Published in final edited form as:

Cell Mol Life Sci. 2014 November ; 71(21): 4221–4241. doi:10.1007/s00018-014-1686-0.

Metabolic circuits in neural stem cells

Do-Yeon Kim,

Department of Pathology and Laboratory Medicine, Weill Cornell Medical College, New York City, NY 10065, USA

Inmoo Rhee, and

Department of Pathology and Laboratory Medicine, Weill Cornell Medical College, New York City, NY 10065, USA, Department of Biochemistry, Gachon University School of Medicine, Incheon 406-799, Korea

Jihye Paik

Department of Pathology and Laboratory Medicine, Weill Cornell Medical College, New York City, NY 10065, USA

Jihye Paik: jep2025@med.cornell.edu

Abstract

Metabolic activity indicative of cellular demand is emerging as a key player in cell fate decision. Numerous studies have demonstrated that diverse metabolic pathways have a critical role in the control of the proliferation, differentiation and quiescence of stem cells. The identification of neural stem/progenitor cells (NSPCs) and the characterization of their development and fate decision process have provided insight into the regenerative potential of the adult brain. As a result, the potential of NSPCs in cell replacement therapies for neurological diseases is rapidly growing. The aim of this review is to discuss the recent findings on the crosstalk among key regulators of NSPC development and the metabolic regulation crucial for the function and cell fate decisions of NSPCs. Fundamental understanding of the metabolic circuits in NSPCs may help to provide novel approaches for reactivating neurogenesis to treat degenerative brain conditions and cognitive decline.

Keywords

Neural stem/progenitor cells; Metabolism; Self-renewal; Differentiation

Introduction

Increasing evidence suggests that there is a functional coupling between energy metabolism, homeostatic regulation of adult stem cells, and tissue functions [1–3]. Stem cells fine-tune the balance between self-renewal and differentiation, thereby sustaining tissue homeostasis throughout adult life. Owing to their unique microenvironment (a hypoxic niche) and their

distinct cell cycle characteristics (often quiescent in adults), stem cells have a distinctive metabolic gene expression pattern and thus may rely on various metabolic pathways. Indeed, a recent metabolomics study has shown that proliferating neural stem/progenitor cells (NSPCs) in the brain had a metabolic state that was distinct from that of proliferating Schwann cells and differentiated neural cells [4]. Impaired NSPC homeostasis and/or reduced production of newborn neurons are associated with depression, dementia, and neurodegenerative disorders, such as Alzheimer's disease. Given the therapeutic potential of endogenous NSPCs, a fundamental understanding of how metabolic changes affect cellular function and fate is necessary. To this end, this review will summarize the metabolic circuits and the key factors involved in adult NSPC homeostasis.

For more than 100 years, it was generally accepted that new neurons are not generated in adult brains. Since the late 1950s, this concept has been refuted by observations of cell division occurring in adult mouse/rat brains through in vivo labeling of newly generated cells with tritiated thymidine or synthetic thymidine analogs [5–8]. Indeed, functional neurons are continuously generated throughout life in two specific 'neurogenic' regions within the intact adult brain: the subgranular zone (SGZ) of the hippocampal dentate gyrus for dentate granule cells, and the subventricular zone (SVZ) of the lateral ventricle wall in the forebrain mainly for interneurons in the olfactory bulb [9–11]. These newborn neurons contribute to the structural and functional integrity of the adult forebrain [12]. A recent study showed that 700 neurons are added daily in the dentate gyrus of adult human brains [13]. Given that the cycling neuronal population is approximated to constitute 35 % of all hippocampal neurons, adult neurogenesis is a dynamic process. These adult-born neurons functionally integrate into the synaptic circuitry of the brain and perform specific functions, including olfaction, learning and memory, pattern separation, and mood control [14].

During adult neurogenesis, NSPCs go through defined stages (Fig. 1a). The criteria for developmental milestones in adult hippocampal neurogenesis include morphologies, marker expression profiles, proliferation capacities, and electrophysiological properties: (1) 'type-1 cells', which are the radial-glia-like stem cells, are rarely dividing predominant precursors. These cells express GFAP and nestin and give rise to type-2 cells by asymmetric division. (2) 'Type-2 cells', which have an irregularly shaped dense nucleus, are transiently amplifying lineage-determined progenitor cells. These cells still express nestin, but are negative for GFAP. (3) 'Type-3 cells', which express the immature neuronal marker doublecortin (DCX) but are nestin-negative, are migratory neuroblasts. These cells have a round-shaped nucleus and are preparing to exit the cell cycle [15, 16]. Similar to the hippocampal SGZ, three different cellular architectures exist in the SVZ. Slowly dividing GFAP-positive type B stem cells give rise to type C transit-amplifying cells, which proliferate rapidly. Subsequently, these type C cells produce type A neuroblast cells, which migrate in the rostral migratory stream towards the olfactory bulbs from the SVZ of the lateral ventricle. The majority of the cells in the adult SVZ are migrating neuroblasts that continue to proliferate [17, 18].

Despite notable progress toward understanding NSPC biology in recent decades, various properties of NSCs remain to be identified. Whereas the tri-potency of NSCs, that is, the capacity of NSCs to generate neurons, astrocytes, and oligodendrocytes, has been well

defined in culture after isolation, it remains to be elucidated whether multiple neuronal cell types can be generated by a single adult NSC. It remains controversial whether other adult brain regions, excluding the SVZ and the SGZ, have NSCs, and if so, if these NSCs can give rise to functional neurons that are ready to integrate into pre-existing neural circuits. Indeed, a recent study demonstrated the generation of interneurons within the striatum. Surprisingly, there is a robust neurogenesis and DCX-positive neuroblasts in the striatum of adult humans. Interestingly, striatal neurogenesis was less detected or not detected in patients with Huntington's disease [19]. Because the role for olfaction is diminished in humans, adult striatal neurogenesis may provide insight on the significance of the NSPCs in the lateral ventricle wall of the brain. Additionally, the environmental cues that control region-specific neurogenesis and how those stimuli regulate the fate of NSPCs remain to be elucidated.

Metabolic adaptation to the microenvironment

The fate of stem cells is controlled by extracellular cues and intrinsic factors. Adult stem cells are hierarchically organized and maintained in a special microenvironment termed the "niche" [20]. NSCs receive signals from neighboring blood vessels, the extracellular matrix proteins found in neurogenic niches, the cerebrospinal fluid, and other brain regions (Fig. 1a). This unique microenvironment and the distinctive morphology of NSCs allow these cells to receive and integrate signals to control their cell cycle.

Response to hypoxic environment

The mammalian brain is a highly oxidative organ, and it accounts for approximately 20 % of bodily oxygen consumption. However, the partial pressure of oxygen in the brain, which ranges between 0.55 and 8 %, is lower than that of ambient air [21]. It has been proposed that stem cell niches, including neurogenic ones, are hypoxic, and stem cells have a selective survival advantage by maintaining an undifferentiated state and low oxidative stress [22]. Furthermore, NSPCs implanted into hypoxic areas of the brain maintain the viability of the surrounding neural cells through HIF-1 α -mediated secretion of vascular endothelial growth factor (VEGF), which demonstrates the specialized adaptability of these cells under conditions of hypoxic insult [23]. Interestingly, multipotent NSCs and oligodendrocyte progenitors (OPCs) are more susceptible to apoptosis at 20 % oxygen than are committed neuronal progenitors, and reduced oxygen promotes multipotency [24]. In line with this finding, an in vitro culture with reduced levels of oxygen enhances survival, alters proliferation, and preconditions NSPCs toward neuronal differentiation, while maintaining them as undifferentiated NSPCs [25–27]. Notably, the dependence on hypoxia inducible factor-1 α (HIF-1 α) expression for the maintenance of the metabolic phenotype was tested in NSPCs. The deletion of exon 1 of the *Hif1a* in NSPCs enhanced oxidative phosphorylation during glycolytic inhibition without changing other parameters of metabolism, including their ability to survive prolonged hypoxia. This study indicated that NSPCs are intrinsically dependent on glycolysis for their survival and that HIF-1 α does not mediate resistance to hypoxia [28].

Several studies have attempted to explain the regulatory links between oxygen concentration and the functions of stem cells. For example, the importance of HIF-1 α -Wnt/ β -catenin signaling in adult hippocampal neurogenesis in the presence of a hypoxic niche has been

demonstrated [29]. Interestingly, this signaling axis does not operate in differentiated cells. Consistent with these findings, the downstream transcriptional target of Wnt signaling, for example, matrix metalloproteinase 9 (MMP9), contributes to the increased NSPC proliferation and migration [30].

To maintain the stemness, embryonic and adult stem cell populations have unique intracellular signaling and associated gene expression signatures. A lowered oxygen environment alters the signaling pathways in stem cells (Fig. 1b). The Notch pathway is conserved to regulate the stem or progenitor cell fates in most multicellular organisms [31], and hematopoietic and neuronal cell differentiation is inhibited by the Notch pathway [32]. Additionally, active Notch signaling regulates NSPC numbers through the inhibition of cell death [33]. Hypoxia activates the expression of Notch-responsive genes, such as HES1 and HEY2, by recruiting HIF-1 α to the promoters of these genes [34]. The activated Notch intracellular domain enhances the recruitment of HIF-1 α to its target promoters and derepresses HIF-1 α function to modulate the responses to hypoxia [35]. In addition, Wnt signaling is another critical regulator of stem cells, which promotes the expansion and self-renewal of NSPCs [36]. Wnt-activated β -catenin enhances HIF-1 α -mediated transcription, which suggests that this critical signaling pathway may regulate cell survival and adaptation to hypoxia [37]. In contrast, maintaining NSPC cultures in 20 % oxygen leads to mitotic arrest and promotes glial differentiation through repressing bone morphogenetic protein (BMP) signaling [38]. These lines of evidence support the idea that oxygen tension dynamically regulates the developmental signaling necessary for cell fate decision and maturation and may account for the malfunction of the NSPCs during diseases and aging.

Reduced oxygen availability induces a distinct gene expression pattern in stem cells. For example, HIF-2 α directly activates Oct4, an essential gene for sustaining the undifferentiated state of embryonic and adult stem cells [39]. These key genes are transcriptionally regulated by large regions of H3K27 methylation and small regions of H3K4 methylation [40, 41]. Currently, it is not entirely clear whether chromatin-based regulation is affected by the oxygen level.

Response to inflammation

A decade ago, studies have found that inflammation could block adult hippocampal neurogenesis. In particular, inflammatory factors, especially IL-6, are detrimental for NSPC survival and differentiation to neurons [42, 43]. In addition, inhibiting inflammatory microglia activation may reduce the death of newborn neurons [44] and/or attenuate hypothalamic–pituitary–adrenal axis activation [45]. Furthermore, a recent study highlights that blockade of IL-6 could largely restore hippocampal neurogenesis in a mouse model with exaggerated inflammatory responses [46]. In line with this, IL-6 and BMP act in concert to inhibit neurogenesis and promote astrocyte differentiation [47]. Because astrocytes and neuronal precursor cells share common cellular origin, it would be possible that suppression of neurogenesis by IL-6 might be due to increased astrocyte differentiation at the expense of neuronal progenitor cells. Further, it is suggested that the Janus Kinase and Signal Transducer and Activator of Transcription (JAK/STAT) 3 pathway initiated by the IL-6 family of cytokines is essential for astrocyte differentiation from NSCs [48]. Consistently,

MEK, a key regulator of gliogenesis, modulates gp130-JAK/ STAT3 cascade, a major cytokine-signaling pathway that promotes astrocyte differentiation [49]. Growing evidence establishes that inflammation may contribute to dysfunction of NSPCs, suggesting anti-inflammatory metabolic intervention may restore adult hippocampal neurogenesis and neuroplasticity.

