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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

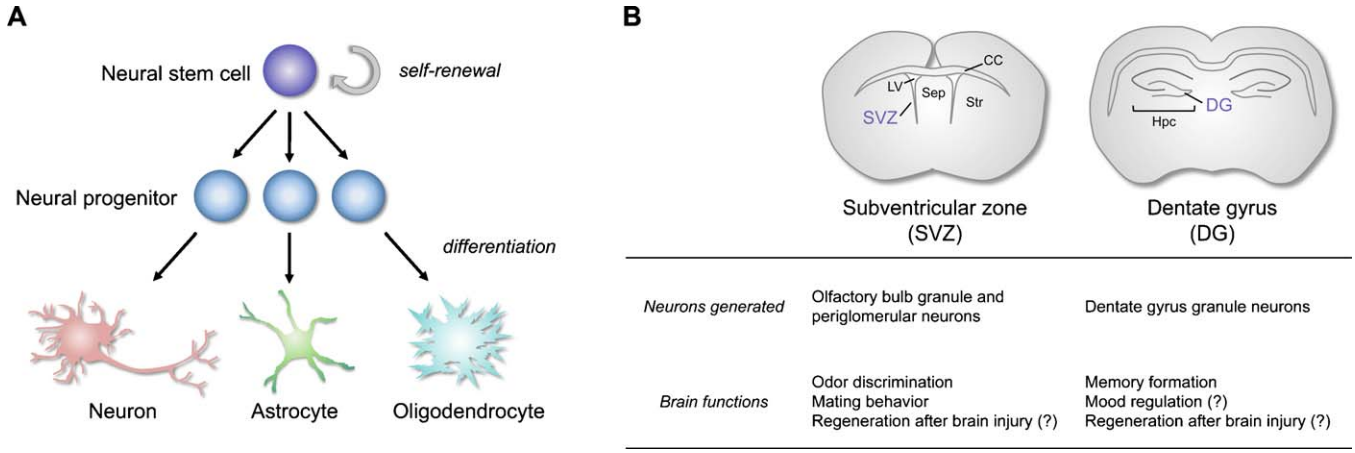

Fig. 1. Adult neural stem cell (NSC) properties. (A) NSCs self-renew and are multipotent. They give rise to neural progenitor cells, which in turn produce differentiated cell types of the brain: neurons, astrocytes, and oligodendrocytes. (B) Adult NSCs are primarily localized in the subventricular zone (SVZ) lining the lateral ventricles and in the subgranular zone of the dentate gyrus (DG) in the hippocampus indicated on images of mouse brain coronal sections. The SVZ is located at a more anterior position than the DG. Function of SVZ and DG NSCs are described in the table. CC, corpus collosum; DG, dentate gyrus; Hpc, hippocampus; LV, lateral ventricle; Sep, septum; Str, striatum; SVZ, subventricular zone.

multipotent NSCs from the adult brain (Gritti et al., 1996; Palmer et al., 1997), questions regarding the functional relevance of neurogenesis and adult NSCs have abounded particularly because of the adult brain's lack of conspicuous regenerative capacity. Loss-of-function experiments (*e.g.* irradiation and genetic ablation) have revealed causative relationships between NSC differentiation into neural progeny and specific brain tasks. The functions of NSCs depend on their location in the brain (SVZ or DG) (Fig. 1B). Specific forms of hippocampal memory formation require intact neurogenesis from adult NSCs in the DG (Clelland et al., 2009; Deng et al., 2009; Farioli-Vecchioli et al., 2008; Imayoshi et al., 2008; Kitamura et al., 2009; Saxe et al., 2006; Shors et al., 2002; C.L. Zhang et al., 2008). While multiple studies support a role for NSC-derived neurogenesis in the DG in memory formation, there are conflicting findings regarding which types of memory are affected. For example, ablation of neurogenesis from adult NSC by either lineage-specific expression of diptheria toxin A (DTA) (Imayoshi et al., 2008), adult neural progenitor-specific death by a thymidine kinase/gancliclovir strategy (Deng et al., 2009), or adult deletion of the *Tlx* gene that is required for NSC proliferation and maintenance (C.L. Zhang et al., 2008) impairs spatial learning whereas in studies using irradiation or an antimotitic compound to eliminate neurogenesis, spatial learning is not impacted (Saxe et al., 2006; Shors et al., 2002). The sources of these differences are not clear, but it is possible that discrepancies between independent findings are the result of the methods use to eliminate neurogenesis and/or NSCs as well as the type of behavioral paradigms employed. In contrast to DG neurogenesis, new olfactory bulb neurons generated from SVZ NSCs are thought to be important for odor discrimination and mating behavior (Breton-Provencher et al., 2009; Gheusi et al., 2000; Mak et al., 2007; Mouret et al., 2009) although one study found odor discrimination is not affected by eliminating adult neurogenesis (Imayoshi et al., 2008).

In addition to functioning in the healthy adult brain, NSCs are also thought to participate in brain repair following injury. Neurogenesis from adult NSCs can act as source of neuronal replacement in damaged cortical regions (Liu et al., 1998; Magavi et al., 2000) and when transplanted into the brain can lead to behavioral improvements in rodent models of neurodegenerative diseases (Chintawar et al., 2009; Vazey et al., 2006). Finally, impaired adult neurogenesis in the DG may contribute to depression or the inability to respond to antidepressants (Encinas et al., 2006; Santarelli et al., 2003) although conflicting findings suggest that further investigation of the significance of neurogenesis for mood regulation is needed (Holick et al., 2008; Zhao et al., 2008).

Much less is known about the role of new oligodendrocytes and astrocytes generated from adult NSCs. While oligodendrocyte production from adult NSCs occurs at relatively low basal levels (Gonzalez-Perez et al., 2009; Jessberger et al., 2008; Menn et al., 2006), their generation from SVZ NSCs is greatly increased following demyelinating injuries (Menn et al., 2006). The importance of astrocytes derived from adult NSCs has not been specifically assessed, but it is likely that like postnatally established parenchymal astrocytes, they contribute to brain function in many ways, including recycling neurotransmitters and metabolites, enabling structural support and blood–brain barrier maintenance, and promoting injured tissue repair (Wang and Bordey, 2008).

2.3. Energy metabolism differences between neural stem cells and differentiated neural cells

The dynamic population of NSCs has the ability to modify the architecture and function of the adult brain, which raises the important question of whether and how adult NSCs are affected by energy metabolism. An emerging idea in the stem cell field is that stem cells possess metabolic characteristics that differ from differentiated cells (Lonergan et al., 2006; McGraw and Mittal, 2010; Nesti et al., 2007; Noble et al., 2005). In the brain, unique features of neurons (*e.g.* electrical excitability and neurotransmission), oligodendrocytes (*e.g.* high lipid levels), and astrocytes (*e.g.* recycling of neurotransmitters and metabolites) also suggest that metabolic requirements of differentiated cells may drastically differ from that of self-renewing, multipotent NSCs. Indeed, gene expression analyses have revealed that from development through adulthood, the transition from a NSC/neural progenitor cell to a differentiated neuron, astrocyte, or oligodendrocyte is associated with numerous transcriptional changes, including at genes associated with metabolism and energy sensing (Bonnert et al., 2006; Geschwind et al., 2001; Gurok et al., 2004; Ivanova et al., 2002; Karsten et al., 2003; Ramalho-Santos et al., 2002). For example, embryonic NSCs cultured from mouse ventricular zone differentially upregulate multiple energy metabolism-associated genes, such as the *Insulin-like growth factor binding protein 3 (Igfbp3)*, *Enolase I*, and *Cytochrome c oxidase subunit VIIa 3*, three genes which are specifically upregulated in NSCs when compared to hematopoietic and embryonic stem cells (Ivanova et al., 2002).

Cultured postnatal NSCs also show significantly higher expression of numerous metabolic genes, such as *Acetyl-coenzyme A synthetase 1*, *Enolase I*, and *Pyruvate dehydrogenase*, compared to differentiating neural cells (Geschwind et al., 2001; Karsten et al., 2003) although other metabolic genes are upregulated during differentiation (*e.g. Glucose-6-phosphate dehydrogenase*) (Gurok et al., 2004). Finally, adult SVZ NSCs have greater expression of the metabolism-associated genes *Hypoxia-inducible factor Hif1α*, *Acetyl-coenzyme A transporter*, and *Igfbp3* compared to differentiated cells of the lateral ventricle (Bonnert et al., 2006; Ramalho-Santos et al., 2002). Thus, specific aspects of energy metabolism may distinguish NSCs from their differentiated counterparts. As these studies examined transcriptional profiles of cultured NSCs, a critical question that remains to be addressed is whether there are significant metabolic differences between quiescent NSCs and the cycling population of NSC/neural progenitor cells.

Given the distinctive expression of certain metabolism-associated genes in NSCs and the fact that providing sufficient amounts of energy to the brain is a central concern for the organism, tight control of energy-dependent processes are likely to exist in NSCs. With the goal of obtaining a greater understanding of factors that control the balance between NSC self-renewal and differentiation in the adult brain, this review attempts to bring together existing evidence that support the notion that adult NSC fate is regulated by cellular and organismal energy metabolism and to raise fundamental questions that still remain in this field. We will draw on studies of NSCs from the developing brain in order to extrapolate mechanisms that are potentially applicable to the adult population, though our particular interest is in understanding how cellular and systemic energy metabolism influence adult NSCs, a pool of cells susceptible to energy alterations over a lifespan.

3. Energy-sensing molecular mechanisms in neural stem cell fate

3.1. The insulin/IGF-1 signaling pathway

3.1.1. Overview of insulin/IGF-1 signaling

Central to the body's ability to coordinate energy intake and expenditure is the insulin/IGF-1 signaling pathway. In response to glucose or energy excess, insulin is released by the β cells of the pancreas and promotes glucose storage in liver and muscle tissues and fat storage in adipose tissue. A related hormone, insulin-like growth factor-1 (IGF-1), is produced by the liver in response to growth hormone, whose production by the pituitary gland is regulated by many factors, including nutrition and exercise. Both insulin and IGF-1 have high affinities for their cognate tyrosine kinase receptors, but there is some low-affinity cross-reactivity (De Meyts and Whittaker, 2002). Insulin/IGF-1 binding leads to a cascade of intracellular events beginning with auto-phosphorylation of the receptor tyrosine kinase, followed by subsequent activation of signaling molecules and pathways, including the PI3K/Akt-mTOR, PI3K/Akt-FoxO, and Ras/MAPK pathways (Fig. 2). Despite their overlapping receptor binding affinities, insulin and IGF-1 can elicit different biological responses. Insulin is generally considered to regulate glucose metabolism while IGF-1 is thought to regulate growth and survival. How the functional differences between insulin and IGF-1 are molecularly determined is not completely understood, but it is thought that critical differences in the structures of insulin and IGF-1 as well as that of their respective receptors influence binding stability and affinity for specific downstream signaling substrates (Blakesley et al., 1996). In addition, the existence of IGF-1 binding proteins (IGFBPs) that regulate IGF-1 binding to its receptor and differences in tissue distribution of the insulin and IGF-1 receptors all contribute to establishing the distinct cellular roles of insulin and IGF-1 (Blakesley et al., 1996).

Insulin and IGF-1 receptors are widely expressed in the brain with relatively similar localizations and are expressed in adult NSCs (Aberg et al., 2003; Hsieh et al., 2004; Lesniak et al., 1988; Yu et al., 2008). Insulin enters the brain across the blood–brain barrier by a receptor-mediated transport system (Banks et al., 1997; Schwartz et al., 1991). Like insulin, IGF-I can cross the blood–brain barrier, though it is also produced in the postnatal and adult brain, particularly in regions that undergo cell divisions, such as the hippocampus, the SVZ, and the olfactory bulb (Bartlett et al., 1991; D'Ercole et al., 1996; Reinhardt and Bondy, 1994), raising the possibility that IGF-1 signaling plays an important role as a paracrine factor for NSC/progenitor proliferation.

