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Energy metabolism in adult neural stem cell fate

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ABSTRACT

The adult mammalian brain contains a population of neural stem cells that can give rise to neurons, astrocytes, and oligodendrocytes and are thought to be involved in certain forms of memory, behavior, and brain injury repair. Neural stem cell properties, such as self-renewal and multipotency, are modulated by both cell-intrinsic and cell-extrinsic factors. Emerging evidence suggests that energy metabolism is an important regulator of neural stem cell function. Molecules and signaling pathways that sense and influence energy metabolism, including insulin/insulin-like growth factor I (IGF-1)-FoxO and insulin/IGF-1-mTOR signaling, AMP-activated protein kinase (AMPK), SIRT1, and hypoxia-inducible factors, are now implicated in neural stem cell biology. Furthermore, these signaling modules are likely to cooperate with other pathways involved in stem cell maintenance and differentiation. This review summarizes the current understanding of how cellular and systemic energy metabolism regulate neural stem cell fate. The known consequences of dietary restriction, exercise, aging, and pathologies with deregulated energy metabolism for neural stem cells and their differentiated progeny will also be discussed. A better understanding of how neural stem cells are influenced by changes in energy availability will help unravel the complex nature of neural stem cell biology in both the normal and diseased state.

Contents

Abbreviations: ACC, adenylate cyclase complex; AICAR, aminoimidazole carboxamide ribonucleotide; AMPK, AMP-activated protein kinase; Aspm, abnormal spindle-like microcephaly-associated; BDNF, brain-derived neurotrophic factor; bFGF, basic fibroblast growth factor; bHLH, basic helix-loop-helix; BMP, bone morphogenetic protein; DG, dentate gyrus; DR, dietary restriction; FoxO, Forkhead box O; HDAC, histone deacetylase; HIF, hypoxia-inducible factor; HSC, hematopoietic stem cell; IGF-1, insulin-like growth factor 1; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; mTORC1, mTOR complex 1; mTORC2, mTOR complex 2; NAD+, nicotinamide adenine dinucleotide; N-CoR, nuclear receptor co-repressor; NSC, neural stem cell; OB, olfactory bulb; OPC, oligodendrocyte progenitor cell; PI3K, phosphoinositide 3-kinase; PIP_3, phosphatidylinositol (3,4,5)-triphosphate; PTEN, phosphatase and tensin homolog; Rb, retinoblastoma protein; ROS, reactive oxidative species; SGZ, subgranular zone; Shh, Sonic hedgehog; Sirt, Sirtuin; SVZ, subventricular zone; UCP2, mitochondrial uncoupling protein 2; VEGF, vascular endothelial growth factor.

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1. Introduction

The past fifty years of exploration into adult mammalian neural stem cell (NSC) biology have greatly expanded our understanding of the basic characteristics of adult NSCs, the numerous environmental conditions and life stages that alter their properties, and the functional relevance of NSCs in the normal and diseased brain. An emerging concept is that adult NSCs are a dynamic population of cells able to sense and respond to changes in energy homeostasis occurring locally in the brain and systemically in the mammalian organism. In this review, we will first provide an overview of adult NSC properties and then describe the current understanding of how energy metabolism influences adult NSC function, with a particular focus on energy-sensing molecules and related signaling pathways that include the insulin/IGF-1-FoxO and insulin/IGF-1-mTOR signaling pathways, AMP-activated protein kinase (AMPK), Sirtuins, and hypoxia-inducible factors (HIFs). We will also outline how fluctuations in global organismal energy state affect adult NSC function. Understanding the connection between energy and adult NSC fate should yield important discoveries relevant for brain health during normal aging and metabolic pathologies, including diabetes, obesity, stroke, and neurodegenerative disease.

2. Adult neural stem cell properties

2.1. Adult neural stem cells

The adult mammalian brain contains pools of NSCs, which can self-renew, *i.e.* produce at least one stem cell daughter upon division, and are multipotent, *i.e.* produce all three cell types of the brain: neurons, astrocytes, and oligodendrocytes (Fig. 1A). NSCs are thought to be relatively quiescent (Doetsch et al., 2002; Kippin et al., 2005; Morshead et al., 1994), entering the cell cycle to produce more rapidly dividing neural progenitors that undergo limited rounds of proliferation and are more committed to specific neural lineages (Bull and Bartlett, 2005). Neural progenitors ultimately yield differentiated progeny, such as new neurons (neurogenesis), that can then integrate into functional circuits in the adult brain.

The current view on the origin of adult NSCs is that they are the descendents of postnatal ventricular zone radial glial cells that are thought to arise from embryonic neuroepithelial cells (Merkle and Alvarez-Buylla, 2006; Merkle et al., 2004). There are far fewer NSCs in the adult brain compared to the developing brain, which likely explains why the brain was long assumed to be solely a post-mitotic tissue. The two principal populations of adult NSCs are located in the subventricular zone (SVZ) lining the lateral ventricles (Morshead et al., 1994) and in the subgranular zone (SGZ) of the dentate gyrus (DG) of the hippocampus (Altman and Das, 1965; Palmer et al., 1997) (Fig. 1B). While NSCs and neurogenesis have now been identified in other regions of the adult mammalian brain, the SVZ and DG are the two niches containing the densest collection of NSCs consistently able to give rise to new neurons (Gould, 2007; Gritti et al., 2002; Pagano et al., 2000). Importantly, humans also exhibit neurogenesis in the SVZ and DG in adulthood (Eriksson et al., 1998; Quinones-Hinojosa et al., 2006) and multipotent NSCs can be cultured from adult human SVZ and DG (Johansson et al., 1999; Kukekov et al., 1999).

SVZ neural progenitors give rise to neuronal precursors (neuroblasts), which migrate along the rostral migratory stream (Doetsch and Alvarez-Buylla, 1996; Lois et al., 1996) toward the olfactory bulb (OB) and differentiate into OB interneurons (Carlen et al., 2002; Lledo et al., 2008; Lois and Alvarez-Buylla, 1994; Luskin, 1993). In contrast, neuroblasts from the SGZ of the DG migrate a much shorter distance to integrate into the DG granule cell layer upon differentiation into neurons (Altman and Das, 1965; Palmer et al., 1997; van Praag et al., 2002). NSCs also have the capacity to produce astrocytes and oligodendrocytes both *in vitro* (Gritti et al., 1996; Palmer et al., 1997) and *in vivo* (Jessberger et al., 2008; Menn et al., 2006; Suh et al., 2007). New oligodendrocytes generated from SVZ NSCs can migrate to areas of dense axonal tracts, such as the corpus collosum and striatum, to generate new myelin for the adult brain (Gonzalez-Perez et al., 2009; Menn et al., 2006).

2.2. Functional importance of neural stem cells in the adult mammalian brain

Since the discovery of adult rat hippocampal neurogenesis by Altman and Das (1965) and the isolation of self-renewing and