Metabolic transition

Metabolic flexibility supports divergent cell fate through coordination with cellular signaling and genetic/epigenetic regulation [50]. This plasticity in the metabolic circuit is especially important to stem cells because they possess relatively low turnover rate and differentiate into specific cell types. Emerging evidence has shown that metabolic demands for maintaining stemness differ from those for differentiated cells. Dividing progenitor cells depend more on aerobic glycolysis, whereas differentiated progeny relies on energetically efficient oxidative phosphorylation [51, 52]. Morphologically, there is a loss of perinuclear mitochondrial arrangement accompanied by a low ATP/cell content, a high rate of oxygen consumption, and an increase in lipid droplets along with the loss of multipotency in differentiating primate stem cells [53].

Similarly, NSPCs show a higher glycolytic demand for energy production, proliferation and survival than do neurons in culture. The glycolytic rate of NSPC declines significantly during differentiation to neurons. Thus, NSPCs display upregulated lactate production, enhanced intracellular lactate dehydrogenase activity, and elevated glucose consumption [28]. In contrast to normal NSPCs, a recent study showed that glioma stem cells are less glycolytic than their differentiated progeny. Glioma stem cells have significantly higher intracellular ATP levels and lower glucose uptake and lactate production than do differentiated glioma cells, which support the notion that glioma cancer stem cells rely more on oxidative phosphorylation [54]. Together, the metabolic state of stem cells tends to be different from that of differentiated progeny and those under different disease contexts, including cancers.

Metabolic pathways in neural stem cells

Unique metabolic features in stem/progenitor cells

In the 1920s, Otto Warburg proposed that cancer cells generate most of their energy via the non-oxidative breakdown of glucose under aerobic conditions, instead of via the oxidation of pyruvate by the Krebs cycle. This aerobic glycolysis conflicts with the idea of the Pasteur effect, i.e., that the rate of glycolysis decreases significantly in the presence of oxygen in most mammalian cells. Emerging evidence suggests that the Warburg effect provides a biosynthetic substrate for cells that have a high need for growth and proliferation [55]. Consistently, the metabolic features of stem cells resemble the features of cancerous cells. Adult stem/progenitor cells are under high pressure to maintain tissue homeostasis by replacing damaged and expired cells: 700 new neurons are born in the adult hippocampus, and 200 billion red blood cells are produced daily. Highly proliferative embryonic stem cells (ESC) rely on glycolysis, regardless of the oxygen availability [56]. During the “reprogramming” from fibroblasts to induced pluripotent stem cells (iPSCs), epigenetic and

metabolic changes occur [57]. Glucose utilization and lactate production are higher in iPSCs, whereas oxygen consumption is lower, than in parental fibroblasts. Additionally, iPSCs have shown increased levels of glycolytic enzymes and reduced levels of factors related to electron transport chains [58]. Notably, the glycolytic changes precede the expression of pluripotency markers [57]. This result suggests that somatic cells require the transition of bioenergetics from mitochondrial oxidation to glycolysis prior to reprogramming into the pluripotent state and that the metabolic changes may not be a simple consequence of acquired pluripotency. Importantly, multiple developmental pathways, such as the Notch, Sonic hedgehog and Wnt pathways, regulate stem cell self-renewal and cellular metabolism [59–63]. It is plausible that specific activation of developmental pathways may drive ‘stem cell-specific metabolic circuits’. Factors and pathways discussed here are summarized in Table 1.

Glycolysis

In mammals, glucose is a pivotal source of cellular carbon; it is also an important fuel that is utilized in a conserved set of metabolic pathways (Fig. 2). Glucose is imported into cells via glucose transporters (GLUT) by facilitated diffusion. Intracellular glucose is phosphorylated by hexokinase (HK) to glucose-6-phosphate (G-6-P), and through glycolysis, it eventually yields pyruvates. In the cytosol, pyruvate is converted to lactate. Alternatively, upon transportation into the mitochondrial matrix, pyruvate is oxidated to acetyl-CoA or carboxylated to form oxaloacetate or malate. Pyruvate oxidation is catalyzed by the multienzyme complex pyruvate dehydrogenase (PDH), the activity of which is highly regulated by its products (acetyl-CoA and NADH) as well as by phosphorylation by PDH kinase (PDK). Acetyl-CoA, the common end product of glucose and fatty acid oxidation, conveys the carbon atoms within the acetyl group to the citric acid cycle to be oxidized for the production of GTP (or ATP) and reducing equivalents NADH₂. Because citric acid cycle intermediates are used for biosynthetic pathways (e.g., amino and nucleic acids), they are constantly removed from the cycle and therefore need to be replenished through an anaplerosis reaction. At the mitochondrial inner membrane, the reducing equivalents (NADH₂ and FADH) and succinate from the citric acid cycle transfer electrons to the electron transport chain for oxidative phosphorylation.

The differentiation of ES cells to NSPCs accompanies a relative increase in glycolysis with decreased mitochondrial oxidative phosphorylation, which suggests the importance of glycolytic regulation in NSPCs [64]. Choice of glycolytic metabolism in proliferating and neurogenic NSPCs is likely to be essential to provide building blocks necessary for cell division and growth. Glycolysis provides precursors for amino acids and nucleic acid synthesis. Hypoxic niche for NSPCs also promotes anerobic glycolysis over oxidative phosphorylation to produce ATP and to minimize oxidative stress. Although glycolysis generates only two ATP per glucose, this process is rapid enough to produce a larger fraction of ATP than mitochondrial oxidative phosphorylation [65]. Concordantly, adult NSPCs express mRNAs and proteins for glycolytic metabolism such as GLUT1 and GLUT3 [66]. Interestingly, stress conditions, such as hypoxia, regulate the densities of these glucose transporters in NSPCs. Developmental cues regulate the glycolysis necessary for neurogenesis. A key mitogen, Sonic Hedgehog, induces the expression of HK2 in cerebellar

granule neuron progenitors [67]. Following glucose import, HK2-mediated glycolysis is essential to cerebellar neurogenesis.

Adult neurogenesis is impaired in obese and diabetic animal models in vivo and also by a diabetic milieu in vitro [68, 69]. As excessive glucose inhibits the proliferation and differentiation of NSPCs and as GLUT1 is required for cell growth during development, it has been hypothesized that a high level of glucose downregulates GLUT1 expression in the late stage of development and decreases glucose uptake in NSPCs. This may lead to abnormal proliferation of NSPCs and thereby results in neural tube anomalies in the embryo in pregnant diabetic animals [70]. Clearly, functional glycolysis is critical for functional NSPCs and normal development.

Pentose phosphate pathway

The glycolytic intermediate G-6-P is utilized for glycogen synthesis or the pentose phosphate pathway (PPP). The PPP in the cytosol of all cells is divided into two branches: the oxidative PPP and the non-oxidative PPP [71]. The oxidative PPP utilizes G-6-P as a substrate through the action of glucose-6-phosphate dehydrogenase (G6PD). By doing so, the primary function of the oxidative PPP is to form reduced nicotinamide adenine dinucleotide phosphate (NADPH), which is important for reductive biosynthesis and for the suppression of cellular oxidative stress by maintaining reduced glutathione (GSH) levels. In the non-oxidative PPP, the production of ribose-5-phosphate and/or xylulose-5-phosphate is important for nucleic acid and nucleotide synthesis or functions as a signaling molecule that regulates transcription [72]. In addition to the PPP, a small amount of G-6-P can enter the hexosamine biosynthetic pathway (HBP), which leads to the formation of UDP-N-acetylglucosamine (GlcNAc), a monosaccharide donor for the O-GlcNAcylation of various proteins. Because the HBP requires not only glucose but also acetyl-CoA and glutamine, it may serve as a metabolic sensor that links the metabolic status to several cellular processes [73].

An in vitro study demonstrated that NSPCs are more sensitive to pharmacological inhibition of the PPP by 6-aminonicotinamide than are differentiated neurons. This result suggests the active reliance of NSPCs on this metabolic pathway [28]. Importantly, studies in mammalian cells and yeast have shown that cellular oxidative stress redirects glucose into the PPP by a feedback regulatory loop that quells the rise in reactive oxygen species (ROS) by generating NADPH [74, 75]. Recently, we demonstrated that FoxO3 deficiency impairs the oxidative arm of the PPP by decreasing phosphogluconate dehydrogenase expression even in the face of increasing ROS [76]. This metabolic alteration may exacerbate oxidative stress in FoxO3-deficient NSPCs. Transketolase, an enzyme that mediates the non-oxidative arm of the PPP, is necessary for the proliferation, growth, and migratory abilities of cultured hippocampal NSPCs. Its knockdown or thiamine deficiency-induced inhibition of transketolase and dysfunctional PPP contributes to impaired hippocampal neurogenesis [77]. Together, these lines of evidence indicate that the importance of the PPP in the control of NSPC function is beginning to emerge.

Glutamine metabolism

Glutamine is the most abundant amino acid in plasma (~0.57 mmol/L) and intracellular muscle fluid (~19.45 mmol/L) [78]. It is an important energy source that also supplies the nitrogen for nucleotide synthesis and maintains non-essential amino acid pools. Glutamine metabolism provides a carbon source that facilitates the cell's ability to use glucose-derived carbon and TCA cycle intermediates as biosynthetic precursors [79]. It is converted to glutamate in reactions catalyzed by a glutaminase (GLS) in which it either donates the amide nitrogen to biosynthetic pathways or is released as ammonia. Glutamate is the most abundant amino acid inside a cell that is generated by a mitochondria-associated GLS (Fig. 3). It goes through a second deamination by glutamate dehydrogenase to yield α -ketoglutarate (α -KG), a TCA cycle intermediate and substrate for dioxygenases that modifies proteins and DNA [80]. In addition, it serves as a precursor of GSH, the major endogenous antioxidant, through direct participation in the neutralization of free radicals and ROS. Glutamine, through the aspartate–malate shuttle, increases the NADPH/NADP (+) ratio, which can suppress oxidative stress [81]. Therefore, glutamine metabolism can contribute to the control of redox balance through GSH biosynthesis and/or NADPH production [82]. Furthermore, glutamine flux regulates mTOR activity, translation and autophagy to coordinate cell growth and proliferation [83]. Cellular uptake of glutamine and its subsequent efflux through SLC7A5/SLC3A2, a bidirectional transporter of glutamine–leucine and other essential amino acids, is the rate-limiting step that activates mTOR.

Adult NSPCs express GLS and incorporate glutamine into the cellular GSH pool, which is necessary for maintaining redox homeostasis [76]. Interestingly, the expression of GLS was similar in wild-type NSPCs and FoxO-null NSPCs, but the activity of GLS was altered in FoxO-null NSPCs. MYC is the most well-characterized regulator of glutaminolysis [84]. Nevertheless, how glutamine metabolism functionally controls NSPCs given MYC as a critical component of the maintenance of stem cell metabolism (see below) needs to be further characterized. Together, recent studies have reinforced the importance of glutamine metabolism in stem cell redox homeostasis, proliferation, protein and nucleic acid metabolism, and epigenetic modifications.