3.1.2. Insulin/IGF-1 function in neural stem cells

Numerous studies have implicated insulin/IGF-1 signaling in NSC maintenance and function. In general, IGF-1 has a stronger mitogenic effect than insulin (Sasaoka et al., 1996) and this appears to be the case in NSCs as well. Transgenic mice overexpressing IGF-

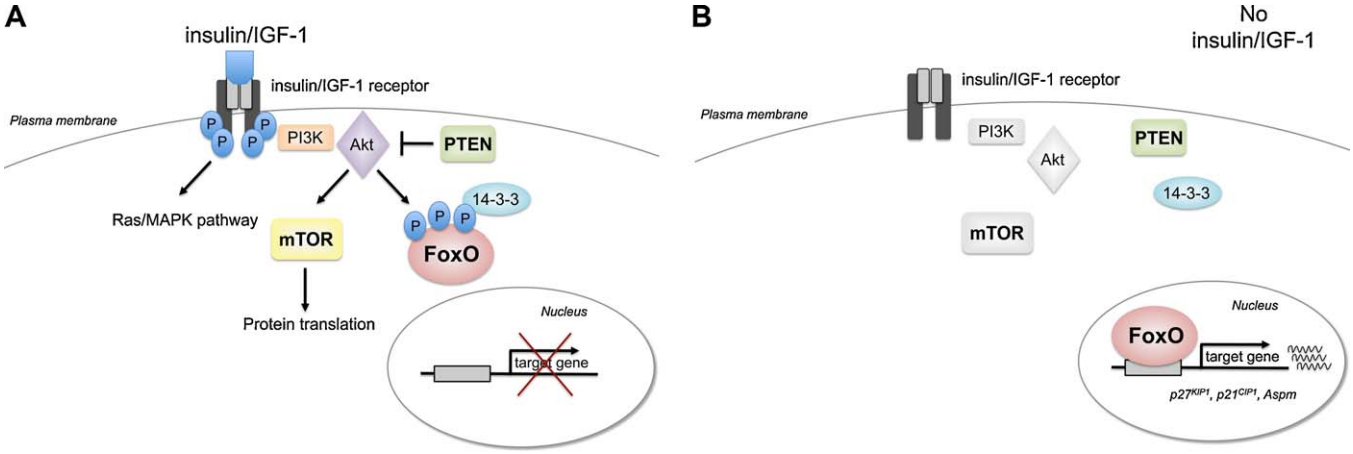

Fig. 2. Components of the insulin/insulin-like growth factor I (IGF-1) signaling pathway implicated in NSC fate. (A) Insulin or IGF-1 bind to their respective tyrosine kinase receptors on the cell membrane. This leads to activation of Akt, which promotes mTOR activation and subsequent upregulation of protein translation. Akt directly phosphorylates FoxO transcription factors, causing them to be retained in the cytoplasm. PTEN is a lipid phosphatase that inhibits Akt activation. The Ras/MAPK pathway is also activated by insulin/IGF-1 receptor binding. (B) In the absence of insulin/IGF-1 signaling, reduced Akt activity minimizes mTOR activation. FoxO factors are unphosphorylated and translocate to the nucleus to regulate transcription of target genes, such as the cell cycle inhibitors $p27^{Kip1}$ and $p21^{Cip1}$ and *Abnormal spindle-like microcephaly-associated* (*Aspm*), which is involved in brain size determination. Shapes in grey indicate proteins in their inactive state. Proteins implicated in NSC biology are in bold.

1 display a large increase in brain growth (Carson et al., 1993; Mathews et al., 1988; Ye et al., 1995), consistent with the possibility that IGF-1 promotes the expansion of embryonic NSCs. Indeed, IGF-1 stimulates embryonic NSC proliferation *in vitro* (Arsenijevic et al., 2001). *In vivo* infusion of IGF-1 in the adult rat hippocampus stimulates NSC proliferation and subsequent differentiation into granule cell layer neurons (Aberg et al., 2000). Similarly, *in vitro* culturing of adult hippocampal NSCs with IGF-1 stimulates NSC proliferation and also acts as an instructive signal for neurogenesis when basic fibroblast growth factor (bFGF) is removed to stimulate differentiation (Aberg et al., 2003). Interestingly, IGF-1 also enhances the production of oligodendrocytes both during development (Carson et al., 1993; Mathews et al., 1988; Ye et al., 1995) and from differentiating adult hippocampal NSCs (Hsieh et al., 2004). The ability of IGF-1 to stimulate NSC proliferation as well as differentiation into both neurons and oligodendrocytes may seem paradoxical. However, its enhancement of proliferation depends on the presence of NSC growth factors (*e.g.* EGF and/or bFGF), which share downstream signaling components, such as Ras/MAPK or PI3K/Akt, with IGF-1 (Aberg et al., 2003; Peltier et al., 2007). The different lineage specification effects of IGF-1 are likely to depend on both its concentration and other signals from the surrounding environmental niche.

Is there a role for insulin in adult NSC fate? Insulin has unique actions in the brain compared to liver and muscle, which store considerable amounts of glucose in the form of glycogen in response to insulin. While a main function of insulin in the brain is to regulate organismal energy homeostasis by acting in hypothalamic feeding centers (Gerozissis, 2003), insulin does influence glucose balance in certain neural cell types. Astrocytes, but not neurons, increase glucose uptake when stimulated by insulin (Heidenrich et al., 1989; Zhu et al., 1990). While it has not been tested whether NSCs display increased glucose uptake in response to insulin, standard media formulations used to culture mouse, rodent, and human NSCs *in vitro* contain insulin, suggesting it is required for survival. Interestingly, insulin withdrawal from adult hippocampal NSC cultures leads to autophagic cell death, a cellular response often deployed under conditions of low energy availability (Yu et al., 2008). High concentrations of insulin induce neuronal differentiation of postnatal NSCs (Han et al., 2008) and culturing embryonic NSCs with both insulin and IGF-1 leads to a greater production of neurons during differentiation compared to cultures stimulated by IGF-1 alone (Arsenijevic and Weiss, 1998), demonstrating that insulin has the ability to induce neurogenesis. The results of these *in vitro* studies should be interpreted with caution as they may depend on culturing parameters, such as growth factor concentrations, oxygen availability, and cell–cell interactions, that do not necessarily reflect the *in vivo* NSC niche. The role of insulin in adult NSCs *in vivo* remains to be explored.

3.1.3. PI3K/Akt/PTEN in neural stem cells

Multiple signaling pathways downstream of insulin/IGF-1 receptor binding have been implicated in adult NSC function (Fig. 2). The PI3K/Akt pathway appears to be central to IGF-1 signaling in adult NSCs as IGF-1 stimulation of cultured NSCs drastically induces the phosphorylation, and thus, activation, of Akt (Kalluri et al., 2007). Furthermore, chemical inhibition of PI3K by the LY294002, but not inhibition of the MAPK pathway by U0126, is sufficient to eliminate the pro-proliferative effects of IGF-1 on adult NSC cultures, suggesting PI3K/Akt is a main mediator of IGF-1 action in adult NSCs. NSCs retrovirally induced to overexpress Akt display enhanced proliferation and reduced capacity to differentiate (Peltier et al., 2007). Importantly, Akt activation is also induced in adult NSCs by binding of other growth factors and signaling ligands, such as bFGF and Sonic hedgehog (Shh) (Peltier et al., 2007), which underscores the idea that cross-talk between signaling pathways is likely to play a significant role in determining adult NSC fate.

The activity of the Akt branch of insulin/IGF-1 signaling can be attenuated by the PTEN lipid/protein phosphatase, which dephosphorylates phosphatidylinositol (3,4,5)-triphosphate (PIP_3) to generate $PI(4,5)P_2$. This reduction in PIP_3 limits the amount of Akt binding at the cellular membrane, which ultimately inhibits Akt activation. Mice with brain-specific deletion of the *Pten* gene exhibit enlargened brains during embryonic stages due to an increase in embryonic neural stem cell number and cell size (Groszer et al., 2001). This increase in embryonic neural stem cell numbers is a result of reduced cell death and increased cellular proliferation because of greater entry of NSCs into the G_1 phase from the G_0 phase of the cell cycle (Groszer et al., 2006). *Pten* deletion also enhances the self-renewal of embryonic and early postnatal NSCs in culture without affecting the differentiation potential of these cells (Groszer et al., 2001). Furthermore, Pten haploinsufficient SVZ NSCs from early postnatal mice proliferate more than wild-type NSCs *in vitro*, have greater migratory abilities *in vitro* and *in vivo*, and are less susceptible to oxidative stress-mediated apoptosis *in vitro* (Li et al., 2002). Thus, in the developing brain, PTEN normally functions to limit the proliferation of NSCs, perhaps to prevent tumor formation and disorderly brain development during stages of major growth. Similarly, in the adult mouse, specific deletion of *Pten* in SVZ NSCs increases the population of self-renewing NSCs and proliferating neural progenitors that can give rise to functional neuronal precursors (Gregorian et al., 2009). In fact, *Pten* deletion results in an increased olfactory bulb mass due to higher levels of neurogenesis in this region and also leads to enhanced habituation to novel odors. This observation indicates that PTEN loss removes the brake on SVZ NSC expansion without comprising the normal biological function of the newborn olfactory bulb neurons. Importantly, even though PTEN is a major tumor suppressor in humans, no tumors were observed in *Pten* null mice up to 2 years of age (Gregorian et al., 2009). It has not been determined whether the loss of PTEN in NSCs instead leads to a premature exhaustion of the NSC population at later ages, a phenomenon which has been observed in other mouse mutants that show enhanced neural progenitor proliferation (*e.g. p21 null* mice, *FoxO null* mice) (Kippin et al., 2005; Paik et al., 2009; Renault et al., 2009). As PTEN is a negative regulator of Akt signaling, it follows that phenotypes of *Pten* null NSCs are relatively similar to effects observed in adult NSCs when stimulated by IGF-1 or retrovirally-induced to overexpress Akt (Peltier et al., 2007).

3.1.4. FoxO transcription factors in neural stem cells

The FoxO family of transcription factors is negatively regulated by the PI3K/Akt branch of the insulin/IGF-1 pathway. There are four FoxO family members in mammals: FoxO1, FoxO3, FoxO4, and FoxO6. Phosphorylation of FoxO1, FoxO3, and FoxO4 by Akt leads to their retention in the cytoplasm, thereby inhibiting their transcriptional activities (Biggs et al., 1999; Brunet et al., 1999; Kops et al., 1999) (Fig. 2). In contrast, FoxO6 phosphorylation by Akt does not affect its subcellular localization, but still inhibits FoxO6 transcriptional activity (van der Heide et al., 2005). FoxO factors are important in many tissues and cell types for the survival and defense response to cellular stress, such as low energy availability and increased oxidative stress levels (Greer and Brunet, 2005). Deletion of FoxO3 or simultaneous deletion of FoxO1, FoxO3, and FoxO4 in the mouse brain has been shown to increase brain size (Paik et al., 2009; Renault et al., 2009). Adult NSCs lacking FoxO1, FoxO3, and FoxO4 show an increased rate of cell cycle entry along with reduced self-renewal and multipotency (Paik et al., 2009). Over prolonged *in vitro* passaging, the triple FoxO knock-out mice undergo apoptosis to a greater degree than

wild-type NSCs. *In vivo*, triple FoxO knock-out mice exhibit reduced numbers of dividing NSCs and neuroblasts after 3 months of age with no difference at 8 weeks of age. Interestingly, specific deletion of FoxO3 in either the whole animal or specifically in the brain is sufficient to reduce the self-renewal capacity and multipotency of adult NSCs (from 3 month and older mice), but not of postnatal NSCs, *in vitro* and *in vivo* (Renault et al., 2009). *FoxO3* null NSCs also exhibit enhanced entry into the cell cycle, suggesting that FoxO3 may act normally to maintain the relative quiescence of NSCs and prevent their premature exhaustion (Renault et al., 2009). Taken together, these results argue that loss of FoxO factors ultimately leads to a depletion of self-renewing NSCs in the older adult mouse due to premature differentiation toward a rapidly proliferating neural progenitor population.

Gene expression analyses comparing NSCs with and without FoxO expression have illuminated the multiple intracellular processes regulated by this family of transcription factors that regulate NSC function. Established FoxO-regulated genes, such as *Cyclin D1* and *Inhibitor of DNA-binding proteins Id1* and *Id2*, as well as novel FoxO targets, including cell cycle genes *Abnormal spindle-like microcephaly-associated (Aspm)* and *Cdk inhibitor 1C*, and oligodendrocyte lineage genes *Myelin basic protein (Mbp)* and *Proteolipid protein 1 (Plp1)*, were identified by Paik et al. (2009) through microarray analysis of triple FoxO knock-out and control embryonic NSCs. Of note is the finding that transcription of the mouse homolog of *ASPM*, a determinant of human cerebral cortex size (Bond et al., 2002), is directly inhibited by FoxO1 and 3, limiting excessive neural progenitor proliferative expansion during development and repressing early exhaustion of the adult NSC pool. Interestingly, the FoxO-dependent transcriptome displays minimal overlap with FoxO-dependent transcriptomes obtained from other cell types, such as hematopoietic stem cells or endothelial cells, indicating the cell-type specific action of FoxO factors (Paik et al., 2007, 2009; Tothova et al., 2007).

