenesis, starting from the observations of Allen in 1912 (Allen, 1912; [17]), to the work of Palmer in 2000 (Palmer et al., 2000; [49]). In this period, neurogenesis was investigated with cell proliferation assays (green box). It was only in 2015, with the works of Fuentealba (Fuentealba et al., 2015; [10]) and Barbosa (Barbosa et al., 2015; [12]), that new neurogenic processes, not dependent on cell proliferation, have been described (yellow box).