One-carbon metabolism

One-carbon transfers mediated by folate play essential roles in major cellular processes, including nucleic acid biosynthesis, amino acid metabolism, and vitamin and methyl group biogenesis [85, 86]. This transfer is composed of the cytosolic/mitochondrial folate cycles and the methionine cycle. The folate cycle is involved in purine and pyrimidine synthesis via the metabolism of tetrahydrofolate (THF). Folate exists in either oxidized or reduced forms, and each serves as a donor of a single carbon in different cellular reactions. The intermediate form methylene–THF is used for the conversion of dUMP (deoxyuridylylate) into dTMP (thymidylylate). The oxidized form of formyl–THF is utilized for the de novo synthesis of purines. Carbon from methyl–THF (reduced form) is used to methylate homocysteine to generate methionine. This reaction is catalyzed by methionine synthase (MTR) and its cofactor vitamin B12. This methionine cycle converts methionine to S-adenosyl methionine (SAM), which is a methyl donor for numerous reactions. SAM becomes S-adenosyl homocysteine (SAH), which is then converted to homocysteine.

Previous studies have demonstrated the critical role of folate in NSPC self-renewal and differentiation. Folate deficiency suppressed the proliferation of adult hippocampal NSPCs in vivo and of embryonic NSPCs in vitro [87]. NSPCs respond to folate with altered Notch signaling, increased cell proliferation [88, 89] and increased neuronal differentiation by enhancing the activity of DNA methyl-transferases (DNMTs) [90, 91]. These reports suggest that one-carbon metabolism may play a critical role in NSPC fate as DNMT maintains progenitor function in self-renewing somatic tissue [92].

A recent study demonstrated that the essential amino acid threonine and SAM metabolism are coupled in pluripotent cells. Threonine, via the action of its dehydrogenase, provides glycine and acetyl coenzyme A, which together are necessary for synthesizing SAM and maintaining the SAM/SAH ratio. Threonine deprivation resulted in a decrease in SAM and a concomitant reduction in histone H3 lysine 4 trimethylation, which caused slowed growth and increased differentiation [93]. This study provides a possible mechanistic link between cellular metabolism and the epigenetic state. Whether the availability of threonine or other amino acid metabolism associated with one-carbon metabolism is necessary for in vivo NSPC function and neurogenesis warrants future investigation.

Lipid metabolism

Two major intracellular lipid metabolism pathways are: (1) the synthesis of lipids to function as structural components of cellular lipid bilayer membranes and as signaling mediators and (2) fatty acid oxidation to produce energy. Recent observations from Knobloch and colleagues highlight the importance of *de novo* lipogenesis in the neurogenesis of adult NSPCs [4]. Proliferating NSPCs showed higher expression levels and enzymatic activities of fatty acid synthase (FASN), the rate-limiting enzyme for lipogenesis, than did the differentiated progeny both in vitro and in vivo. Ablation of *Fasn* in mouse NSPCs impairs neurogenesis. Mechanistically, SPOT14, a context-dependent modulator of *de novo* lipogenesis [94, 95], inhibits lipid synthesis to suppress the proliferation of NSPCs by reducing the level of malonyl-CoA which is an essential substrate for FASN. Controlling FASN activity is important to ensure that stem cells maintain their pool against a premature depletion. In contrast, the fatty acid oxidation (FAO) pathway is a series of dehydrogenation, hydration, oxidation and thiolysis reactions that remove the 2-carbon acetyl-CoA from fatty acids, which then feed into the Krebs cycle to generate ATP. The importance of FAO is demonstrated as a major driver of the stem cell state by the maintenance of increased numbers of quiescent adult HSCs. FAO is active in LSK HSCs, whereas it is undetectable in differentiated cells. Inhibition of mitochondrial FAO by deletion of *Ppard*, a critical regulator of the transcriptional program underlying FAO, reduced functional HSCs, whereas pharmacological PPAR δ activation improved HSC maintenance. Mechanistically, the inhibition of FAO increased symmetric cell divisions, which results in a premature depletion of HSCs [96]. Whether FAO is a functionally essential metabolic component in the maintenance of quiescent adult NSCs in vivo remains to be determined. In addition, cholesterol, one of the key lipid constituents of the plasma membrane, is important for the formation and maintenance of the CNS. Ablation of cholesterol biosynthesis through conditional knockout of squalene synthase in NSPCs reduced the size of the embryonic mouse brain [97]. A recent study reported that many

genes expressed by SOX2-positive NSPCs of DG are enriched in gene ontology categories associated with the generation of energy, lipid metabolism and catabolic processes such as *Bmp6*, *Apoe*, *Acacb*, *Igfbp7*, *Edf1*, *Irs*, *Lrp1*, *Cpt1a*, *Pparc1a*, *Acaa2*, and *Acs16* [98]. This finding is in line with previous studies, which suggest the emerging importance of a lipid metabolic program in DG NSPCs.

Factors regulating metabolic circuits in neural stem cells

RTK–PI3K/PTEN–PDK1–Akt pathway

Neurogenesis is greatly dependent on extracellular cues [99, 100]. The regulation of NSPC proliferation by epidermal growth factor and fibroblast growth factor signaling has been well described [101]. Insulin-like growth factor (IGF)-1 increases the proliferation and neuronal differentiation of NSPCs [102]. Consistently, transgenic mice that overexpress IGF-1 have larger brains with greater numbers of neurons [103]. Additionally, the peripheral in vivo infusion of IGF-1 stimulates neurogenesis in the adult rat hippocampus [104]. The PI3K–Akt pathway is downstream of receptor tyrosine kinases and regulates the proliferation and cell fate of NSPCs. A recent study demonstrated that endogenous ROS enhances self-renewal and neurogenesis both in vitro and in vivo in a PI3K–Akt pathway-dependent manner [105]. The importance of this pathway in NSPCs is further supported by multiple lines of in vivo evidence. Phosphatase and tensin homolog (PTEN) functionally antagonizes the PI3K–Akt pathway. Brain-specific PTEN null mice showed a dramatically increased brain volume through increased cell proliferation, decreased cell death, and enlarged cell size. In addition, PTEN restricts self-renewal of NSPCs both in vitro and in vivo [106, 107]. Phosphoinositide-dependent kinase 1 (PDK1) is an upstream activator of Akt and contributes to the early generation of OPCs from NPCs [108]. Ablation of PDK1 in NSCs resulted in a reduction in the number of SOX10 and platelet-derived growth factor receptor α (PDGFR α)-positive OPCs within the neocortex and the striatum during embryogenesis. Furthermore, the PDK1–Akt pathway regulates, through activation of Mash1, neuronal differentiation and subtype specification during telencephalic development [109]. The reduced brain size and weight with the smaller ventricular system in PKB gamma/Akt3-deficient mice suggest that Akt is crucial for postnatal brain development [110]. Deletion of GSK-3, a downstream effector of Akt, resulted in massive hyperproliferation of NSPCs at the expense of both intermediate neural progenitors and postmitotic neurons. These effects were associated with the dysregulation of Wnt, Sonic Hedgehog, Notch and fibroblast growth factor signaling [111]. Together, these lines of evidence have shown that the RTK–PI3K/PTEN–PDK1–AKT–GSK3 axis is a critical regulator of NSPC homeostasis during brain development.

The PI3K–Akt pathway constitutes a major regulator of cellular metabolism. The activation of this pathway upregulates glucose, glutamine and lipid metabolism through downstream effectors such as FoxO, mTOR, HIF-1 α , Myc, and p53, as discussed below. In addition, Akt directly regulates a number of metabolic enzymes [112], representing a master regulator of the metabolic network within a cell. For example, Akt stimulates glycolysis by increasing the expression and membrane translocation of glucose transporters and by phosphorylating key glycolytic enzymes, such as hexokinase (HK) and phosphofructokinase 2 (also known

as PFKFB3) [113, 114]. Akt also activates ectonucleoside triphosphate diphosphohydrolase 5 (ENTPD5), an enzyme that supports increased protein glycosylation in the endoplasmic reticulum and indirectly increases glycolysis by creating an ATP hydrolysis cycle [115].

FoxO

As a key downstream effector of the PI3K–Akt pathway, FoxO transcription factors (FoxOs) are involved in cellular proliferation, differentiation, survival, ROS detoxification and metabolism [116–118]. Increasing evidence has indicated that FoxOs are crucial in correctly reinforcing stem cell fates. FoxO1 regulates pluripotent self-renewing circuitry by directly activating the expression of Oct4 and Sox2 in human ESCs [119]. In addition, FoxO4 is necessary for the neural differentiation of ESCs [120]. FoxO1 is also essential for spermatogonial stem cell self-maintenance and spermatogenesis [121]. In particular, FoxOs play important roles in adult stem cell homeostasis and maintenance. FoxO deficiency in HSCs results in the accumulation of ROS and the hyperproliferation of the HSC population, which leads to the reduction of the long-term repopulating capacity of HSCs [118, 122]. Consistently, the targeted ablation of FoxO isoforms has resulted in the early depletion of NSPCs, which further supports the importance of FoxO in maintaining the regenerative potential of adult brains [123]. A previous study reported that FoxO3 regulates a range of genes involved in glucose metabolism and the adaptation to hypoxia in NSPCs and that its ablation resulted in age-progressive NSPC depletion [124]. A recent endeavor to link metabolic regulation by FoxO to NSPC fate has revealed that FoxO3 regulates glucose and glutamine metabolism to suppress oxidative stress in NSPCs [76]. FoxO3-deficient NSPCs had decreased levels of mitochondria-localized HK2 through reduction of pAKT, which eventually resulted in the disruption of glucose uptake. Additionally, accumulated ROS by FoxO3 ablation lowered the activity of pyruvate kinase M2 (PKM2), a rate-limiting glycolytic enzyme, which also contributes to the glycolysis defect. The increase in ROS is due, in part, to altered glutamine metabolism. The decreased incorporation of ¹³C- isotope labeled glutamine-derived glutamate into the cellular GSH pool explains that decreased GLS activity accounts for oxidative stress in FoxO3-deficient NSPCs [76]. Together, this study emphasized the importance of glucose and glutamine metabolism in neural stem cell maintenance.

Notably, a recent study by van der Vos et al. identified glutamine synthetase (GLUL) as a transcription target of FoxOs [125]. The activation of FoxO3 and FoxO4 upregulates the expression and activity of GLUL, which, in turn, results in the elevation of glutamine levels. Furthermore, FoxO-mediated glutamine upregulation contributes to the inhibition of mTOR signaling and the induction of autophagy. Autophagy is a lysosomal degradation pathway that allows cells to recycle damaged organelles for energy and biosynthesis. Deficiencies in this pathway are associated with neurodegeneration and impair neuronal differentiation. Autophagic flux and LC3 lipidation increase, along with the increased expression of Atg7, Becl1, Ambra1 and LC3, are required for the early neuronal differentiation of embryonic NSPCs. Consistently, Atg5- and Ambra1-deficient NSPCs display defective neuronal differentiation [126]. Ablation of FIP200, a gene essential for autophagy induction, resulted in p53 activation and a progressive loss of NSPCs and impairment in neuronal differentiation specifically in the postnatal brain [127]. It remains to be determined whether

FoxO-dependent glutamine metabolism contributes to NSPC differentiation through supporting autophagy.