Examination of gene expression differences between adult NSCs specifically lacking FoxO3 and wild-type NSCs emphasizes a role for this family member in promoting cellular quiescence, oxidative stress resistance, and inhibition of premature oligodendrocyte differentiation (Renault et al., 2009). Oligodendrocyte lineage-associated genes that were found to have increased expression in triple FoxO knock-out NSCs (*Mbp* and *Plp1*) (Paik et al., 2009) were also determined to be upregulated in *FoxO3* null NSCs (Renault et al., 2009), suggesting that FoxO3 may the primary FoxO family member responsible for modulating the oligodendrocyte gene expression program in NSCs. The analysis of genes regulated by FoxO3 in NSCs also revealed a novel function for FoxO3 in the transcriptional regulation of genes involved in the cellular response to hypoxia (low oxygen). For example, genes known to be upregulated in hypoxic brain and other tissues, such as *DNA-damage-inducible transcript 4 protein* (*Ddit4*), *N-myc downstream regulated 1 (Ndrg1)*, *Endoplasmic oxioreduction-1-like protein (Ero1l)*, and *Vascular endothelial growth factor a* (*Vegfa)*, were downregulated in *FoxO3* null NSCs (Renault et al., 2009). Consistent with these observations, *FoxO3* null NSCs had a defect in neurosphere-forming ability, particularly under low oxygen (2%) culture conditions (see Section 3.4) (Renault et al., 2009). Taken together, the FoxO family of transcription factors appears to be necessary for both promoting quiescence of self-renewing, multipotent NSCs, as well as orchestrating a cellular response to conditions that threaten the integrity of the stem cell compartment.

3.1.5. mTOR in neural stem cells

The protein mammalian target of rapamycin (mTOR) is positively regulated by insulin/IGF-1 signaling and has been shown to mediate some of the cellular actions of the PI3K/Akt pathway (Hay and Sonenberg, 2004; Scott et al., 1998). However, there is relatively little known yet about the specific actions of mTOR in NSCs. In embryonic rat NSCs, insulin elicits Akt activation and the consecutive phosphorylation and activation of mTOR (Han et al., 2008). This increase in mTOR activity correlates with a dose-dependent increase in the number of new neurons generated during differentiation in response to insulin stimulation. Rapamycin, an inhibitor of one of the mTOR-containing complexes (mTORC1), reverses this insulin-dependent enhancement of neurogenesis, suggesting that mTORC1 is the main mediator of the neurogenic effect of insulin. How mechanistically mTOR influences neurogenesis is not yet clear, though it may be acting through one of its established targets, like the serine/threonine kinase p70S6K, which phosphorylates the S6 ribosomal protein, or the eukaryotic translation initiation factor 4E-BP, to promote protein translation (Gingras et al., 2001; Hay and Sonenberg, 2004). It is also possible that mTOR acts as a mediator of cross-talk between insulin/IGF-1 signaling and other pathways in adult NSCs. In embryonic NSCs, Notch pathway activation increases phosphorylation of mTOR (Androutsellis-Theotokis et al., 2006). Inhibition of mTOR by rapamycin is sufficient to eliminate the Notch-dependent increase in embryonic NSC survival (Androutsellis-Theotokis et al., 2006). It also remains to be determined whether the mTOR pathway functions in NSCs *in vivo* and in adult NSCs, but there is some evidence to suggest that mTOR activity extends to these scenarios. *In vitro* exposure of adult NSCs to CD95, classically considered an apoptosis-promoting factor, leads to activation of mTOR though the PI3K/Akt pathway and an increase in global levels of translation, increased survival, and enhanced neuronal differentiation of NSCs (Corsini et al., 2009). Furthermore, overexpression of CD95L, the ligand of the CD95 receptor, by *in vivo* lentiviral infection of NSCs in the SVZ of adult mice increases the number of neuroblasts in this region, supporting the idea that activation of mTOR in adult SVZ NSCs may be important for promoting neuronal differentiation *in vivo*.

3.1.6. Comparison of PTEN, FoxO, and mTOR actions in neural stem cells

As several signaling components downstream of insulin/IGF receptors have been shown to function in NSC biology (PTEN, FoxOs, mTOR), it is worthwhile to compare and contrast the different phenotypes in the various loss-of-function experiments. By inactivating Akt, Pten leads to the activation of FoxO transcription factors. Indeed, *Pten* heterozygote NSCs display increased levels of FoxO phosphorylation (Li et al., 2002). Thus, one would expect that *Pten* loss should induce all of the phenotypes of FoxO deletion in adult NSCs. Both mouse knock-outs exhibit larger brains due to increased cell numbers, yet PTEN, but not FoxO factors, also regulates cell size (Groszer et al., 2001; Paik et al., 2009). Both FoxO factors and PTEN promote quiescence of NSCs. However, *Pten* loss does not appear to compromise long-term NSC self-renewal, whereas loss of FoxO factors induces a transition from NSC to a progenitor population, eventually leading to a depletion of adult NSCs. Considering the fact that hematopoietic cells (HSCs) lacking *Pten* ultimately display impaired self-renewal due to short-term population expansion (Zhang et al., 2006), it is possible that if examined at older ages, *Pten* null mice would also exhibit a depleted NSC pool. Interestingly, *Pten* null NSCs also retain their ability to make normal olfactory bulb neurons, suggesting the differentiation ability of NSCs is not significantly affected. These important differences may be due to compensation of PTEN loss by downstream factors that would enable NSCs to maintain their self-renewal and multipotency in the absence of PTEN. In contrast, deletion of FoxO factors may lead to more serious alterations of NSC function as possibilities for compensa-

tion may be more limited with the loss of critical transcriptional regulators.

An outstanding question is whether the FoxO family of transcription factors or mTOR is the primary mediator of insulin/IGF-1 signaling action in adult NSCs, especially given the lack of perfect overlap between *FoxO* null and *Pten* null NSC phenotypes. The relatively limited experimental evidence testing the importance of mTOR in adult NSCs makes this distinction currently difficult. The main known functions of mTOR are to regulate protein synthesis, nutrient metabolism, cell growth, and cell cycle progression (Sarbassov et al., 2005a), all of which are key cellular processes for NSCs. FoxO factors are also regulators of the cell cycle and can influence many other critical cellular events, including DNA damage repair, apoptosis, and the hypoxia response. Thus, it is likely that both FoxO factors and mTOR have overlapping as well as unique functions in adult NSCs. Of note is that mTOR, in complex with rictor (mTORC2), has been shown to activate Akt in human cancer cells (Sarbassov et al., 2005b), a feedback loop that could negatively regulate FoxO activity. Further examination of mTOR function downstream of IGF-1 signaling and in the context of FoxO activity would create a more complete picture of how the energy-sensing insulin/IGF-1 signaling pathway regulates the fate of adult NSCs.

3.1.7. The role of insulin/IGF-1 signaling in neural stem cells and in aging

Given the overall positive effect of insulin/IGF-1 signaling on NSC proliferation and neuronal and oligodendrocytic lineage specification, it is interesting to consider that *low* insulin/IGF-1 signaling levels can extend lifespan and promote a greater healthspan in multiple model organisms (Bluher et al., 2003; Clancy et al., 2001; Friedman and Johnson, 1988; Holzenberger et al., 2003; Kenyon et al., 1993; Tatar et al., 2001). Interestingly, reducing IGF-1 receptor levels has recently been shown to improve cognition in a mouse model of Alzheimer's disease (E. Cohen et al., 2009). Taken together with the pro-proliferative effects of insulin/IGF-1 signaling on NSCs, these observations would suggest that relatively low levels of insulin/IGF-1 signaling, which are beneficial for lifespan and brain health, would paradoxically negatively impact the important NSC population and adult neurogenesis. This apparent contradiction between the multiple consequences of insulin/IGF-1 signaling may be resolved by the concept that the proliferation dynamics of adult NSCs must be a balance between relative quiescence and cell cycling in order to both preserve the NSC pool over a lifespan as well as contribute new neural cells to the brain. This concept has been supported by studies of *FoxO* null and *p21* null mice, in which the excessive release of relatively quiescent adult NSCs into the cell cycle leads to the exhaustion of the pool of NSCs later in life (Kippin et al., 2005; Paik et al., 2009; Renault et al., 2009). Thus, both overabundant or insufficient production of new progeny from NSCs may be detrimental to adult brain function. It is likely that the net value of high insulin/IGF-1 signaling in adult NSCs for the brain is when it occurs only sporadically, in local niches, or in unique situations when new neural cells are critically needed (*i.e.* brain injury, neurodegenerative disease).

3.2. AMPK

AMP-activated protein kinase (AMPK) is a central energy sensor and regulator of metabolic processes. It is activated by stimuli that elicit a high cellular [AMP] to [ATP] ratio, including dietary restriction, exercise, ischemia, and hypoxia (Kahn et al., 2005) (Fig. 3A). AMPK is a heterotrimeric protein that consists of three subunits (α, β, γ), each with multiple isoforms. The γ subunit contains AMP-binding domains that sense changes in the [AMP] to [ATP] ratio (Hawley et al., 1996). The α subunit contains the catalytic domain that becomes exposed when AMP binds the γ subunit (Crute et al., 1998). The β subunit stabilizes the interaction between all three subunits. Conditions of low energy (high [AMP]:[ATP]) increase the likelihood of AMPK phosphorylation by upstream kinases, such as LKB1, calcium/calmodulin-dependent protein kinase kinase beta (CaMKKβ), and TGF-β-activated kinase-1 (Tak1) (Hawley et al., 2003, 2005; Hurley et al., 2005; Lizcano et al., 2004; Momcilovic et al., 2006; Shaw et al., 2004; Woods et al., 2005). AMP binding also prevents dephosphorylation of AMPK, further ensuring the sustained activity of AMPK under low energy availability (Sanders et al., 2007). Since the AMPK-activating kinase CAMKKβ is itself activated by an increase in intracellular calcium, AMPK integrates both energy levels and calcium signaling. The dependency of AMPK activation on relative cellular levels of AMP and ATP has earned it the appropriate title of cellular "fuel gauge" (Kahn et al., 2005).

Upon activation, AMPK acts in a variety of tissues to restore cellular ATP levels (Kahn et al., 2005). Some of the known

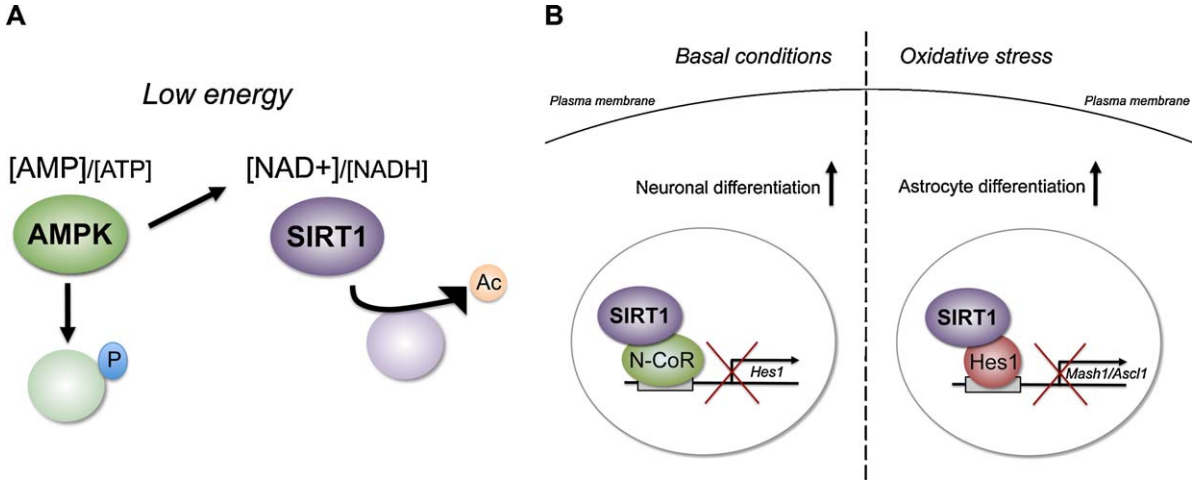

Fig. 3. The energy-sensing enzymes AMP-activated protein kinase (AMPK) and Sirt1. (A) In low energy conditions, the ratio of [AMP] to [ATP] and the ratio of [NAD+] to [NADH] increase. AMPK is activated by a high [AMP] to [ATP] ratio and Sirt1 is activated by a high [NAD+] to [NADH] ratio. Activated AMPK phosphorylates substrates and promotes synthesis of NAD+, which contributes to Sirt1 activation. Sirt1 deacetylates substrates that include histones and transcription factors. (B) Sirt1 function in NSC differentiation is modulated by oxidative state. Under differentiating conditions, Sirt1 interacts with N-CoR at the Hes1 promoter to inhibit Hes1 expression, which promotes neuronal differentiation. Under oxidative, differentiating conditions, Sirt1 binds to Hes1 at the Mash1/Ascl1 promoter to repress Mash1/Ascl1 expression, which promotes differentiation of astrocytes at the expense of neuronal differentiation.