TSC/mTOR

TSC-regulated mTOR is necessary for the maintenance and functions of NSPCs by regulating self-renewal, differentiation, and terminal maturation. Cortical embryonic NSPCs of *Tsc1^{L/L} Emx1-Cre* mice showed defective self-renewal due to the attenuation of PI3K–Akt activation [128]. This is due to the hyperactivation of mTORC1–S6K, which causes negative feedback regulation of the upstream PI3K–Akt. Consistent with the defects seen in other stem cell compartments, mTOR hyperactivation increased NSPC numbers, followed by premature neuronal differentiation and impaired maturation, both during embryonic and postnatal development. Consistent with these findings, the targeted deletion of *Tsc1* in embryonic NSPCs has led to megalencephaly and the formation of giant cells in the cerebral cortex [129, 130]. Furthermore, the ablation of *Tsc1* in postnatal SVZ NSPCs by a *Nestin-CreERT2* transgene caused nodular masses outgrowing into the ventricles [131]. Together, these studies demonstrated that aberrant mTOR hyperactivation in NSPCs leads to deleterious dysregulation.

mTOR integrates growth signals and nutrient availability. The activation of mTOR leads to protein and lipid biosynthesis and cell growth [132]. Mechanistically, mTOR directly stimulates mRNA translation and ribosome biogenesis and indirectly causes metabolic changes by altering other key regulators. For example, mTOR activates the translation of HIF-1 α even under normoxic conditions, thereby upregulating glucose uptake and aerobic glycolysis (see below). Furthermore, a recent study demonstrated that mTORC1 promotes glutamine anaplerosis by activating glutamate dehydrogenase (GDH). This regulation requires transcriptional repression of SIRT4, which is the mitochondria-localized SIRT that inhibits GDH. Mechanistically, mTORC1 represses SIRT4 by promoting the proteasome-mediated destabilization of cAMP-responsive element binding 2 (CREB2) (Fig. 3) [133]. Additionally, mTOR signaling regulates lipid homeostasis [134, 135]. mTOR upregulates cholesterol biosynthetic gene expression and lipogenesis, whereas it suppresses lipolysis and fatty acid oxidation [136]. In contrast to its effect in vitro, Rapamycin treatment in vivo leads to dyslipidemia and hypercholesterolemia in patients due to defects in lipid mobilization and transport [137]. Whether mTOR-regulated lipid metabolism is operative in NSPCs outside adipose and hepatic tissues remains to be determined.

HIF-1 α

HIF-1 α is responsible for the transcription of hypoxia-regulated genes. In most cells, HIF-1 α is constitutively produced but rapidly degraded. Hydroxylation of HIF-1 α by prolyl hydroxylases recruits the VHL E3 ubiquitin ligase, which leads to proteolytic destruction. To date, oxygen-regulated HIF-1 α has been shown to play a critical role in regulating glucose and glutamine-derived central carbon utilization in mammalian cells [138].

Adult stem cells, including NSPCs, reside in hypoxic niches, and the development states of these cells are affected by oxygen availability. Therefore, it is conceivable that oxygen-sensitive regulator HIF signaling is closely related to their fates [139]. Indeed, studies

performed in HSCs generally support the critical role of HIF-mediated function in maintaining stem cells. The disruption of HIF-1 α /ARNT heterodimers through the depletion of *Arnt* led to failed hypoxia-mediated progenitor proliferation as well as a decreased hematopoietic progenitor population during development [140]. Furthermore, HIF-1 α deletion progressively increased cell cycling and decreased long-term repopulation capacity in adult HSCs [141]. Quiescent HSCs slowly cycle, causing low-level oxidative stress. This prevents undue differentiation and premature exhaustion of HSCs [142]. Therefore, HSCs maintain intracellular hypoxia and a suitable amount of HIF-1 α for their quiescence. However, the result that the overexpression of HIF-1 α impaired the transplantation capacity suggests the requirement of a fine-tuned regulation at the HIF-1 α level.

As mentioned earlier, *Hif-1 α* deletion impairs hippo-campal neurogenesis by suppressing NSPC proliferation, differentiation and neuronal maturation. This defect correlates with a decline in Wnt/ β -catenin signaling in the SGZ, which clearly suggests the critical role of HIF-1 α in NSPC biology [29]. A number of studies have demonstrated that intermittent hypoxia increased neurogenesis in the adult rat SVZ and hippocampus, thereby contributing to memory and learning [143–145]. Hypoxia increases cyclin D1 expression through activation of JNK in rat NSPCs in vitro, suggesting a novel mechanism for hypoxia-induced proliferation of NSPCs [146]. This occurs, in part, by HIF-1 α -dependent proliferation of NSPCs and subsequent increases in newly generated neurons [147]. Studies using hyperbaric oxygen treatment also reported enhanced proliferation and neuronal differentiation of NSPCs [148]. These effects are presumably due to the stabilization of HIF-1 α , as previously reported [149].

HIF-1 α regulates multiple steps of glycolysis [150]. Extracellular glucose is imported into cells through GLUT1, the expression of which is regulated by HIF-1 α [151]. Glucose is, in turn, phosphorylated by hexokinase to generate G-6-P. HK2, which is a hexokinase isoform and a key mediator of aerobic glycolysis, is a target gene of HIF-1 α [152]. HIF-1 α , in cooperation with c-MYC, induces pyruvate dehydrogenase kinase 1 (PDK1) and suppresses oxidative phosphorylation by blocking the entry of pyruvate into the TCA cycle [142]. As described previously, HSCs maintain stabilized HIF-1 α , which leads to elevated rates of glucose consumption and lactate production and reduced levels of mitochondrial oxidative phosphorylation and oxygen consumption [153].

HIF-1 α directs glutamine-derived carbons away from the TCA cycle to be used for fatty acid synthesis [138]. This isocitrate dehydrogenase 1 (IDH1)-dependent pathway of the reductive carboxylation of glutamine-derived α -KG for *de novo* lipogenesis is particularly critical for cellular proliferation under hypoxia [154]. A recent report forged a mechanistic link between hypoxia-suppressed glutamine oxidation and lipid synthesis [155]. The activation of HIF-1 α activates the E3 ubiquitin ligase SIAH2, which induces the degradation of a subunit of the mitochondrial enzyme α -KG dehydrogenase. Decreased glutamine oxidation counter activates its reductive carboxylation to citrate and fatty acid synthesis. Together, accumulating evidence supports the idea that HIF-1 α facilitates metabolic adaptation upon redox change and the mobilization of NSPCs to proliferate, differentiate, or migrate in and out of the hypoxic niche.

Sirtuin

Sirtuin is a family of nicotinamide adenine dinucleotide (NAD)-dependent deacetylases. Thus, it integrates cellular energy status and stress. SIRT1 and 2 are present both in the nucleus and the cytoplasm in different cellular contexts, whereas SIRT3, SIRT4, and SIRT5 are mitochondrial and SIRT6 and SIRT7 are constitutively nuclear [156, 157]. Recent studies have emphasized its role in cellular metabolism and energetics. Studies in knockout mice have revealed that the SIRT family regulates lifespan, genomic stability and metabolism [157].

SIRT1 activates PGC-1 α , the master regulator of mitochondria biogenesis, and inhibits glycolysis [158]. Consistently, SIRT1 promotes cellular autophagy, a process that is tightly coupled with mitochondria metabolism [159]. Similarly, recent studies have demonstrated that SIRT3 and SIRT6 deacetylate and inactivate HIF-1 α and thus suppress glycolytic metabolism [160, 161].

In particular, SIRT3 is the major mitochondrial deacetylase, and multiple targets have been identified and shown to be important for cellular metabolic homeostasis. For example, SIRT3 deacetylates OXPHOS complexes I, II, and III, consequently increasing mitochondrial aerobic respiration. SIRT3 knockout mice also display reduced mitochondrial oxidation and increased ROS [162]. Furthermore, it deacetylates and activates IDH2. Thus, SIRT3 also protects cells from oxidative stress by increasing the GSH/GSSG ratio [163]. Superoxide dismutase (SOD) is another substrate of SIRT3 that is activated upon caloric restriction [164]. A recent study demonstrated that the expression of SIRT3 regulates HSC self-renewal under stress or at an old age by maintaining mitochondrial metabolic homeostasis and suppressing ROS [165]. These findings suggest SIRT3 is critical for the suppression of cellular oxidative stress and necessary for mitochondria metabolism.

As described previously, SIRT also has a profound role in glutamine metabolism. SIRT4, through its ADP ribo-sylation of GDH, inhibits glutamine metabolism in the mitochondria [166]. In contrast, SIRT3 has been proposed to activate GDH activity through its deacetylation [167, 168]. Interestingly, SIRT3-deficient mice are metabolically unremarkable under basal conditions, suggesting that it may have cellular context-dependent activity. How different SIRTs oppositely regulate GDH and orchestrate cellular metabolism requires further investigation.

In NSPCs, SIRT1 is expressed and regulated during self-renewal and neurogenic differentiation [169]. The knockdown of SIRT1 does not affect proliferation but does enhance the neuronal differentiation of NSPCs. Another study demonstrated that SIRT1 responds to redox stress and alters the NSPC cell fate decision toward preferred differentiation into the astroglial lineage. The mechanism by which SIRT1 is activated by ROS is unclear, but it mediates deacetylation of histone H3K9 in the MASH1 promoter by SIRT1 and the subsequent downregulation of the pro-neuronal transcription factor MASH1 [170]. In contrast, a separate study reported that SIRT1 represses the Notch1-Hes1 pathway, and its transient translocation into the nucleus is necessary for the neuronal differentiation of NSPCs [171]. Notably, a recent study that exploited a conditional SIRT1 knockout driven by the Nestin-Cre-ERT2 transgene described that the main phenotype of SIRT1-deficient

NSPCs is the expansion of OPCs in the adult SVZ [172]. Together, SIRT1 clearly has an indispensable function in NSPC fate decision. How developmental cues, aging, and the level of stress influence the activity of SIRT1 as well as other SIRT family members in NSPCs and the outcome warrants further investigation.

Of note, SIRT is regulated by dietary restriction, pharmacological interventions and intracellular redox potential [173]. Its activity may be mediated through other factors such as FoxO, p53, Myc, and HIF-1 α . Identifying its cellular substrates and the mechanism of gene expression changes is an active area of investigation given its role in adult stem cell homeostasis and organismal aging.

MYC

MYC is necessary for the normal development of the neural system: in the mouse, knocking out *c-myc* is lethal at embryonic day 10.5 with defects in neural development [174], and the reduced expression of *N-myc* disrupts early embryogenesis and postnatal brain growth [175]. Confirmation of MYC expression during fetal brain development [176] and in NSPCs [177] implies that MYC also contributes to the NSPC fate decision. Indeed, a fraction of the MYC-overexpressing cells retain the self-renewal capacity even under differentiation-inducing culture conditions. Conditional deletion of *N-myc* in nestin-expressing NSPCs decreases the whole brain size and obstructs cerebellar development due to the disrupted neuronal differentiation [178]. Deletion of either *c-* or *N-myc* or both genes in NSPCs driven by nestin-cre causes microcephaly, which accompanies a strong reduction in the cerebellar granule neural progenitors and mature granule neurons, phenocopying the genetic disorder of Feingold syndrome [179]. MYC-deficient brains exhibit the down-regulation of genes involved in protein and nucleotide metabolism, mitosis, and chromatin structure as well as the upregulation of genes associated with differentiation [180]. These findings support the notion that MYC has a profound role in the cell fate decision of NSPCs by inhibiting differentiation as well as directing active cellular metabolism.