substrates of AMPK include acetyl-coA carboxylase 1 (ACC1), CREB regulated transcription coactivator 2 (CRTC2), tuberous sclerosis 2 protein (TSC2), and glycogen synthase, (Carling and Hardie, 1989; Davies et al., 1992; Inoki et al., 2003; Koo et al., 2005). AMPK-mediated phosphorylation of these and other AMPK substrates can positively or negatively regulate target activity, resulting in enhanced cellular intake of glucose and increased fatty acid oxidation. AMPK also functions to reduce the energy-consuming synthesis of lipids, proteins, and glycogen and to limit gluconeogenesis. Thus, because of the multitude of cellular and systemic effects that it orchestrates in response to a high [AMP] to [ATP] ratio, AMPK is considered to be a master regulator of energy homeostasis and its actions are relevant for organismal development, longevity, and disease treatments (Greer et al., 2007a; Hardie, 2008; Steinberg and Kemp, 2009; Zhou et al., 2001).

While the majority of the cellular functions ascribed to AMPK are related to controlling glucose and fat metabolism, there is an increasing interest in understanding the role of AMPK in NSC self-renewal and multipotency. The brains of 2-week-old AMPK $\beta1^{-/-}$ mice are half the size of wild-type brains and exhibit significant cerebellar atrophy, reduction in cerebral cortex volume, and loss of the dentate gyrus (Dasgupta and Milbrandt, 2009), suggesting that abrogation of AMPK activity affects NSCs of the developing brain. Indeed, the embryonic NSCs of these AMPK $\beta1^{-/-}$ mice have reduced proliferative capacity in the ventricular zone. Once the progeny of embryonic AMPK subunit $\beta1^{-/-}$ NSCs migrate out of the ventricular zone, they undergo increased apoptosis compared to wild-type NSCs. The proliferation and apoptosis phenotypes of AMPK $\beta1^{-/-}$ NSCs appears to be largely cell-autonomous as reintroduction of the β1 subunit into NSCs is sufficient to nearly completely restore levels of proliferation and apoptosis back to those of wild-type NSCs (Dasgupta and Milbrandt, 2009). Interestingly, the proliferation defects of AMPK $\beta1^{-/-}$ NSCs appear to depend on the hypophosphorylated state of the cell cycle regulator retinoblastoma protein (Rb), which was found to be a direct substrate of AMPK although the phosphorylation site in Rb does not match the optimal AMPK consensus site (Gwinn et al., 2008). In AMPK $\beta1^{-/-}$ NSCs, hypophosphorylated Rb leads to a defect in the G2–M transition of the cell cycle, a non-canonical role for Rb, which is well-established to regulate the G0–G1 transition in its phosphorylated state (Burkhart and Sage, 2008). Additional *in vitro* experiments from this study indicate that culturing cells in low glucose conditions increases the growth rate of embryonic wild-type NSCs in an AMPK β1-dependent manner, suggesting that low energy-sensing by AMPK promotes NSC cell proliferation (Dasgupta and Milbrandt, 2009). Promotion of NSC proliferation by AMPK is somewhat counterintuitive given that mitosis is an energy-consuming process. However, it is possible that AMPK-mediated Rb phosphorylation under low energy conditions ensures that NSCs already in the cell cycle are able to pass through the G2–M checkpoint. This action of AMPK would allow NSCs to wait for energy levels to be restored at the G0–G1 checkpoint, a less precarious cellular state than the G2–M transition. In sum, results from this AMPK β1 knock-out mouse demonstrate that AMPK activity is essential for brain development, in part through the regulation of proliferation and survival of the progeny of embryonic NSCs.

Surprisingly, work by another group appears to demonstrate the opposite effect of AMPK on embryonic NSC proliferation and phosphorylation of Rb. Stimulation of embryonic NSCs by the AMPK activator AICAR leads to inhibition of proliferation (Zang et al., 2009), which contrasts with the phenotype of the AMPK $\beta1^{-/-}$ NSCs (Dasgupta and Milbrandt, 2009). Furthermore, AICAR reduced levels of phospho-Rb, again in opposition to the results from AMPK $\beta1^{-/-}$ NSCs and the finding that AMPK can directly phosphorylate Rb. Given that AICAR is not completely specific for AMPK and inhibition of AMPK by compound C was able to only partially rescue the effect of AICAR on cell cycle arrest, it is important to consider these results with caution. In addition, global deletion of the AMPK $\beta1^{-/-}$ subunit may affect embryonic NSCs in ways that are non cell-autonomous. Clearly, deeper investigation into the dynamics of AMPK action in embryonic and adult NSCs is needed.

The full array of potential AMPK functions in NSCs has not been explored, but there is evidence from other neural cell types that suggests AMPK may also play a pro-survival role in NSCs under conditions of altered energy metabolism. Activation of AMPK protects against glucose deprivation or hypoxia-induced cell death of embryonic hippocampal neurons (Culmsee et al., 2001) and partially guards against oxidative stress-induced cell death of an immortalized cerebellar cell line (Park et al., 2009). It is possible that AMPK plays an analogous role in providing protection against oxidative stress in adult NSCs. Interestingly, AMPK regulates molecules that are implicated in NSC regulation (*e.g.* FoxO3, p53, mTOR, and SIRT1) (Canto et al., 2009; Cheng et al., 2004; Fulco et al., 2003; Greer et al., 2007b; Inoki et al., 2003; Jones et al., 2005). The effects of AMPK on these targets have been shown in cell types other than NSCs so it remains to be determined whether similar interactions have a relevant function in adult NSCs.

An intriguing question is whether AMPK also exerts effects on adult NSCs in a cell non-autonomous manner, that is, through its function in other tissues. Distinguishing between cell-autonomous and systemic effects of AMPK on adult NSCs would benefit from a system for specific AMPK deletion in the NSC population. The existence of multiple isoforms of each of three subunits of AMPK complicates the generation of mice and cells lacking any AMPK activity. However, it would be possible to abrogate AMPK activity in adult NSC by manipulating expression of one its upstream activating kinases LKB1, although LKB1 also targets other AMPK-related kinases (Lizcano et al., 2004). The *in vitro* and *in vivo* use of AMPK-specific activators or inhibitors (Cool et al., 2006; Zhou et al., 2001) may also help reveal whether AMPK activity is necessary for adult NSC self-renewal and differentiation. Finally, it would be interesting to test whether dietary restriction and exercise, both of which increase AMPK activity, require AMPK to exert their effects on adult hippocampal NSC and newly generated neurons (Section 6) (Lee et al., 2000; van Praag, 2008; Winder and Hardie, 1996).

3.3. Sirtuins

3.3.1. The Sirtuin family of protein deacetylases

A key family of proteins involved in sensing fluctuating energy levels is the highly conserved protein deacetylases collectively known as Sirtuins. Sirtuins are homologous to the yeast Sir2 protein, which silences mating-type loci, telomeres, and ribosomal DNA (Aparicio et al., 1991; Gottlieb and Esposito, 1989; Rine and Herskowitz, 1987) and is most well-known for its ability to extend lifespan when overexpressed in yeast, worms, and flies (Kaeberlein et al., 1999; Rogina and Helfand, 2004; Tissenbaum and Guarente, 2001). The seven mammalian Sirtuins (SIRT1–7) are categorized as Class III histone deacetylases (HDAC) due to their unique dependence on the coenzyme nicotinamide adenine dinucleotide (NAD+) (Imai et al., 2000). Because NAD+ is reduced to NADH in glycolysis and the citric acid cycle, the ratio of [NAD+] to [NADH] is inversely proportional to energy availability. In addition, NADH can competitively inhibit the Sirtuin-catalyzed deacetylase reaction and its levels are reduced by dietary restriction (S.J. Lin et al., 2004). Sirtuins should have greater enzymatic activity under conditions of low energy (high [NAD+] to [NADH] ratio), and consequently, are poised to respond to changes in cellular energy status. Furthermore, dietary restriction, a well-known intervention that extends lifespan (Weindruch and Walford, 1988), leads to an

increase of Sirtuin protein expression in variety of tissues. In the brain, SIRT1 and SIRT6 are upregulated in response to dietary restriction (Cohen et al., 2004; Kanfi et al., 2008). Conversely, a high fat and sucrose diet is accompanied by decreased SIRT1 expression in the hippocampus and cerebral cortex (Wu et al., 2006), demonstrating the dynamics of SIRT1 expression in response to energy consumption. Thus, regulation of Sirtuins can occur both at the level of their expression and their enzymatic activity.

The acetylated substrates of Sirtuins include the lysine residues on histone and non-histone proteins. The deacetylation reaction produces the deacetylated protein, an end-product inhibitor nicotinamide, and 2′-O-acetyl-ADP-ribose (Tanner et al., 2000; Tanny and Moazed, 2001). By removing acetyl groups, Sirtuins modulate the biological activity of their substrates, leading to significant changes in gene expression and cellular status. For example, SIRT1 and SIRT6 can deacetylate specific lysine residues on histone tails (SIRT1: histone 1 lysine 26 (H1K26), H3K9, H3K14, H3K56, H4K16; SIRT6: H3K9, H3K56) to induce greater transcriptional silencing (Das et al., 2009; Imai et al., 2000; Kawahara et al., 2009; Michishita et al., 2008, 2009; Vaquero et al., 2004; Yang et al., 2009). SIRT1 also deacetylates many other targets, such as the transcription factors FoxO3 and p53, to promote or repress their activity (Brunet et al., 2004; Luo et al., 2001; Motta et al., 2004; Vaziri et al., 2001). An alternative reaction that can be catalyzed by select Sirtuins (SIRT1, SIRT4, SIRT6) is the transfer of ADP-ribosyl group from NAD+ to an acceptor protein although the significance of this reaction is only beginning to be understood (Du et al., 2009; Haigis et al., 2006; Liszt et al., 2005). Despite being relatively similar in sequence, the Sirtuins possess a remarkable variety of cellular roles and have disparate subcellular localizations.

3.3.2. SIRT1 in neural stem cells

To date, the only Sirtuin that has been directly implicated in NSC biology is SIRT1, which has the closest homology (45.9%) to the yeast Sir2 of all the mammalian Sirtuins (Imai et al., 2000). SIRT1 is primarily a nuclear protein although there are reports indicating it may also translocate to the cytoplasm (Hisahara et al., 2008; Jin et al., 2007; Michishita et al., 2005). In embryonic NSCs exposed to oxidative conditions *in vitro*, *Sirt1* is transcriptionally upregulated (Prozorovski et al., 2008). It is required for the ability of oxidative stress to induce differentiating NSCs to adopt an astrocytic fate at the expense of the neuronal lineage (Prozorovski et al., 2008) (Fig. 3B). The mechanism of this neural fate switch under oxidative stress involves SIRT1 association with the bHLH transcriptional repressor and mediator of Notch signaling Hes1 at the promoter of Mash1/Ascl1, a bHLH transcriptional activator of neuronal differentiation. Conversely, *in vivo* knockdown of SIRT1 in embryonic brains treated with oxidizing agents results in increased Mash1/Ascl1 expression and neuronal differentiation. Thus, inhibition of Mash1/Ascl1 expression by the SIRT1-Hes1 complex is thought to repress neurogenesis under oxidative stress conditions *in vitro* and *in vivo*. The use of oxidizing agents to reveal the effect of SIRT1 on NSCs raises the question of the physiological relevance of this mechanism of NSC regulation by SIRT1. Oxidative stress is indeed present in a range of age-associated neuropathologies (Emerit et al., 2004), emphasizing the need to determine whether SIRT1 functions in the adult NSC population that could potentially contribute to brain repair. Excessive astrocyte production induced by oxidative stress may also have clinical significance as glial scars can inhibit neuroregeneration (Asher et al., 2000). Finally, given that SIRT1 can bind and regulate many regions in the genome of embryonic stem cells (Oberdoerffer et al., 2008), unbiased identification of all SIRT1 genomic binding sites in NSCs would help reveal a network of genes by which SIRT1 exerts its effects on NSC fate choice.

In striking contrast with the findings of Prozorovski et al., another group found that SIRT1 promotes neuronal differentiation of embryonic NSCs under basal, non-oxidative *in vitro* conditions through its interaction with the co-repressor N-CoR (Hisahara et al., 2008) (Fig. 3B). Furthermore, SIRT1 and N-CoR was shown to suppress expression at the Hes1 promoter, which may underlie the increase in neurogenesis. The opposing effects of SIRT1 on NSC lineage choice demonstrated by these independent studies raise the possibility that SIRT1 function in NSC differentiation depends heavily on the redox state of the cells, underscoring the significance of oxidative state on NSC fate (Fig. 3B and Section 3.4).

SIRT1 interacts with and/or deacetylates a broad array of proteins, several of which have critical roles in NSC biology. The FoxO1, FoxO3, and FoxO4 transcription factors are well-established SIRT1 targets (Greer and Brunet, 2005), and as described in Section 3.1.4, are important for regulating adult NSC homeostasis. Many studies have demonstrated SIRT1 modulation of FoxO transcriptional activity in the context of oxidative stress (Alcendor et al., 2007; Brunet et al., 2004; Frescas et al., 2005; Kitamura et al., 2005; Kobayashi et al., 2005; Motta et al., 2004; van der Horst et al., 2004; Yang et al., 2005), however, functional interaction between SIRT1 and FoxO factors in NSCs remains to be tested. There may also be a functional interaction between SIRT1 and p53, a transcription factor that limits the proliferation of NSCs and is a well-known substrate of SIRT1 (Luo et al., 2001; Meletis et al., 2006; Vaziri et al., 2001). Furthermore, SIRT1 has recently been shown to positively modulate the Wnt signaling pathway (Holloway et al., 2010). Wnt signaling promotes neural progenitor proliferation and neurogenesis in the adult SVZ and the dentate gyrus (Lie et al., 2005; Qu et al., 2010; Yu et al., 2006) and it is not unlikely that SIRT1's positive regulation of the Dishevelled proteins downstream of Wnt support this effect (Holloway et al., 2010). Finally, SIRT1 is itself regulated by Tlx and AMPK, both of which are implicated in NSC maintenance. The orphan nuclear receptor Tlx supports adult NSC proliferation by promoting HDAC-mediated repression at the p21 promoter (Shi et al., 2004; Sun et al., 2007). Tlx has recently been shown to upregulate *Sirt1* expression in human cancer cells (Iwahara et al., 2009), raising the possibility that SIRT1 mediates some of Tlx's actions in adult NSCs under normal and/or oxidative conditions. AMPK activates SIRT1 indirectly by promoting synthesis of the coenzyme NAD+ (Canto et al., 2009; Fulco et al., 2003). In sum, evidence supports the idea that SIRT1 may act in multiple signaling networks to regulate NSC fate.

3.3.3. Potential roles for SIRT2–7 in neural stem cells

The roles of two other nuclear Sirtuins, SIRT6 and SIRT7, in adult NSCs are not yet established. Given their actions in other cell types, it is tempting to speculate on their potential function in NSCs. SIRT6 is crucial for genomic stability, acting as a H3K9 and H3K56 deacetylase at telomeric DNA regions (Michishita et al., 2008, 2009; Yang et al., 2009) in human fibroblasts. SIRT6 might also be necessary for the replicative lifespan of adult NSCs, which depend on telomere maintenance for proper proliferation and neuronal differentiation (Ferron et al., 2004).

SIRT7 associates with ribosomal DNA (rDNA) in the nucleolus and activates RNA polymerase I-mediated transcription in human and mouse cancer cell lines (Ford et al., 2006). It is possible that SIRT7 counterbalances the SIRT1-mediated repression of rDNA transcription (Murayama et al., 2008), allowing cells to quickly fine-tune levels of ribosome production under fluctuating energy conditions in NSCs.

SIRT2 is the only Sirtuin primarily localized to the cytoplasm (Afshar and Murnane, 1999; Michishita et al., 2005). In the brain, SIRT2 protein expression increases concomitantly with the developmental timing of myelination and SIRT2 expression

increases as postnatal oligodendrocyte precursor cells (OPCs) differentiate into oligodendrocytes *in vitro* (Li et al., 2007). By deacetylating the cytoskeletal component α-tubulin, SIRT2 inhibits the differentiation and maturation of oligodendrocytes, perhaps acting as an endogenous limit on oligodendrocyte production (Li et al., 2007). If SIRT2 acts similarly in the oligodendrocyte lineage derived from adult NSCs, there would be significant implications for human degenerative conditions affecting the oligodendrocyte population, such as multiple sclerosis and leukodystrophies. As SIRT2 can deacetylate FoxO1 and FoxO3 to regulate their transcriptional activities (Wang et al., 2007; Wang and Tong, 2009), it is also possible that under conditions of changing energy availability and/or oxidative stress, SIRT2 acts through FoxO factors to influence NSC homeostasis (Paik et al., 2009; Renault et al., 2009).

The mitochondrial Sirtuins (SIRT3, SIRT4, SIRT5) have also not been investigated specifically in the context of NSCs. They each possess unique activities in the mitochondria to regulate energy metabolism and evidence suggests that SIRT3 also influences cell survival during genotoxic and metabolic stress (Haigis et al., 2006; Hirschey et al., 2010; Kim et al., 2010; Lombard et al., 2007; Nakagawa et al., 2009; Scher et al., 2007). Questions that remain to be answered include whether energy excess or deprivation influences the stem cell properties of NSCs via changes in mitochondrial function and whether these effects are mediated by Sirt3, Sirt4, and/or Sirt5.

3.4. Oxygen sensing and HIF signaling

As oxygen is the final electron acceptor in the electron transport chain of aerobic respiration, ensuring sufficient oxygen availability is of vital importance for metabolic function. Like all cell types, NSCs are capable of sensing and responding to low oxygen concentrations in the local environment. Indeed, adult NSCs in both the SVZ and the DG are positioned in close proximity to blood vessels (within 10–12 μm for the SVZ) (Palmer et al., 2000; Shen et al., 2008; Tavazoie et al., 2008) indicating that factors communicated from the blood, including oxygen, are part of the niche that influences NSC biology. Importantly, excess oxygen, in the form of oxidative stress, can be as detrimental to NSCs as the absence of oxygen (Limoli et al., 2004a; H.J. Lin et al., 2004) (see Section 4). It is now becoming clear that intracellular oxygen-sensing mechanisms can actually regulate the self-renewal, proliferation, and differentiation of NSCs both *in vitro* and *in vivo* (Panchision, 2009; Zhu et al., 2005).

3.4.1. Effects of low oxygen on neural stem cells

The oxygen concentration in the adult brain is estimated to be around 2%, (range 0.1–5.3%) which is 10 times lower than the atmospheric O_2 levels (20%) at which NSCs are traditionally cultured (Silver and Erecinska, 1998; Zhu et al., 2005). Numerous *in vitro* studies from a variety of NSC populations have indicated that lowering O_2 levels to physiological concentrations can dramatically impact NSC self-renewal and fate (Chen et al., 2007; Milosevic et al., 2005; Morrison et al., 2000; Pistollato et al., 2007; Renault et al., 2009; Santilli et al., 2010; Storch et al., 2001; Studer et al., 2000). Culturing rat embryonic NSCs at 3% O_2 leads to higher rates of proliferation and lower rates of cell death, resulting in a greater population expansion compared to cells grown at atmospheric O_2 levels (Studer et al., 2000). Upon differentiation, embryonic NSCs grown in lowered oxygen also give rise to a greater percentage of tyrosine hydroxylase-positive (TH+) dopaminergic neurons compared to control NSCs (Studer et al., 2000), suggesting that oxygen-sensing signaling can also modulate cell fate specificity of progenitor cells. Interestingly, in similar mouse studies, the effect of low oxygen to promote NSC proliferation and survival could only be observed when cultures were obtained from embryonic ventral midbrain but not forebrain, demonstrating a degree of region specificity of this effect (Milosevic et al., 2005). Furthermore, both embryonic mouse NSCs and immortalized human fetal NSCs grown at 2% or 5% O_2 generate greater numbers of colonies containing neurons, astrocytes, and oligodendrocytes when differentiated, indicating that the multipotency property of NSCs is preserved to a higher degree at low oxygen compared to atmospheric culture conditions (Chen et al., 2007; Santilli et al., 2010). Oxygen availability has also been demonstrated to have multiple levels of action as 20% O_2 reduces oligodendrocyte production by promoting both the premature differentiation of oligodendrocyte progenitor cells and the cell death of differentiated oligodendrocytes (Chen et al., 2007; Pistollato et al., 2007). Adult NSC proliferation also appears to be positively regulated by low-oxygen culturing (Renault et al., 2009), but an in-depth characterization of oxygen's effect on the adult NSC population is still needed.

These *in vitro* experiments illuminate a fascinating role for oxygen availability in NSC fate. The oxygen concentrations used in these studies (2–5%) are close to those in the normal brain, which raises questions regarding the response of NSCs *in vivo* to conditions when oxygen is lower than normal physiological levels (<1–2%). This latter scenario can be considered true "hypoxia" although the term "hypoxia" is also used to describe oxygen concentrations below atmospheric levels (20%). Do the principles obtained from NSC culture experiments hold when NSCs are exposed to true hypoxia *in vivo*? A complete lack of oxygen (anoxia), which occurs during transient ischemic stroke, can induce NSC proliferation and neurogenesis (Arvidsson et al., 2002; Jin et al., 2006; Macas et al., 2006; Marti-Fabregas et al., 2010; Nakatomi et al., 2002; Yagita et al., 2001) (see Section 7.3). This observation suggests that regulation of NSC via reduction of oxygen availability is a relevant process *in vivo*. Slight fluctuations in oxygen levels are likely to occur in the immediate NSC niche and may be a dynamic source of NSC regulation.

3.4.2. The HIF signaling pathway

The primary mechanism of low oxygen (hypoxia) sensing is mediated by hypoxia-inducible factors (HIFs). The HIF1 complex consists of a constitutively expressed HIF1β, also known as ARNT, and a post-translationally regulated HIF1α subunit (Wang et al., 1995). HIF2α and HIF3α isoforms exist but are not as widely expressed as HIF1α, which is notably abundantly expressed in embryonic neural precursors and more highly expressed in adult SVZ NSCs compared to differentiated cells (Jain et al., 1998; Panchision, 2009; Ramalho-Santos et al., 2002). Normally, HIF1α protein is present at low levels due to proteolytic degradation activities that require oxygen (Huang et al., 1998; Kallio et al., 1999; Salceda and Caro, 1997). In low oxygen environments, hydroxylation of two proline residues of HIF1α protein is inhibited, preventing the recognition of HIF1α protein by the proteasome (Bruick and McKnight, 2001; Jiang et al., 1996). Once stabilized, HIF1α acts with HIF1β as a dimeric transcription factor that binds to the hypoxia response element (HRE) and activates the transcription of many genes including *Vegf*, *Erythropoietin*, *Enolase I*, *Glucose transporter 1*, *p21*, and *Igfbp1, 2, and 3* (Carmeliet et al., 1998; Ebert et al., 1995; Feldser et al., 1999; Forsythe et al., 1996; Semenza et al., 1994; Sharp and Bernaudin, 2004; Tazuke et al., 1998). This HIF1-dependent transcriptional response leads to alterations in angiogenesis, glucose metabolism and cell cycle, which together enable the cell and tissue to adapt to a hypoxic environment (Sharp and Bernaudin, 2004).