MYC controls self-renewal and differentiation in adult stem cells, but its function differs depending on the types of stem cells and the contexts. In bone marrow, the conditional deletion of *c-myc* was found to lead to the accumulation of HSCs mainly as a result of differentiation failure [181]. In contrast, the knockout of MYC in mammary basal cells was found to result in the impairment of self-renewal and the diminishment of the progenitor population [182]. Unexpectedly, MYC promotes the differentiation of NSPCs, rather than their proliferation [183]. The depletion of endogenous MYC in radial glial precursors inhibits differentiation, whereas the overexpression of MYC induces neurogenesis. This finding is in contrast to previous reports that demonstrated the mitogenic activity of MYC in dissociated cells in culture. In this recent study, MYC was shown to drive differentiation by inhibiting Notch signaling and by increasing neurogenic cell division, eventually resulting in a depletion of progenitor cells within the intact polarized tissue [168]. These findings indicate an unexpected role of MYC in the control of NSC stemness versus differentiation in vivo.

MYC is critical in the transcriptional and post-transcriptional regulation of stem cell maintenance. MYC-mediated metabolic regulations in stem cells remain an active area of

investigation. It has been suggested that MYC controls embryonic and adult stem cell physiology, in part, through the regulation of cellular glutamine metabolism [184]. MYC stimulates mitochondrial glutaminolysis through coordinated transcriptional and post-transcriptional programs. It transcriptionally activates two main glutamine transporters, SLC1A5 and SLC38A5, which results in the reprogramming of mitochondrial metabolism to depend on glutamine catabolism. This MYC-dependent glutaminolysis stimulation reduces the entry of glucose carbon into the TCA cycle and triggers cellular addiction to glutamine as an energy source [185]. In addition, MYC enhances mitochondrial GLS expression and glutamine metabolism by suppressing microRNAs miR-23a/b [84].

MYC enhances aerobic glycolysis by directly regulating the transcription of glycolytic genes [186]. Most glycolytic genes have conserved MYC-binding E boxes (ENO1, HK2, or LDHA) or can be induced by MYC even without canonical E boxes (GAPD and TPI1) [187]. In addition to transcriptional regulation, MYC has been shown to promote aerobic glycolysis in cancer cells by promoting RNA splicing through the controlled expression of hnRNP splicing factors [188]. In glioblastoma, mTORC2 was shown to regulate glycolytic metabolism through c-MYC [189]. It remains to be determined whether suppressed glycolysis is the major cause of NSPC proliferation defects upon MYC ablation. Together, these lines of evidence indicates that MYC regulates key aspects of NSPC function, including ribosomal and mitochondrial biogenesis, glucose and glutamine metabolism, lipid synthesis, and cell cycle progression [184].

p53

The expression of p53 within NSPC-rich neurogenic regions has been reported [190]. p53 regulates NSPCs at multiple levels. Knockout mouse studies have suggested its role in cell death during postnatal hippocampal neurogenesis [191]. The loss of p53 enhanced adult SVZ NSPC self-renewal [192]. This finding is consistent with the knockout phenotype of p21, its bona fide transcriptional target [193]. p53 deletion in NSPCs and the telencephalon resulted in an elevation in ROS and PI3K–Akt signaling, which was linked to enhanced neurogenesis. By contrast, the down-regulation of ROS levels and PI3K signaling in *p53*^{-/-}NSPCs ameliorated the defect [194]. Simultaneously, the reported effect of an in vitro culture condition with 20 % oxygen on the decreased proliferation and enhanced glial differentiation of NSPCs was ascribed to p53 activation [24, 38].

In agreement with in vivo evidence, the biochemical characterization of *p53*^{-/-}cells suggested its role in maintaining cellular redox potential. First, p53-induced glycolysis and the apoptosis regulator (TIGAR), a p53-inducible fructose 2,6-bisphosphatase, antagonize glycolysis. TIGAR redirects glucose to the PPP and increases the production of NADPH required for maintaining reduced GSH, which leads to the subsequent reduction of cellular ROS levels [195, 196]. Consistently, *p53*^{-/-}mice display enhanced glycolysis and an increase in ROS [197, 198]. Furthermore, p53 regulates the balance between mitochondrial respiration and glycolytic metabolism. This regulation is accomplished by activating synthesis of cytochrome c oxidase 2 (SCO2), which is critical for the assembly of the cytochrome c oxidase (COX) complex [199].

p53 transcriptionally activates mitochondrial glutaminase 2 (GLS2) as part of DNA damage responses [200, 201]. GLS2 increases the mitochondrial conversion of glutamine to glutamate, which contributes to the production of GSH and energy. In addition to these findings, p53 engages in crosstalk with the PI3K–Akt pathway through multiple avenues and indirectly contributes to cellular metabolism. For example, p53 has been shown to upregulate PTEN and to suppress PI3K–Akt signaling, thereby opposing the metabolic activity driven by this major regulatory pathway [202].

Metabolic control of epigenetic alteration in NSPCs

Recently, cellular metabolism and the epigenetic control of gene expression, especially DNA and/or histone methylation, have been reported to have an important role in the differentiation process. Isocitrate dehydrogenase 1 (IDH1) and its mitochondrial homolog IDH2 are notable examples. Mutations in IDH1/2 are most frequent in acute myeloid leukemia (AML) and the gliomas in different human cancers [203, 204]. The neomorphic IDH1/2 mutations in tumors catalyze a NADPH-dependent reduction of α -KG to R-2-hydroxyglutarate (2-HG) [205]. This metabolic alteration results in DNA hypermethylation through the inhibition of TET2, an α -KG-dependent ten–eleven translocation (TET) family of DNA hydroxylases. A recent study demonstrated a proleukemogenic activity of 2-HG that impairs hematopoietic differentiation by inhibiting TET2 [206, 207]. Additionally, 2-HG competitively inhibits the α -KG-dependent Jmjc domain that contains histone demethylases, which suggests an explanation for the altered abundance of histone methylation marks in mutant IDH-expressing cells [208, 209]. Consistent with these proposed mechanisms, IDH1/2 mutations also alter cell fate determination in NSPCs. The enforced expression of mutant IDH1(R132H) interferes with neural differentiation, and this differentiation blockade of non-transformed cells is based on the enhancement of repressive H3K9 methylation and CpG-island hypermethylation [210]. Consistent with previous reports that suggest a role for IDH1/2 mutants in epigenetic reprogramming [210, 211], a recent study reported that IDH mutant-specific small-molecule inhibitors induce the expression of genes and cell markers associated with glial-specific differentiation in glioma cells and the reduction of repressive chromatin marks (H2K9 and H3K27 trimethylation) at the promoters of induced genes [212].

Conclusion

As exemplified in the aforementioned examples of metabolic regulation of NSPC fate, clinical testing of targeted metabolic therapies to boost neurogenesis is well justified. Many pharmacological interventions for metabolic syndromes and abnormalities are currently available. The identification and characterization of new targets is imperative for developing novel therapeutic strategies that exploit the regenerative potential of resident NSPCs against neurodegenerative diseases. To this end, additional studies are needed to demonstrate the functional significance of epigenetic modifications and specific gene expression patterns affected by cellular metabolism.

Additional evidence supports the possibility that grafted NSPCs may replace damaged or injured cells and improve motor function in neurodegenerative conditions [213]. In

particular, studies are now seeking to tailor cell replacement therapy to each patient. Currently, the ex vivo manipulation and expansion of NSPCs is a popular approach to understanding this intriguing cell type. A better understanding and design of the most suitable micro-environment-mimicking culture conditions will ensure better progress toward generating neural cells for the various therapies that are under development.

Acknowledgments

This work is supported by the Ellison Medical Foundation (AG-NS-0646-10 to J-H. P), the Weill Cornell Medical College, and the Sidney Kimmel Foundation (SKF-092 to J-H. P).

References

1. Xu X, Duan S, Yi F, Ocampo A, Liu GH, Izpisua Belmonte JC. Mitochondrial regulation in pluripotent stem cells. *Cell Metab.* 2013; 18(3):325–332.10.1016/j.cmet.2013.06.005 [PubMed: 23850316]
2. Shyh-Chang N, Daley GQ, Cantley LC. Stem cell metabolism in tissue development and aging. *Development.* 2013; 140(12):2535–2547.10.1242/dev.091777 [PubMed: 23715547]
3. Ochocki JD, Simon MC. Nutrient-sensing pathways and metabolic regulation in stem cells. *J Cell Bio.* 2013; 203(1):23–33.10.1083/jcb.201303110 [PubMed: 24127214]
4. Knobloch M, Braun SM, Zurkirchen L, von Schoultz C, Zam-boni N, Arauzo-Bravo MJ, Kovacs WJ, Karalay O, Suter U, Machado RA, Roccio M, Lutolf MP, Semenkovich CF, Jess-berger S. Metabolic control of adult neural stem cell activity by Fasn-dependent lipogenesis. *Nature.* 2013; 493(7431):226–230.10.1038/nature11689 [PubMed: 23201681]
5. Sidman RL, Miale IL, Feder N. Cell proliferation and migration in the primitive ependymal zone: an autoradiographic study of histogenesis in the nervous system. *Exp Neurol.* 1959; 1:322–333. [PubMed: 14446424]
6. Altman J. Are new neurons formed in the brains of adult mammals? *Science.* 1962; 135(3509): 1127–1128. [PubMed: 13860748]
7. Altman J. Autoradiographic investigation of cell proliferation in the brains of rats and cats. *Anatomical Rec.* 1963; 145:573–591.
8. Altman J, Das GD. Postnatal neurogenesis in the guinea-pig. *Nature.* 1967; 214(5093):1098–1101. [PubMed: 6053066]
9. Gage FH. Mammalian neural stem cells. *Science.* 2000; 287(5457):1433–1438. [PubMed: 10688783]
10. Zhao C, Deng W, Gage FH. Mechanisms and functional implications of adult neurogenesis. *Cell.* 2008; 132(4):645–660.10.1016/j.cell.2008.01.033 [PubMed: 18295581]
11. Ma DK, Bonaguidi MA, Ming GL, Song H. Adult neural stem cells in the mammalian central nervous system. *Cell Res.* 2009; 19(6):672–682.10.1038/cr.2009.56 [PubMed: 19436263]
12. Imayoshi I, Sakamoto M, Ohtsuka T, Takao K, Miyakawa T, Yamaguchi M, Mori K, Ikeda T, Itohara S, Kageyama R. Roles of continuous neurogenesis in the structural and functional integrity of the adult forebrain. *Nat Neurosci.* 2008; 11(10):1153–1161.10.1038/nn.2185 [PubMed: 18758458]
13. Spalding KL, Bergmann O, Alkass K, Bernard S, Salehpour M, Huttner HB, Bostrom E, Westerlund I, Vial C, Buchholz BA, Possnert G, Mash DC, Druid H, Frisen J. Dynamics of hippocampal neurogenesis in adult humans. *Cell.* 2013; 153(6):1219–1227.10.1016/j.cell.2013.05.002 [PubMed: 23746839]
14. Carlen M, Cassidy RM, Brismar H, Smith GA, Enquist LW, Frisen J. Functional integration of adult-born neurons. *Current Biol.* 2002; 12(7):606–608.
15. Duan X, Kang E, Liu CY, Ming GL, Song H. Development of neural stem cell in the adult brain. *Curr Opin Neurobiol.* 2008; 18(1):108–115.10.1016/j.conb.2008.04.001 [PubMed: 18514504]