3.4.3. HIF1 signaling as mediator of the effects of low oxygen on neural stem cells

HIF1 signaling is integral to normal NSC function during development. Mice with specific brain deletion of the *Hif1α* gene

exhibit hydrocephalus and have fewer neural cells, which is due, in part, to an increase in apoptosis (Tomita et al., 2003). As mature adults, brain-specific *Hif1α* knock-out mice have impaired spatial memory consolidation (Tomita et al., 2003). These results indicate that HIF1α activity is likely to be an essential factor in embryonic NSCs for normal brain development and function. HIF1 signaling has also been shown to underlie the effects of low oxygen on cultured NSCs (Milosevic et al., 2005; Studer et al., 2000). Embryonic midbrain-derived NSCs lacking HIF1α have reduced survival and proliferation at 3% O_2 culture conditions (Milosevic et al., 2007). Furthermore, loss of HIF1α in embryonic NSCs decreases the production of TH+ dopaminergic neurons upon differentiation. Neurons generated from *Hif1α*$^{-/-}$ embryonic NSCs also have reduced branching and morphological complexity compared to wild-type neurons. Interestingly, the reduced proliferation and production of TH+ neurons can be partially rescued by supplementing culture media with VEGF, the protein product of one HIF1α target gene. These studies suggest that the oxygen-sensing HIF1α factor and its downstream target gene effectors play a crucial role in embryonic NSCs and neurogenesis and may also have a substantial effect on the adult NSC population, though this is still unclear.

3.4.4. Mechanisms of HIF1 action in neural stem cells

HIF1α appears to regulate NSC properties through a variety of different molecules. The well-described HIF1α target genes encode proteins that are important for coping with limited oxygen, such as *Glucose transporter I* and *Enolase* (regulation of glucose metabolism) and *Vegf* (vasculature biology). HIF1α-dependent induction of *Igfbp1, 2, and 3*, whose protein products can alter the half-life and signaling potency of IGF-1, may also mediate the pro-proliferative effect of HIF1α activation in low oxygen conditions. As described above, VEGF is partially responsible for the positive effect of low oxygen culturing on proliferation of embryonic NSCs (Milosevic et al., 2007). It is also possible that HIF1α acts through the stem cell-promoting Notch signaling pathway. In primary embryonic rat NSCs, the canonical Notch signaling pathway is required for the beneficial effects of mild hypoxia (1% O_2) on NSC proliferation and self-renewal (Gustafsson et al., 2005). In fact, HIF1α can bind to Notch-responsive promoters to promote transcription of Notch target genes in a C2C12 myoblast cell line (Gustafsson et al., 2005), an interaction that may also mediate the Notch-dependent effects of hypoxia on NSCs.

Importantly, there is some evidence that links the actions of HIF1α with other energy-sensing signaling pathways known to regulate NSC biology. For example, adult NSCs lacking FoxO3 exhibit reduced expression of genes involved in the hypoxia response, including *Ddit4*, *Ndrg1*, *Ero1l*, and *Vegfa* (Renault et al., 2009). The positive effect of low oxygen (2% O_2) culture conditions on neurosphere formation from wild-type NSC is not exhibited by *Foxo3 null* NSCs, further indicating a relationship between transcription factors important for NSC self-renewal and hypoxic signaling. In contrast, in other mammalian cell types, FoxO3 has been shown to indirectly inhibit HIF1α-mediated gene transcription in response to hypoxia (Bakker et al., 2007; Emerling et al., 2008). It is possible that FoxO3 both indirectly inhibits HIF-mediated transcription and directly modulates hypoxia-dependent gene transcription (Renault et al., 2009). The energy-sensing deacetylase SIRT1 and the signaling molecule mTOR have also been demonstrated to promote HIF signaling (Arsham et al., 2003; Brugarolas et al., 2004; Dioum et al., 2009; Dunlop and Tee, 2009; Land and Tee, 2007; Lim et al., 2010), expanding the potential connections between energy and oxygen-sensing signaling in NSCs. Future studies aimed at understanding the molecular interactions between HIF signaling and other established NSC transcription factor signaling modules, such as Bmi1-p16^{Ink4a}, p53-p21, and Wnt, should help unravel how cell-intrinsic NSC fate modulators interact with oxygen availability in the niche to regulate NSC fate (Gustafsson et al., 2005; Kippin et al., 2005; Lie et al., 2005; Mazumdar et al., 2009; Meletis et al., 2006; Molofsky et al., 2003, 2005, 2006).

3.4.5. The hypoxia connection between neural stem cells and brain cancer stem cells

While still in its infancy, research into signaling pathways downstream of oxygen sensing in NSCs will likely provide a greater understanding of NSC biology in developing, aging, and diseased brain states. Brain cancer stem cells, which are thought to be the self-renewing source of new cancer cells within a brain tumor (Galli et al., 2004; Singh et al., 2003; Vescovi et al., 2006), are often referenced in connection with NSCs as both populations self-renew, produce multiple differentiated neural cell types, and are known to localize near blood vessels. Indeed, there is some evidence to suggest that NSCs may be the source of some cancer stem cells (Jackson and Alvarez-Buylla, 2008; Jackson et al., 2006; Vescovi et al., 2006). Tumors are known to be a hypoxic environment (Ljungkvist et al., 2007). As in NSCs, HIF signaling seems to be critical for the maintenance of brain cancer stem cells when in hypoxic conditions (Heddleston et al., 2010; Jogi et al., 2002; Soeda et al., 2009). Interestingly, it has been proposed that brain cancer stem cells require a lower concentration of oxygen than NSCs to obtain the full pro-proliferative benefits of hypoxia (Panchision, 2009; Pistollato et al., 2009). Thus, distinguishing the similarities and differences in oxygen requirements and oxygen-sensing mechanisms and their downstream consequences between brain cancer stem cells and NSCs may illuminate vital biological properties of normal and malignant cell types.

4. Redox state in neural stem cell fate

Metabolic processes generate byproducts that have a significant impact on cellular function. In particular, oxidative phosphorylation in the mitochondria can produce reactive oxidative species (ROS) when oxygen is not fully reduced to H_2O. ROS are normally neutralized by antioxidants (*e.g.* ascorbic acid) and enzymes (*e.g.* Cu/Zn superoxide dismutase (SOD), Mn superoxide dismutase (SOD2) and catalase). However, under conditions of cellular stress, ROS can accumulate to high levels that lead to DNA damage and oxidation of lipids and proteins. High levels of ROS can eventually induce cell death through the activation of multiple signaling pathways, including the p53 pathway and NFκB signaling (Martindale and Holbrook, 2002; Vollgraf et al., 1999; Yin et al., 1998). Amplifying stem cell populations may have developed specific mechanisms to combat dangerous accumulation of free radicals that could potentially lead to the depletion of these important sources of regeneration, or, on the other hand, lead to the development of cancer through mutation accumulation. Indeed, NSCs cultured from early postnatal mice display a higher rate of mitochondrial activity, yet have lower ROS levels than differentiated neuronal and glial cells (Madhavan et al., 2006). The reduced ROS levels may be due to the higher expression of the mitochondrial uncoupling protein 2 (UCP2) and the antioxidant enzyme glutathione peroxidase in NSCs than in their differentiated counterparts both *in vitro* and *in vivo* (Madhavan et al., 2006). The expression of one of the main antioxidant enzymes, SOD1, has also been documented in NSCs of the postnatal SVZ, rostral migratory stream, and SGZ of the dentate gyrus (Faiz et al., 2006) and SOD2 expression is upregulated in embryonic NSCs during oxidative stress induced by a mitochondrial toxin (Madhavan et al., 2008), suggesting that NSCs critically depend on diverse antioxidant activities to preserve the balance of ROS. It would be informative to determine whether NSCs from adult mammals, and particularly

from older adults, have diminished antioxidant mechanisms and whether this is causally related to the significant reduction in NSC function with age (Kuhn et al., 1996; Molofsky et al., 2006).

Evidence from oligodendrocyte progenitor cells (OPCs), hematopoietic stem cells (HSCs), and NSCs indicates that ROS can also act as important regulators of the balance between stem cell self-renewal/proliferation and differentiation (Lekli et al., 2009; Noble et al., 2005; Prozorovski et al., 2008; Smith et al., 2000; Tothova et al., 2007). In fact, fluctuations in oxidative state of only 10–15% can influence the fate of a progenitor cell (Noble et al., 2005; Smith et al., 2000). In cultured OPCs, a reducing intracellular environment confers a better cellular response to mitogens for cell proliferation and survival whereas an oxidizing environment increases the cellular response to signals for differentiation and apoptosis (Noble et al., 2005).

There are reasons to believe that similar redox regulation of self-renewal and differentiation exists in NSCs. First, the growth factor bFGF used to culture NSCs reduces ROS levels in adult rat hippocampal NSCs grown at high density (Limoli et al., 2004b), suggesting that pathways that promote NSC self-renewal and proliferation may act, in part, through regulation of ROS, which in turn would help determine whether NSCs maintain their stem cell state or proceed to differentiation. Second, adult NSCs lacking FoxO1, FoxO3, and FoxO4 show reduced self-renewal capacity as well as increased levels of ROS (Paik et al., 2009). Because these FoxO1,3,4-null NSCs have altered expression of ROS-detoxifying enzymes, such as peroxiredoxin, glutathione peroxidase 1, and sestrin3 (SESN3), one mechanism by which FoxOs may contribute to NSC self-renewal is by limiting accumulation of ROS. Indeed, impaired self-renewal of FoxO1,3,4-null NSCs can be nearly fully rescued by exposure to the antioxidant N-acetyl cysteine (NAC) or expression of SESN3 (Paik et al., 2007). Furthermore, in embryonic NSCs, the deacetylase SIRT1 is upregulated by oxidative conditions and is necessary for the ability of oxidizing agents to drive NSCs to become astrocytes instead of neurons upon differentiation (Prozorovski et al., 2008). Thus, in addition to influencing the balance between self-renewal and differentiation, ROS can also alter the specific cell lineage choice of differentiating NSCs. Whether or not FoxO factors and SIRT1 interact in the response to ROS has not yet been studied in NSCs, but this interaction has been documented in other cell types (Brunet et al., 2004; Motta et al., 2004; van der Horst et al., 2004). More work is needed to determine how exactly these fate choices are made in response to ROS, that is, to dissect out whether ROS-responsive mechanisms operate differently in astrocyte, neuron, and oligodendrocyte differentiation.

5. Neurotrophic signaling, cellular energy metabolism, and neural stem cell fate

How do energy metabolism and neurotrophic signaling, which is an important determinant of embryonic and postnatal NSC fate, intersect to regulate adult NSCs? While the extent of information currently available on this topic is relatively limited, there are several compelling arguments for its further investigation. First, exercise and dietary restriction influence adult NSC proliferation and survival of neuronal progeny, in part, through neurotrophin signaling (Lee et al., 2000, 2002a,b; Li et al., 2008) (see Sections 6.1 and 6.2). Second, the intracellular signaling pathways involved in energy-sensing and the neurotrophin response are largely overlapping. This section will describe the role of neurotrophins in NSC function and will present the evidence for crosstalk between neurotrophin signaling and energy metabolism for the regulation of NSC fate.

Neurotrophins are secreted proteins that regulate the growth, survival, and/or function of nerve cells. This group of proteins includes BDNF, nerve growth factor (NGF), neurotrophin 3 (NT-3), and neurotrophin 4 (NT-4). Neurotrophins bind to neurotrophic receptors that include the tropomyosin receptor kinase (Trk) family of receptors (TrkA, TrkB, and TrkC) and p75 (p75Ntr) to transduce a cascade of intracellular signaling that begins with autophosphorylation of receptor tyrosine kinases. The neurotrophic receptor p75Ntr lacks an intracellular tyrosine kinase domain and acts to potentiate or inhibit the activation of Trk receptors in response to certain ligands (Barker and Shooter, 1994; Bibel et al., 1999; Clary and Reichardt, 1994; Dechant, 2001; Hantzopoulos et al., 1994; Huang and Reichardt, 2003; Verdi et al., 1994).

A prominent result of neurotrophin action on NSCs is the induction of neurogenesis, and many studies have investigated the neurogenic effect on NSCs derived from embryonic and postnatal brains. In embryonic NSC cultures, BDNF, NT-3, and NT-4 enhance neurogenesis and promote neurite outgrowth (Ghosh and Greenberg, 1995; Hosomi et al., 2003; Lim et al., 2007; Lu et al., 2008; Ohtsuka et al., 2009; Shen et al., 2010). Indeed, inhibition of TrkB and/or TrkC signaling in the embryonic brain inhibits NSC proliferation and delays neurogenesis (Bartkowska et al., 2007). In postnatal NSC cultures, BDNF, but not NT-3, promotes neuronal differentiation and neurite outgrowth (Ahmed et al., 1995; Shetty and Turner, 1998). The importance of neurotrophic signaling for hippocampal neurogenesis is demonstrated by the finding that deletion of the TrkB receptor in the postnatal brain leads to a significant reduction in postnatal hippocampal neural progenitor proliferation *in vivo* and *in vitro* (Li et al., 2008). Furthermore, mice completely lacking p75Ntr have reduced hippocampal volume, reduced neurogenesis, and increased neuroblast cell death (Catts et al., 2008). Multiple studies have shown that *p75Ntr* mutant mice are impaired in certain spatial memory tasks and have depressive tendencies (Catts et al., 2008; Peterson et al., 1999; Wright et al., 2004), phenotypes that have been linked with an impairment of neurogenesis from hippocampal NSCs. In addition, mice in which the neurotrophin NT-3 is specifically deleted in the brain beginning at development display a reduction in differentiation and survival of newly generated adult hippocampal neurons (Shimazu et al., 2006). These mice show diminished long-term potentiation (LTP) and impaired performance in the Morris Water Maze, a navigation task which tests hippocampal-dependent spatial memory (Shimazu et al., 2006). These studies using whole animal knock-out or brain-specific deletion of neurotrophic signaling components suggest that adult NSCs and their differentiating progeny rely on neurotrophins for normal function.

Indeed, several studies have indicated that neurotrophin signaling is important for adult NSCs. The neurotrophin receptor p75Ntr is expressed in a subset of proliferating NSC/neural progenitors in the adult SVZ (Giuliani et al., 2004; Young et al., 2007) and is required for neuronal induction by BDNF of adult SVZ NSCs *in vitro* (Young et al., 2007). In the adult hippocampus, the TrkB receptor is expressed throughout the DG, including in the NSC population (Li et al., 2008) and its expression is upregulated in adult hippocampal NSCs upon exposure to retinoic acid *in vitro*, allowing the neurotrophins BDNF and NT-3 to promote the maturation of differentiating neurons (Takahashi et al., 1999). The significance of neurotrophin signaling for adult NSCs and their progeny is likely to be revealed under circumstances of changing environmental stimuli that alter neurotrophin availability. For example, increased production of BDNF in the dietary restricted rodent brain promotes the survival of new neurons produced by adult hippocampal NSCs (Lee et al., 2000, 2002a,b). Furthermore, the TrkB receptor is required for the increase in hippocampal neural progenitor proliferation induced by voluntary exercise (Li et al., 2008) (see Sections 6.1 and 6.2). Further investigation of the roles of neurotrophins in adult NSCs would greatly expand our understanding of the confluence of factors involved in adult neurogenesis.

Neurotrophins BDNF, NGF, NT-3, and NT-4 have all been shown in NSCs to activate the PI3K/Akt pathway and the MAPK pathway (Nguyen et al., 2009; Ohtsuka et al., 2009). NT-3 and NT-4 can also activate the PI3K/Akt and MAPK pathways (Lim et al., 2007; Shen et al., 2010), although NT-3 has also been shown to inhibit the activation of the PI3K pathway by the growth factor FGF-2 (Jin et al., 2005). It is possible that the consequences of neurotrophins on intracellular signaling depend on timing and concentration of neurotrophin exposure as well as the presence of other stimulatory factors. Nonetheless, the shared signaling pathways of energy sensing molecules and neurotrophic factors suggest there is a great deal of crosstalk and interaction between these two modules that regulate NSC fate. For example, given that neurotrophins have been shown to regulate the expression of bHLH transcription factors, including Mash1/Ascl1, Math1, and NeuroD, in embryonic NSCs to influence neuronal differentiation (Ito et al., 2003), it is interesting to consider the possibility that other transcription factors downstream of energy-sensing modules, such as FoxO factors, may cooperate with bHLH transcription factors to influence the course of differentiation of NSCs. Another possibility is that under certain cellular conditions that alter energy metabolism, including a hypoxic or reducing state, the transcription and production of neurotrophins as paracrine factors in the NSC niche may be significantly modulated. Many questions regarding the elements and effects of neurotrophin signaling in the context of a changing cellular and systemic energy metabolism remain to be explored.

6. Effects of systemic energy metabolism on neural stem cell fate

NSCs are not only regulated by immediate signaling due to alterations in intracellular energy metabolism but are also influenced by changes to systemic energy availability and the subsequent organismal response. Fluctuations in net energy levels lead to a collection of cellular and systemic changes throughout the body. While the brain does not modulate its glucose and fat storage in the same way liver, muscle, and adipose tissues do in response to low energy availability, it is significantly affected by changing energy supply via metabolites, hormones, and other factors that can cross the blood–brain barrier. This section will focus on two contrasting manipulations of energy supply, dietary restriction and exercise, which impact hippocampal circuitry through the regulation of neuron survival or production from adult NSCs, respectively (Fig. 4).

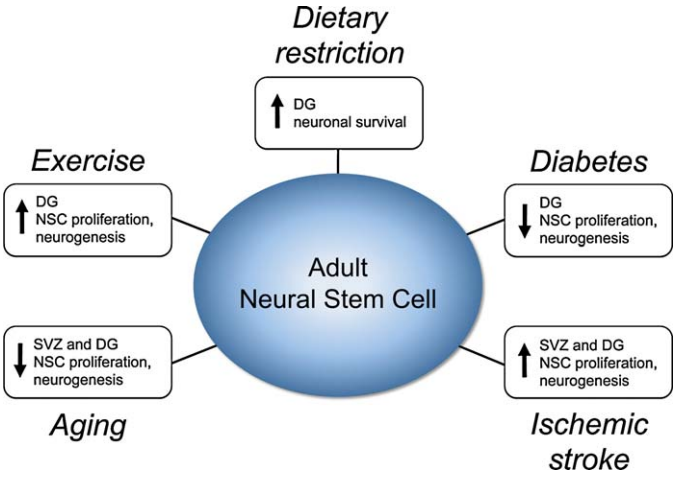

Fig. 4. Effects of altered systemic energy metabolism on adult NSC fate. Dietary restriction promotes survival of newborn dentate granule cells while exercise stimulates NSC proliferation and subsequent neurogenesis in the dentate gyrus (DG). Aging reduces proliferation of both subventricular zone (SVZ) and DG NSCs, leading to decreased neurogenesis. It is also thought that total numbers of NSCs decline with age. Diabetes is associated with reduced DG NSC proliferation and neurogenesis while ischemic stroke can lead to increased NSC proliferation and neurogenesis in both the SVZ and DG depending on the location of the occlusion.

6.1. Dietary restriction

Dietary restriction (DR) is the practice of reducing calorie intake (20–40%) without malnutrition. It has been shown to extend the average lifespan by up to 50% in many animal organisms, including mammals, and provides health benefits for non-human primates (Colman et al., 2009; Lakowski and Hekimi, 1998; Mair and Dillin, 2008; Weindruch and Walford, 1982, 1988). DR can delay the onset of age-related conditions such as cancer, heart disease, diabetes, and neurodegeneration (Hursting et al., 2001; Lane et al., 1999; Mattson, 2000). The multitude of health benefits conferred by DR is thought to result from the ensuing action of the energy-sensing pathways described above in many tissues of the body, including the brain (Bordone and Guarente, 2005).

Dietary restriction increases the survival of new neurons produced by NSCs in the adult dentate gyrus (DG). Adult rodents (mice and rats) that consume approximately 30% fewer calories than *ad libitum* control rodents through a 3-month regimen of feeding every other day display an increase in newly generated neurons in the DG granule cell layer (Lee et al., 2000, 2002a,b). Interestingly, neural progenitor proliferation is not affected by DR; rather, the survival of newly generated cells in the DG granule cell layer is increased. The increased production of brain-derived neurotrophic factor (BDNF) by CA1 hippocampal pyramidal neurons in response to DR may be partially responsible for DR-induced increase in neuronal survival (Lee et al., 2000, 2002a), likely by acting on immature neurons directly rather than on NSCs or neuronal progenitors. Another study employing a different method of DR (gradual increase of calorie restriction up to 40%) found no effect on neurogenesis, but instead revealed an increase in the production of glial cells in the hilar layer of the dentate gyrus (Bondolfi et al., 2004). The reasons for this disparity may be attributable to differences in feeding regimen in terms of age of DR initiation and subsequent brain tissue analysis or in the method of restriction (every other day feeding vs. daily 40% calorie reduction). Currently, a specific assessment of the effect of DR on long-term NSC maintenance has not been reported, but it is tempting to speculate how this diet regimen could influence the NSC population.

The energy-sensing pathways described in Section 3 are altered by DR regimens. SIRT1 protein levels are increased in the brain in response to DR (Chen et al., 2008; Cohen et al., 2004). DR may also increase enzymatic activity of SIRT1 given that its coenzyme NAD+ is present at higher levels in conditions of energy depletion. As DR is associated with promoting DNA damage repair, inducing heterochromatin states, and modifying gene expression (Vaquero and Reinberg, 2009), it is likely that the SIRT1 histone deacetylase is one of the mechanisms by which DR affects chromatin states and that this action has functional relevance for gene expression in NSCs in organisms undergoing DR. In addition to potential cell-intrinsic effects of SIRT1 on NSCs in response to DR, there is also evidence that actions of brain SIRT1 in the dietary-restricted mouse lead to significant changes in endocrine signaling, which could in turn play a role on NSCs. For example, DR-mediated reduction of serum IGF-1 levels depends on expression of SIRT1 in the brain (D.E. Cohen et al., 2009; Dunn et al., 1997; Masoro et al., 1992). Given the positive effect of IGF-1 on NSC proliferation and neuronal/oligodendroglial differentiation, it is possible that by reducing IGF-1 levels, DR could promote the maintenance of the NSC population by inhibiting excessive proliferation and premature differentiation. Interestingly, acute (6 days) DR reduces serum

IGF-1 levels in humans, but chronic (1 year+) DR does not alter IGF-1 levels in the serum (Fontana et al., 2008; Thissen et al., 1994). This observation emphasizes the important differences between humans and model species and also suggests that there may be differences between the effects of transient and prolonged food reductions on NSCs and neurogenesis.

In addition to alterations in levels of neurotrophins, SIRT1, and IGF-1 in the brain, DR leads to the upregulation of SIRT6, another Sirtuin family member involved in chromatin regulation (Kanfi et al., 2008), but does not affect SIRT2, SIRT3, SIRT4 expression in the brain (SIRT5 and SIRT7 brain expression regulation by DR has not yet tested) (Haigis et al., 2006; Hirschey et al., 2010; Wang et al., 2007). Activity of AMPK in the hippocampus is also increased in rats in response to 40% DR (Dagon et al., 2005). Whether DR influences Sirtuin and AMPK expression and/or activity specifically in the NSCs is not known yet. Finally, DR leads to a reduction in oxidative stress in the brain, which is achieved, in part, by increasing levels of the antioxidants coenzyme Q_{10} and α-tocopherol as well as the activity of redox enzymes on plasma membrane (Hyun et al., 2006). It remains to be determined whether changes in redox enzyme activities and oxidation occur in the NSC population in response to DR.

A more complete understanding of the effects of DR on NSCs and the surrounding niche is still required. For example, how does a lifetime of DR affect the age-associated decline in the pool of adult NSCs? Is there a similar effect of DR in the SVZ and the DG? How does DR influence the production of all different cell types from NSCs, including neurons, astrocytes and oligodendrocytes? And finally, given the positive effect of DR on NSC proliferation and neurogenesis, how does excess energy, as is often the case in obesity, affect the NSC population?

6.2. Exercise

While not equivalent to DR, exercise is an alternative method of lowering net energy levels and has consistently been shown to upregulate hippocampal NSC proliferation and neurogenesis in rodents (van Praag, 2008). The effects of exercise on human NSCs and neurogenesis are not known, but physical activity is associated with enhanced cognitive function in humans (Hillman et al., 2008). Voluntary running increases proliferation and neurogenesis in the mouse and correlates with enhanced performance in tasks testing long-term potentiation, spatial learning, and spatial pattern separation, of which the latter two are considered to be dependent on hippocampal adult neurogenesis (Clelland et al., 2009; Creer et al., 2010; van Praag et al., 1999a,b). Current evidence indicates that the beneficial effect of running on neurogenesis is mediated by the action of released hormones and growth factors. Both IGF-1 and VEGF individually mediate part of the effect of running on neurogenesis (Carro et al., 2000; Fabel et al., 2003; Trejo et al., 2001). Growth hormone receptor knock-out mice do not display increases in NSC proliferation due to running (Blackmore et al., 2009). The impact of growth hormone signaling on exercise-induced NSC proliferation is likely to be at least partially mediated by its effect on IGF-1 release. Neurotrophic signaling also appears to be required for the effect of exercise on NSC proliferation as mice lacking the TrkB receptor in the postnatal brain fail to show an increase in NSC proliferation in the DG after voluntary running (Li et al., 2008). Maturation of newly generated neurons in the hippocampus is also promoted by running (Redila and Christie, 2006; Zhao et al., 2006), emphasizing that these new neurons integrate and function in the existing hippocampal circuitry. Interestingly, running's effect on NSCs is specific to DG NSCs as exercise does not seem to affect proliferation of SVZ NSCs or their differentiation into olfactory bulb interneurons (Brown et al., 2003). The mechanisms that determine the specificity of the hippocampal NSC response to exercise are not yet clear.