16. Kempermann G, Jessberger S, Steiner B, Kronenberg G. Milestones of neuronal development in the adult hippocampus. *Trends Neurosci.* 2004; 27(8):447–452.10.1016/j.tins.2004.05.013 [PubMed: 15271491]
17. Garcia-Verdugo JM, Doetsch F, Wichterle H, Lim DA, Alvarez-Buylla A. Architecture and cell types of the adult sub-ventricular zone: in search of the stem cells. *J Neurobiol.* 1998; 36(2):234–248. [PubMed: 9712307]
18. Shen Q, Wang Y, Kokovay E, Lin G, Chuang SM, Goderie SK, Roysam B, Temple S. Adult SVZ stem cells lie in a vascular niche: a quantitative analysis of niche cell–cell interactions. *Cell Stem Cell.* 2008; 3(3):289–300.10.1016/j.stem.2008.07.026 [PubMed: 18786416]
19. Ernst A, Alkass K, Bernard S, Salehpour M, Perl S, Tisdale J, Possnert G, Druid H, Frisen J. Neurogenesis in the striatum of the adult human brain. *Cell.* 2014; 156(5):1072–1083.10.1016/j.cell.2014.01.044 [PubMed: 24561062]
20. Fuentealba LC, Obernier K, Alvarez-Buylla A. Adult neural stem cells bridge their niche. *Cell Stem Cell.* 2012; 10(6):698–708.10.1016/j.stem.2012.05.012 [PubMed: 22704510]
21. Erecinska M, Silver IA. Tissue oxygen tension and brain sensitivity to hypoxia. *Respir Physiol.* 2001; 128(3):263–276. [PubMed: 11718758]
22. Mohyeldin A, Garzon-Muvdi T, Quinones-Hinojosa A. Oxygen in stem cell biology: a critical component of the stem cell niche. *Cell Stem Cell.* 2010; 7(2):150–161.10.1016/j.stem.2010.07.007 [PubMed: 20682444]
23. Harms KM, Li L, Cunningham LA. Murine neural stem/progenitor cells protect neurons against ischemia by HIF-1 α -regulated VEGF signaling. *PLoS One.* 2010; 5(3):e9767.10.1371/journal.pone.0009767 [PubMed: 20339541]
24. Chen HL, Pistollato F, Hoepfner DJ, Ni HT, McKay RD, Panchision DM. Oxygen tension regulates survival and fate of mouse central nervous system precursors at multiple levels. *Stem Cells.* 2007; 25(9):2291–2301.10.1634/stemcells.2006-0609 [PubMed: 17556599]
25. Studer L, Csete M, Lee SH, Kabbani N, Walikonis J, Wold B, McKay R. Enhanced proliferation, survival, and dopaminergic differentiation of CNS precursors in lowered oxygen. *J Neurosci.* 2000; 20(19):7377–7383. [PubMed: 11007896]
26. Felfly H, Zambon AC, Xue J, Muotri A, Zhou D, Snyder EY, Haddad GG. Severe Hypoxia: consequences to neural stem cells and neurons. *J Neurol Res.* 2011; 1(5)10.4021/jnr70w
27. Morrison SJ, Csete M, Groves AK, Melega W, Wold B, Anderson DJ. Culture in reduced levels of oxygen promotes clonogenic sympathoadrenal differentiation by isolated neural crest stem cells. *J Neurosci.* 2000; 20(19):7370–7376. [PubMed: 11007895]
28. Candelario KM, Shuttleworth CW, Cunningham LA. Neural stem/progenitor cells display a low requirement for oxidative metabolism independent of hypoxia inducible factor-1 α expression. *J Neurochem.* 2013; 125(3):420–429.10.1111/jnc.12204 [PubMed: 23410250]
29. Mazumdar J, O'Brien WT, Johnson RS, LaManna JC, Chavez JC, Klein PS, Simon MC. O₂ regulates stem cells through Wnt/ β -catenin signalling. *Nat Cell Biol.* 2010; 12(10):1007–1013.10.1038/ncb2102 [PubMed: 20852629]
30. Ingraham CA, Park GC, Makarenkova HP, Crossin KL. Matrix metalloproteinase (MMP)-9 induced by Wnt signaling increases the proliferation and migration of embryonic neural stem cells at low O₂ levels. *J Biol Chem.* 2011; 286(20):17649–17657.10.1074/jbc.M111.229427 [PubMed: 21460212]
31. Artavanis-Tsakonas S, Rand MD, Lake RJ. Notch signaling: cell fate control and signal integration in development. *Science.* 1999; 284(5415):770–776. [PubMed: 10221902]
32. de la Pompa JL, Wakeham A, Correia KM, Samper E, Brown S, Aguilera RJ, Nakano T, Honjo T, Mak TW, Rossant J, Conlon RA. Conservation of the Notch signalling pathway in mammalian neurogenesis. *Development.* 1997; 124(6):1139–1148. [PubMed: 9102301]
33. Androutsellis-Theotokis A, Leker RR, Soldner F, Hoepfner DJ, Ravin R, Poser SW, Rueger MA, Bae SK, Kittappa R, McKay RD. Notch signalling regulates stem cell numbers in vitro and in vivo. *Nature.* 2006; 442(7104):823–826.10.1038/nature04940 [PubMed: 16799564]
34. Gustafsson MV, Zheng X, Pereira T, Gradin K, Jin S, Lundkvist J, Ruas JL, Poellinger L, Lendahl U, Bondesson M. Hypoxia requires notch signaling to maintain the undifferentiated cell state. *Dev Cell.* 2005; 9(5):617–628.10.1016/j.devcel.2005.09.010 [PubMed: 16256737]

35. Zheng X, Linke S, Dias JM, Zheng X, Gradin K, Wallis TP, Hamilton BR, Gustafsson M, Ruas JL, Wilkins S, Bilton RL, Brismar K, Whitelaw ML, Pereira T, Gorman JJ, Ericson J, Peet DJ, Lendahl U, Poellinger L. Interaction with factor inhibiting HIF-1 defines an additional mode of cross-coupling between the Notch and hypoxia signaling pathways. *Proc Natl Acad Sci USA*. 2008; 105(9):3368–3373.10.1073/pnas.0711591105 [PubMed: 18299578]
36. Chenn A, Walsh CA. Regulation of cerebral cortical size by control of cell cycle exit in neural precursors. *Science*. 2002; 297(5580):365–369.10.1126/science.1074192 [PubMed: 12130776]
37. Kaidi A, Williams AC, Paraskeva C. Interaction between beta-catenin and HIF-1 promotes cellular adaptation to hypoxia. *Nat Cell Biol*. 2007; 9(2):210–217.10.1038/ncb1534 [PubMed: 17220880]
38. Pistollato F, Chen HL, Schwartz PH, Basso G, Panchision DM. Oxygen tension controls the expansion of human CNS precursors and the generation of astrocytes and oligodendrocytes. *Mol Cell Neurosci*. 2007; 35(3):424–435.10.1016/j.mcn.2007.04.003 [PubMed: 17498968]
39. Covello KL, Kehler J, Yu H, Gordan JD, Arsham AM, Hu CJ, Labosky PA, Simon MC, Keith B. HIF-2 α regulates Oct-4: effects of hypoxia on stem cell function, embryonic development, and tumor growth. *Genes Dev*. 2006; 20(5):557–570.10.1101/gad.1399906 [PubMed: 16510872]
40. Azuara V, Perry P, Sauer S, Spivakov M, Jorgensen HF, John RM, Gouti M, Casanova M, Warnes G, Merkenschlager M, Fisher AG. Chromatin signatures of pluripotent cell lines. *Nat Cell Biol*. 2006; 8(5):532–538.10.1038/ncb1403 [PubMed: 16570078]
41. Bernstein BE, Mikkelsen TS, Xie X, Kamal M, Huebert DJ, Cuff J, Fry B, Meissner A, Wernig M, Plath K, Jaenisch R, Wagschal A, Feil R, Schreiber SL, Lander ES. A bivalent chromatin structure marks key developmental genes in embryonic stem cells. *Cell*. 2006; 125(2):315–326.10.1016/j.cell.2006.02.041 [PubMed: 16630819]
42. Monje ML, Toda H, Palmer TD. Inflammatory blockade restores adult hippocampal neurogenesis. *Science*. 2003; 302(5651):1760–1765.10.1126/science.1088417 [PubMed: 14615545]
43. Vallieres L, Campbell IL, Gage FH, Sawchenko PE. Reduced hippocampal neurogenesis in adult transgenic mice with chronic astrocytic production of interleukin-6. *J Neurosci*. 2002; 22(2):486–492. [PubMed: 11784794]
44. Ekdahl CT, Claasen JH, Bonde S, Kokaia Z, Lindvall O. Inflammation is detrimental for neurogenesis in adult brain. *Proc Natl Acad Sci USA*. 2003; 100(23):13632–13637.10.1073/pnas.2234031100 [PubMed: 14581618]
45. Shintani F, Nakaki T, Kanba S, Sato K, Yagi G, Shiozawa M, Aiso S, Kato R, Asai M. Involvement of interleukin-1 in immobilization stress-induced increase in plasma adrenocorticotrophic hormone and in release of hypothalamic monoamines in the rat. *J Neurosci*. 1995; 15(3 Pt 1):1961–1970. [PubMed: 7891145]
46. Ji R, Tian S, Lu HJ, Lu Q, Zheng Y, Wang X, Ding J, Li Q. TAM receptors affect adult brain neurogenesis by negative regulation of microglial cell activation. *J Immunol*. 2013; 191(12):6165–6177.10.4049/jimmunol.1302229 [PubMed: 24244024]
47. Taga T, Fukuda S. Role of IL-6 in the neural stem cell differentiation. *Clin Rev Allergy Immunol*. 2005; 28(3):249–256.10.1385/CRIAI:28:3:249 [PubMed: 16129909]
48. Namihira M, Nakashima K. Mechanisms of astrocyto-genesis in the mammalian brain. *Curr Opin Neurobiol*. 2013; 23(6):921–927.10.1016/j.conb.2013.06.002 [PubMed: 23827784]
49. Li X, Newbern JM, Wu Y, Morgan-Smith M, Zhong J, Charron J, Snider WD. MEK is a key regulator of gliogenesis in the developing brain. *Neuron*. 2012; 75(6):1035–1050.10.1016/j.neuron.2012.08.031 [PubMed: 22998872]
50. Folmes CD, Dzeja PP, Nelson TJ, Terzic A. Metabolic plasticity in stem cell homeostasis and differentiation. *Cell Stem Cell*. 2012; 11(5):596–606.10.1016/j.stem.2012.10.002 [PubMed: 23122287]
51. Folmes CD, Park S, Terzic A. Lipid metabolism greases the stem cell engine. *Cell Metab*. 2013; 17(2):153–155.10.1016/j.cmet.2013.01.010 [PubMed: 23395162]
52. Agathocleous M, Love NK, Randlett O, Harris JJ, Liu J, Murray AJ, Harris WA. Metabolic differentiation in the embryonic retina. *Nat Cell Biol*. 2012; 14(8):859–864.10.1038/ncb2531 [PubMed: 22750943]

53. Lonergan T, Brenner C, Bavister B. Differentiation-related changes in mitochondrial properties as indicators of stem cell competence. *J Cell Physiol.* 2006; 208(1):149–153.10.1002/jcp.20641 [PubMed: 16575916]
54. Vlashi E, Lagadec C, Vergnes L, Matsutani T, Masui K, Poulou M, Popescu R, Della Donna L, Evers P, Dekmezian C, Reue K, Christofk H, Mischel PS, Pajonk F. Metabolic state of glioma stem cells and nontumorigenic cells. *Proc Natl Acad Sci USA.* 2011; 108(38):16062–16067.10.1073/pnas.1106704108 [PubMed: 21900605]
55. Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science.* 2009; 324(5930):1029–1033.10.1126/science.1160809 [PubMed: 19460998]
56. Chung S, Dzeja PP, Faustino RS, Perez-Terzic C, Behfar A, Terzic A. Mitochondrial oxidative metabolism is required for the cardiac differentiation of stem cells. *Nat Clin Prac Cardiovasc Med.* 2007; 4(Suppl 1):S60–S67.10.1038/ncpca-rdio0766
57. Folmes CD, Nelson TJ, Martinez-Fernandez A, Arrell DK, Lindor JZ, Dzeja PP, Ikeda Y, Perez-Terzic C, Terzic A. Somatic oxidative bioenergetics transitions into pluripotency-dependent glycolysis to facilitate nuclear reprogramming. *Cell Metab.* 2011; 14(2):264–271.10.1016/j.cmet.2011.06.011 [PubMed: 21803296]
58. Panopoulos AD, Izpisua Belmonte JC. Anaerobicizing into pluripotency. *Cell Metab.* 2011; 14(2):143–144.10.1016/j.cmet.2011.07.003 [PubMed: 21803281]
59. Reya T, Morrison SJ, Clarke MF, Weissman IL. Stem cells, cancer, and cancer stem cells. *Nature.* 2001; 414(6859):105–111.10.1038/35102167 [PubMed: 11689955]
60. Taipale J, Beachy PA. The Hedgehog and Wnt signalling pathways in cancer. *Nature.* 2001; 411(6835):349–354.10.1038/35077219 [PubMed: 11357142]
61. Teperino R, Amann S, Bayer M, McGee SL, Loipetzberger A, Connor T, Jaeger C, Kammerer B, Winter L, Wiche G, Dalgaard K, Selvaraj M, Gaster M, Lee-Young RS, Febbraio MA, Knauf C, Cani PD, Aberger F, Penninger JM, Pospisilik JA, Esterbauer H. Hedgehog partial agonism drives Warburg-like metabolism in muscle and brown fat. *Cell.* 2012; 151(2):414–426.10.1016/j.cell.2012.09.021 [PubMed: 23063129]
62. Landor SK, Mutvei AP, Mamaeva V, Jin S, Busk M, Borra R, Gronroos TJ, Kronqvist P, Lendahl U, Sahlgren CM. Hypo- and hyperactivated Notch signaling induce a glycolytic switch through distinct mechanisms. *Proc Natl Acad Sci USA.* 2011; 108(46):18814–18819.10.1073/pnas.1104943108 [PubMed: 22065781]
63. Esen E, Chen J, Karner CM, Okunade AL, Patterson BW, Long F. WNT-LRP5 signaling induces Warburg effect through mTORC2 activation during osteoblast differentiation. *Cell Metab.* 2013; 17(5):745–755.10.1016/j.cmet.2013.03.017 [PubMed: 23623748]
64. Birket MJ, Orr AL, Gerencser AA, Madden DT, Vitelli C, Swistowski A, Brand MD, Zeng X. A reduction in ATP demand and mitochondrial activity with neural differentiation of human embryonic stem cells. *J Cell Sci.* 2011; 124(Pt 3):348–358.10.1242/jcs.072272 [PubMed: 21242311]
65. Guppy M, Greiner E, Brand K. The role of the Crabtree effect and an endogenous fuel in the energy metabolism of resting and proliferating thymocytes. *Eur J Biochem.* 1993; 212(1):95–99. [PubMed: 8444168]
66. Maurer MH, Geomor HK, Burgers HF, Schelshorn DW, Kuschinsky W. Adult neural stem cells express glucose transporters GLUT1 and GLUT3 and regulate GLUT3 expression. *FEBS Lett.* 2006; 580(18):4430–4434.10.1016/j.febslet.2006.07.012 [PubMed: 16854415]
67. Gershon TR, Crowther AJ, Tikunov A, Garcia I, Annis R, Yuan H, Miller CR, Macdonald J, Olson J, Deshmukh M. Hexokinase-2-mediated aerobic glycolysis is integral to cerebellar neurogenesis and pathogenesis of medulloblastoma. *Cancer Metab.* 2013; 1(1):2. [PubMed: 24280485]
68. Suh SW, Fan Y, Hong SM, Liu Z, Matsumori Y, Weinstein PR, Swanson RA, Liu J. Hypoglycemia induces transient neurogenesis and subsequent progenitor cell loss in the rat hippocampus. *Diabetes.* 2005; 54(2):500–509. [PubMed: 15677508]
69. Alvarez EO, Beauquis J, Revsin Y, Banzan AM, Roig P, De Nicola AF, Saravia F. Cognitive dysfunction and hippo-campal changes in experimental type 1 diabetes. *Behav Brain Res.* 2009; 198(1):224–230.10.1016/j.bbr.2008.11.001 [PubMed: 19041902]

70. Fu J, Tay SS, Ling EA, Dheen ST. Aldose reductase is implicated in high glucose-induced oxidative stress in mouse embryonic neural stem cells. *J Neurochem.* 2007; 103(4):1654–1665.10.1111/j.1471-4159.2007.04880.x [PubMed: 17727625]
71. Horecker BL, Mehler AH. Carbohydrate metabolism. *Annu Rev Biochem.* 1955; 24:207–274.10.1146/annurev.bi.24.070155.001231 [PubMed: 13249356]
72. Doiron B, Cuif MH, Chen R, Kahn A. Transcriptional glucose signaling through the glucose response element is mediated by the pentose phosphate pathway. *J Biol Chem.* 1996; 271(10): 5321–5324. [PubMed: 8621383]
73. Wellen KE, Lu C, Mancuso A, Lemons JM, Ryczko M, Dennis JW, Rabinowitz JD, Collier HA, Thompson CB. The hexosamine biosynthetic pathway couples growth factor-induced glutamine uptake to glucose metabolism. *Genes Dev.* 2010; 24(24):2784–2799.10.1101/gad.1985910 [PubMed: 21106670]
74. Anastasiou D, Pouligiannis G, Asara JM, Boxer MB, Jiang JK, Shen M, Bellinger G, Sasaki AT, Locasale JW, Auld DS, Thomas CJ, Vander Heiden MG, Cantley LC. Inhibition of pyruvate kinase M2 by reactive oxygen species contributes to cellular antioxidant responses. *Science.* 2011; 334(6060):1278–1283. [PubMed: 22052977]
75. Gruning NM, Rinnerthaler M, Bluemlein K, Mulleder M, Wamelink MM, Lehrach H, Jakobs C, Breitenbach M, Ralser M. Pyruvate kinase triggers a metabolic feedback loop that controls redox metabolism in respiring cells. *Cell Metab.* 2011; 14(3):415–427.10.1016/j.cmet.2011.06.017 [PubMed: 21907146]
76. Yeo H, Lyssiotis CA, Zhang Y, Ying H, Asara JM, Cantley LC, Paik JH. FoxO3 coordinates metabolic pathways to maintain redox balance in neural stem cells. *The EMBO J.* 2013; 32(19): 2589–2602.10.1038/emboj.2013.186
77. Zhao Y, Pan X, Zhao J, Wang Y, Peng Y, Zhong C. Decreased transketolase activity contributes to impaired hippo-campal neurogenesis induced by thiamine deficiency. *J Neurochem.* 2009; 111(2): 537–546.10.1111/j.1471-4159.2009.06341.x [PubMed: 19686241]
78. Bergstrom J, Furst P, Noree LO, Vinnars E. Intracellular free amino acid concentration in human muscle tissue. *J Appl Physiol.* 1974; 36(6):693–697. [PubMed: 4829908]
79. DeBerardinis RJ, Mancuso A, Daikhin E, Nissim I, Yudkoff M, Wehrli S, Thompson CB. Beyond aerobic glycolysis: transformed cells can engage in glutamine metabolism that exceeds the requirement for protein and nucleotide synthesis. *Proc Natl Acad Sci USA.* 2007; 104(49):19345–19350.10.1073/pnas.0709747104 [PubMed: 18032601]
80. Hensley CT, Wasti AT, DeBerardinis RJ. Glutamine and cancer: cell biology, physiology, and clinical opportunities. *J Clin Invest.* 2013; 123(9):3678–3684.10.1172/JCI69600 [PubMed: 23999442]
81. Son J, Lyssiotis CA, Ying H, Wang X, Hua S, Ligorio M, Perera RM, Ferrone CR, Mullarky E, Shyh-Chang N, Kang Y, Fleming JB, Bardeesy N, Asara JM, Haigis MC, DePinho RA, Cantley LC, Kimmelman AC. Glutamine supports pancreatic cancer growth through a KRAS-regulated metabolic pathway. *Nature.* 2013; 496(7443):101–105.10.1038/nature12040 [PubMed: 23535601]
82. Mates JM, Perez-Gomez C, Nunez de Castro I, Asenjo M, Marquez J. Glutamine and its relationship with intracellular redox status, oxidative stress and cell proliferation/death. *Int J Biochem Cell Biol.* 2002; 34(5):439–458. [PubMed: 11906817]
83. Nicklin P, Bergman P, Zhang B, Triantafellow E, Wang H, Nyfeler B, Yang H, Hild M, Kung C, Wilson C, Myer VE, MacKeigan JP, Porter JA, Wang YK, Cantley LC, Finan PM, Murphy LO. Bidirectional transport of amino acids regulates mTOR and autophagy. *Cell.* 2009; 136(3):521–534.10.1016/j.cell.2008.11.044 [PubMed: 19203585]
84. Gao P, Tchernyshyov I, Chang TC, Lee YS, Kita K, Ochi T, Zeller KI, De Marzo AM, Van Eyk JE, Mendell JT, Dang CV. c-Myc suppression of miR-23a/b enhances mitochondrial glutaminase expression and glutamine metabolism. *Nature.* 2009; 458(7239):762–765.10.1038/nature07823 [PubMed: 19219026]
85. Locasale JW. Serine, glycine and one-carbon units: cancer metabolism in full circle. *Nat Rev Cancer.* 2013; 13(8):572–583.10.1038/nrc3557 [PubMed: 23822983]