A potential conundrum lies in the observation that exercise promotes hippocampal NSC proliferation and neurogenesis in a partially IGF-1-dependent manner and dietary restriction increases survival of new neurons produced by adult hippocampal NSCs but is associated with decreased serum IGF-1 levels. How can these phenotypes be reconciled? DR appears to promote the neuronal survival without affecting proliferation or actual neuronal production of NSCs (Lee et al., 2000), suggesting that the reduction in serum IGF-1 levels under DR is not a relevant factor for proliferation and neuronal differentiation from NSCs in this context. This emphasizes that the mechanisms underlying the beneficial effects of DR and exercise on NSCs and brain function in general are likely to be distinct or at least not completely overlapping.

7. Effects of aging and pathologies with deregulated energy metabolism and oxygen homeostasis on adult neural stem cells

Aging and many pathological conditions both within and outside the nervous system are associated with disordered energy metabolism and ROS imbalances. Given the evidence for a role of metabolism and its by-products in NSC fate presented above, it is important to consider how a pathological condition can ultimately lead to changes in NSC function as a consequence of altered energy metabolism. In this section, we will describe the consequences of aging as well as two examples of pathologies in which energy and oxygen homeostasis are deregulated (diabetes and ischemic stroke) on adult NSCs and neurogenesis (Fig. 4). An improved understanding of the effect of these and other medical conditions on NSCs has the potential to both uncover the networks of factors that contribute to NSC maintenance and differentiation and increase awareness of potential side effects of diseases and their treatments.

7.1. Aging

The inevitable process of aging leads to detrimental changes to the adult NSC SVZ and DG populations in both total number and proliferation, resulting in fewer newly produced neurons (Ben Abdallah et al., 2010; Bondolfi et al., 2004; Enwere et al., 2004; Kuhn et al., 1996; Lugert et al., 2010; Maslov et al., 2004; Molofsky et al., 2006). The age-dependent decline in neurogenesis is also observed in primates (Gould et al., 1999). While our understanding of these age-related effects on NSC fate is still not complete, the decline of NSC function with age appears to be mediated by alterations in both cell-intrinsic and cell-extrinsic mechanisms that promote NSC maintenance and neuronal differentiation. An age-related increase in the expression of the senescence regulator $p16^{INK4a}$ in NSC/progenitors is thought to be one cell-intrinsic cause of the diminishing the pool of adult NSC/progenitors (Molofsky et al., 2006). Levels of the growth factors bFGF, VEGF, and IGF-1 decrease with age in the hippocampus (Shetty et al., 2005) and may contribute to the reduction in progenitor proliferation and production of neurons and oligodendrocytes (Hsieh et al., 2004) in the aging brain. Furthermore, plasma IGF-1 levels decline with age in rodents and humans (Rudman, 1985; Rudman et al., 1981). However, given the stimulatory effect of IGF-1 on NSC proliferation and the need to preserve a pool of relatively quiescent adult NSCs, it is not obvious what would be the net effect of declining IGF-1 levels during aging on NSC proliferation and neurogenesis. Heterochronic parabiosis experiments in which a young and old mouse share a circulatory system would help tease apart the systemic effect of the aging organism on NSC function (Conboy et al., 2005).

The brain also displays aging-related declines in metabolic function that may directly and indirectly influence NSC maintenance. There is an age-associated increase in oxidative damage to nuclear DNA (Hamilton et al., 2001), protein oxidation (Cini and Moretti, 1995), and lipid oxidation (O'Donnell and Lynch, 1998). Furthermore, the total antioxidant capacity of the hippocampus and several other brain structures is reduced in old brains (Siqueira et al., 2005). If these age-dependent alterations occur in NSCs themselves, a reduction in cell survival may result and contribute to the depletion of the aging NSC pool. A cell type in the brain with such altered metabolic and mitochondrial function are astrocytes. Astrocytes from old mice display reduced cell growth, decreased mitochondrial membrane potential, and are more sensitive to oxidative stress compared to astroctyes from young adult mice (Lin et al., 2007). "Old" astrocytes also have a reduced capacity to provide neuroprotection in co-cultures with NGF-differentiated PC12 cells. It remains to be determined whether such metabolic changes in cells in close proximity of NSCs *in vivo* (part of the NSC niche) during aging lead to alterations in NSC function. An important unanswered question related to this observation is whether the ratio of NAD+/NADH is altered in the aging NSC niche and how this impacts NAD+-dependent metabolic pathways and enzymes (Houtkooper et al., 2010), such as the family of Sirtuin deacetylases. Finally, the deregulation of cellular metabolism and redox homeostasis that occurs in aging has also been observed in many neurodegenerative diseases, including Alzheimer's disease and multiple sclerosis (Bishop et al., 2010; Gilgun-Sherki et al., 2004; Penberthy and Tsunoda, 2009), suggesting that NSC self-renewal and differentiation may be altered in such brain pathologies.

7.2. Diabetes as an example of disordered metabolism

Diabetes is a common metabolic disorder that is characterized by an inability to either produce insulin (type I) or to respond to insulin (type II). As a result, inappropriately managed diabetes leads to unregulated glucose levels, either excessive amounts of glucose (hyperglycemia) or insufficient levels of glucose (hypoglycemia), both of which can be detrimental to neurogenesis originating from adult NSCs.

Several independent studies of rodent diabetes models have indicated that diabetes is associated with reduced neural progenitor proliferation and neurogenesis. Type II diabetic mice that carry a mutation in the leptin receptor and streptozotocin (STZ)-induced type I diabetic mice and rats display reduced proliferation and neurogenesis in the DG (Jackson-Guilford et al., 2000; Saravia et al., 2004; Stranahan et al., 2008a; W.J. Zhang et al., 2008). The mechanism appears to be independent of the direct action of glucose and insulin in the DG since levels of these molecules in the whole hippocampus do not differ between diabetic and control animals (Stranahan et al., 2008a). Glucocorticoid signaling may mediate the negative effects of diabetes on brain function, and possibly on NSC fate given the negative effect of elevated corticosteroid levels on hippocampal neurogenesis in old mice (Cameron and McKay, 1999). Indeed, diabetic mice show increased levels of the steroid hormone corticosterone and reducing corticosterone levels back to control levels of healthy mice rescues the diabetes-induced impairment of learning and memory (Stranahan et al., 2008a). Diabetes is also associated with vasculature dysfunction which may also contribute to the changes that occur to NSC that lie close to blood vessels in both the SVZ and DG. Hypoglycemia, which can be caused by excessive amounts of insulin in diabetes treatment, induces a transient increase in DG neural progenitor proliferation followed by reduced progenitor proliferation below baseline as well as loss of newly formed DG granule neurons in rats (Suh et al., 2005). Thus, glucose imbalance that occurs in diabetes interferes with new neuron production and survival from adult NSCs. Following NSC number and multipotency throughout the life of diabetic model rodents will be key to determine how NSC number and function change with age in this metabolic disease.

It is possible that defects in neurogenesis have a functional consequence as learning and memory are compromised in diabetic mice (Alvarez et al., 2009; Stranahan et al., 2008b). This may also play a role in the cognitive decline observed in humans with diabetes (Kodl and Seaquist, 2008). However, a causal relationship between reduced adult neurogenesis in diabetes and impaired cognitive function has not yet been shown.

Interestingly, a widely used medication for diabetes is the AMPK activator metformin (Fryer et al., 2002; Zhou et al., 2001). Since AMPK may be important for proliferation and stress resistance of NSCs (Section 3.2), it is possible that metformin treatment provides an additional benefit to patients with diabetes by preserving NSC function or at least inhibiting a reduction in NSC function that is associated with diabetes. In fact, type II diabetic rats treated with metformin display an increased in hippocampal NSC proliferation and neuroblast production compared to control diabetic rats (Hwang et al., 2010), suggesting there may be similar consequences of metformin treatment in human diabetic patients. The mechanism of metformin's effects has not been established, but it would be important to determine whether it is AMPK-dependent and whether downstream activation of Sirt1 by AMPK is functionally relevant in NSC fate (Canto et al., 2009).

7.3. Ischemic stroke as an example of severe glucose-oxygen deprivation

Ischemic stroke is highly prevalent in the aging population and a leading cause of chronic disability in the United States (Lloyd-Jones et al., 2009). It is often caused by a thrombosis in a small blood vessel in the brain, but may also result from atherosclerosis. Upon loss of blood supply for a period of time, neural cells become deprived of glucose and oxygen. Persistent loss of blood supply eventually leads to anoxia-induced death of cells, including NSCs, in the vicinity of the blockage. However, transient ischemic stroke in both rodents and humans has been shown to induce proliferation of adult SVZ and DG NSCs and subsequent neurogenesis, a consequence that could potentially aid the recovery of the brain (Arvidsson et al., 2002; Jin et al., 2006; Macas et al., 2006; Marti-Fabregas et al., 2010; Nakatomi et al., 2002; Yagita et al., 2001).

Several metabolism-related factors are likely to contribute to the proliferative and neurogenic effects on NSC following ischemic stroke. First, stroke induces hypoxia. As described in Section 3.4, a mild hypoxia can induce NSC proliferation and neurogenesis. Second, hypoxia may also induce changes in NSCs indirectly through the increased production of angiopoietin-2 in endothelial cells following stroke (Hackett et al., 2000; Lin et al., 2000; Liu et al., 2007; Mandriota and Pepper, 1998; Mandriota et al., 2000; Oh et al., 1999). A growth factor for angiogenesis, angiopoietin-2 stimulates migration and differentiation of adult SVZ NSCs into neurons *in vitro* (Liu et al., 2009). The beneficial effect of angiopoietin-2 on NSCs appears to be cell-intrinsic as it induces the binding of the transcription factor C/EBPβ on the promoter of the β-III tubulin neuronal gene (also known as Tuj1) and through down-regulation of pro-glial and anti-neurogenic BMP cytokines. The effect of ischemic stroke on NSC proliferation and neurogenesis may also be mediated by increased IGF-1 expression and release by astrocytes as well as greater expression of IGF-1 receptors in neural progenitors of the SVZ and DG (Yan et al., 2006). Infusion of antibodies against IGF-1 inhibits the proliferation of neural progenitors following ischemia, suggesting that IGF-1

action on NSCs may be one of the effectors of ischemia-induced neural progenitor proliferation. An unexplored question is whether the energy-sensing AMPK and Sirtuin enzymes are activated by glucose deprivation during ischemic stroke and whether this has functional consequences for NSCs. Finally, considering that the post-ischemia environment is characterized by a significant degree of inflammation (Hoehn et al., 2005), which can be damaging for neurogenesis and survival of new neurons (Carpentier and Palmer, 2009), dietary manipulations and exercise potentially constitute a therapeutic intervention to promote neuronal survival and functional neurogenesis in stroke victims.

8. Conclusions

Adult NSCs are a population of self-renewing cells that contribute new neurons, astrocytes, and oligodendrocytes to the brain throughout life. Evidence for their function in memory formation, mood regulation, and regeneration following tissue injury provides compelling motivation for further investigation of NSC biology. The proliferation, survival, and differentiation characteristics of adult NSCs are influenced by a variety of factors, many of which are associated with energy metabolism and can be altered through lifestyle interventions that include dietary restriction and exercise. It is also becoming clear that energy-sensing molecules interact with intracellular pathways known to orchestrate NSC self-renewal, proliferation, and differentiation, indicating the significance of metabolism dynamics for normal NSC biology. As interest in the subject of energy metabolism in NSC fate grows, we will inevitably achieve a better understanding of the molecular mechanisms that determine adult NSC fate in response to changing energy availability both in the local NSC niche and in the entire organism.

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