86. Tibbetts AS, Appling DR. Compartmentalization of Mammalian folate-mediated one-carbon metabolism. *Annu Rev Nutr.* 2010; 30:57–81.10.1146/annurev.nutr.012809.104810 [PubMed: 20645850]
87. Kruman II, Mouton PR, Emokpae R Jr, Cutler RG, Mattson MP. Folate deficiency inhibits proliferation of adult hippo-campal progenitors. *NeuroReport.* 2005; 16(10):1055–1059. [PubMed: 15973147]
88. Zhang X, Liu H, Cong G, Tian Z, Ren D, Wilson JX, Huang G. Effects of folate on notch signaling and cell proliferation in neural stem cells of neonatal rats in vitro. *J Nutr Sci Vitaminol.* 2008; 54(5):353–356. [PubMed: 19001765]
89. Liu H, Cao J, Zhang H, Qin S, Yu M, Zhang X, Wang X, Gao Y, Wilson JX, Huang G. Folic acid stimulates proliferation of transplanted neural stem cells after focal cerebral ischemia in rats. *J Nutr Biochem.* 2013; 24(11):1817–1822.10.1016/j.jnutbio.2013.04.002 [PubMed: 23850087]
90. Luo S, Zhang X, Yu M, Yan H, Liu H, Wilson JX, Huang G. Folic acid acts through DNA methyltransferases to induce the differentiation of neural stem cells into neurons. *Cell Biochem Biophys.* 2013; 66(3):559–566.10.1007/s12013-012-9503-6 [PubMed: 23292356]
91. Li W, Yu M, Luo S, Liu H, Gao Y, Wilson JX, Huang G. DNA methyltransferase mediates dose-dependent stimulation of neural stem cell proliferation by folate. *J Nutr Biochem.* 2013; 24(7):1295–1301.10.1016/j.jnutbio.2012.11.001 [PubMed: 23332600]
92. Sen GL, Reuter JA, Webster DE, Zhu L, Khavari PA. DNMT1 maintains progenitor function in self-renewing somatic tissue. *Nature.* 2010; 463(7280):563–567.10.1038/nature08683 [PubMed: 20081831]
93. Shyh-Chang N, Locasale JW, Lyssiotis CA, Zheng Y, Teo RY, Ratanasirintrauwoot S, Zhang J, Onder T, Unternaehrer JJ, Zhu H, Asara JM, Daley GQ, Cantley LC. Influence of threonine metabolism on S-adenosylmethionine and histone methylation. *Science.* 2013; 339(6116):222–226.10.1126/science.1226603 [PubMed: 23118012]
94. Zhu Q, Mariash A, Margosian MR, Gopinath S, Fareed MT, Anderson GW, Mariash CN. Spot 14 gene deletion increases hepatic de novo lipogenesis. *Endocrinology.* 2001; 142(10):4363–4370.10.1210/endo.142.10.8431 [PubMed: 11564699]
95. Moncur JT, Park JP, Memoli VA, Mohandas TK, Kinlaw WB. The “Spot 14” gene resides on the telomeric end of the 11q13 amplicon and is expressed in lipogenic breast cancers: implications for control of tumor metabolism. *Proc Natl Acad Sci USA.* 1998; 95(12):6989–6994. [PubMed: 9618526]
96. Ito K, Carracedo A, Weiss D, Arai F, Ala U, Avigan DE, Schafer ZT, Evans RM, Suda T, Lee CH, Pandolfi PP. A PML-PPAR- δ pathway for fatty acid oxidation regulates hematopoietic stem cell maintenance. *Nat Med.* 2012; 18(9):1350–1358.10.1038/nm.2882 [PubMed: 22902876]
97. Saito K, Dubreuil V, Arai Y, Wilsch-Brauninger M, Schwudke D, Saher G, Miyata T, Breier G, Thiele C, Shevchenko A, Nave KA, Huttner WB. Ablation of cholesterol biosynthesis in neural stem cells increases their VEGF expression and angiogenesis but causes neuron apoptosis. *Proc Natl Acad Sci USA.* 2009; 106(20):8350–8355.10.1073/pnas.0903541106 [PubMed: 19416849]
98. Bracko O, Singer T, Aigner S, Knobloch M, Winner B, Ray J, Clemenson GD Jr, Suh H, Couillard-Despres S, Aigner L, Gage FH, Jessberger S. Gene expression profiling of neural stem cells and their neuronal progeny reveals IGF2 as a regulator of adult hippocampal neurogenesis. *J Neurosci.* 2012; 32(10):3376–3387.10.1523/JNEUROSCI.4248-11.2012 [PubMed: 22399759]
99. Tavazoie M, Van der Veken L, Silva-Vargas V, Louissaint M, Colonna L, Zaidi B, Garcia-Verdugo JM, Doetsch F. A specialized vascular niche for adult neural stem cells. *Cell Stem Cell.* 2008; 3(3):279–288.10.1016/j.stem.2008.07.025 [PubMed: 18786415]
100. Panchision DM. The role of oxygen in regulating neural stem cells in development and disease. *J Cell Physiol.* 2009; 220(3):562–568.10.1002/jcp.21812 [PubMed: 19441077]
101. Tropepe V, Sibilia M, Ciruna BG, Rossant J, Wagner EF, van der Kooy D. Distinct neural stem cells proliferate in response to EGF and FGF in the developing mouse telencephalon. *Develop Biol.* 1999; 208(1):166–188.10.1006/dbio.1998.9192 [PubMed: 10075850]
102. Arsenijevic Y, Weiss S, Schneider B, Aebischer P. Insulin-like growth factor-I is necessary for neural stem cell proliferation and demonstrates distinct actions of epidermal growth factor and fibroblast growth factor-2. *J Neurosci.* 2001; 21(18):7194–7202. [PubMed: 11549730]

103. O'Kusky JR, Ye P, D'Ercole AJ. Insulin-like growth factor-I promotes neurogenesis and synaptogenesis in the hippocampal dentate gyrus during postnatal development. *J Neurosci*. 2000; 20(22):8435–8442. [PubMed: 11069951]
104. Aberg MA, Aberg ND, Hedbacker H, Oscarsson J, Eriksson PS. Peripheral infusion of IGF-I selectively induces neurogenesis in the adult rat hippocampus. *J Neurosci*. 2000; 20(8):2896–2903. [PubMed: 10751442]
105. Le Belle JE, Orozco NM, Paucar AA, Saxe JP, Mottahedeh J, Pyle AD, Wu H, Kornblum HI. Proliferative neural stem cells have high endogenous ROS levels that regulate self-renewal and neurogenesis in a PI3K/Akt-dependant manner. *Cell Stem Cell*. 2011; 8(1):59–71.10.1016/j.stem.2010.11.028 [PubMed: 21211782]
106. Groszer M, Erickson R, Scripture-Adams DD, Dougherty JD, Le Belle J, Zack JA, Geschwind DH, Liu X, Kornblum HI, Wu H. PTEN negatively regulates neural stem cell self-renewal by modulating G0-G1 cell cycle entry. *Proc Natl Acad Sci USA*. 2006; 103(1):111–116.10.1073/pnas.0509939103 [PubMed: 16373498]
107. Groszer M, Erickson R, Scripture-Adams DD, Lesche R, Trumpp A, Zack JA, Kornblum HI, Liu X, Wu H. Negative regulation of neural stem/progenitor cell proliferation by the Pten tumor suppressor gene in vivo. *Science*. 2001; 294(5549):2186–2189.10.1126/science.1065518 [PubMed: 11691952]
108. Watatani K, Hirabayashi Y, Itoh Y, Gotoh Y. PDK1 regulates the generation of oligodendrocyte precursor cells at an early stage of mouse telencephalic development. *Genes Cells*. 2012; 17(4):326–335.10.1111/j.1365-2443.2012.01591.x [PubMed: 22390626]
109. Oishi K, Watatani K, Itoh Y, Okano H, Guillemot F, Nakajima K, Gotoh Y. Selective induction of neocortical GABAergic neurons by the PDK1-Akt pathway through activation of Mash1. *Proc Natl Acad Sci USA*. 2009; 106(31):13064–13069.10.1073/pnas.0808400106 [PubMed: 19549840]
110. Tschopp O, Yang ZZ, Brodbeck D, Dummmler BA, Hemmings-Mieszczyk M, Watanabe T, Michaelis T, Frahm J, Hemmings BA. Essential role of protein kinase B gamma (PKB gamma/Akt3) in postnatal brain development but not in glucose homeostasis. *Development*. 2005; 132(13):2943–2954.10.1242/dev.01864 [PubMed: 15930105]
111. Kim WY, Wang X, Wu Y, Doble BW, Patel S, Woodgett JR, Snider WD. GSK-3 is a master regulator of neural progenitor homeostasis. *Nat Neurosci*. 2009; 12(11):1390–1397.10.1038/nn.2408 [PubMed: 19801986]
112. Robey RB, Hay N. Is Akt the “Warburg kinase”?-Akt-energy metabolism interactions and oncogenesis. *Semin Cancer Biol*. 2009; 19(1):25–31.10.1016/j.semcancer.2008.11.010 [PubMed: 19130886]
113. Elstrom RL, Bauer DE, Buzzai M, Karnauskas R, Harris MH, Plas DR, Zhuang H, Cinalli RM, Alavi A, Rudin CM, Thompson CB. Akt stimulates aerobic glycolysis in cancer cells. *Cancer Res*. 2004; 64(11):3892–3899.10.1158/0008-5472.CAN-03-2904 [PubMed: 15172999]
114. Robey RB, Hay N. Mitochondrial hexokinases, novel mediators of the antiapoptotic effects of growth factors and Akt. *Oncogene*. 2006; 25(34):4683–4696.10.1038/sj.onc.1209595 [PubMed: 16892082]
115. Fang M, Shen Z, Huang S, Zhao L, Chen S, Mak TW, Wang X. The ER UDPase ENTPD5 promotes protein N-glycosylation, the Warburg effect, and proliferation in the PTEN pathway. *Cell*. 2010; 143(5):711–724.10.1016/j.cell.2010.10.010 [PubMed: 21074248]
116. Greer EL, Brunet A. FOXO transcription factors at the interface between longevity and tumor suppression. *Oncogene*. 2005; 24(50):7410–7425.10.1038/sj.onc.1209086 [PubMed: 16288288]
117. Paik JH, Kollipara R, Chu G, Ji H, Xiao Y, Ding Z, Miao L, Tothova Z, Horner JW, Carrasco DR, Jiang S, Gilliland DG, Chin L, Wong WH, Castrillon DH, DePinho RA. FoxOs are lineage-restricted redundant tumor suppressors and regulate endothelial cell homeostasis. *Cell*. 2007; 128(2):309–323.10.1016/j.cell.2006.12.029 [PubMed: 17254969]
118. Tothova Z, Kollipara R, Huntly BJ, Lee BH, Castrillon DH, Cullen DE, McDowell EP, Lazo-Kallanian S, Williams IR, Sears C, Armstrong SA, Passegue E, DePinho RA, Gilliland DG. FoxOs are critical mediators of hematopoietic stem cell resistance to physiologic oxidative stress. *Cell*. 2007; 128(2):325–339.10.1016/j.cell.2007.01.003 [PubMed: 17254970]

119. Zhang X, Yalcin S, Lee DF, Yeh TY, Lee SM, Su J, Mungamuri SK, Rimmele P, Kennedy M, Sellers R, Landthaler M, Tuschl T, Chi NW, Lemischka I, Keller G, Ghaffari S. FOXO1 is an essential regulator of pluripotency in human embryonic stem cells. *Nat Cell Biol.* 2011; 13(9): 1092–1099.10.1038/ncb2293 [PubMed: 21804543]
120. Vilchez D, Boyer L, Lutz M, Merkwirth C, Morante I, Tse C, Spencer B, Page L, Masliah E, Berggren WT, Gage FH, Dillin A. FOXO4 is necessary for neural differentiation of human embryonic stem cells. *Aging Cell.* 2013; 12(3):518–522.10.1111/ace.12067 [PubMed: 23551888]
121. Goertz MJ, Wu Z, Gallardo TD, Hamra FK, Castrillon DH. Foxo1 is required in mouse spermatogonial stem cells for their maintenance and the initiation of spermatogenesis. *J Clin Invest.* 2011; 121(9):3456–3466.10.1172/JCI57984 [PubMed: 21865646]
122. Miyamoto K, Araki KY, Naka K, Arai F, Takubo K, Yamazaki S, Matsuoka S, Miyamoto T, Ito K, Ohmura M, Chen C, Hos-okawa K, Nakauchi H, Nakayama K, Nakayama KI, Harada M, Motoyama N, Suda T, Hirao A. Foxo3a is essential for maintenance of the hematopoietic stem cell pool. *Cell Stem Cell.* 2007; 1(1):101–112.10.1016/j.stem.2007.02.001 [PubMed: 18371339]
123. Kang JY, Nan X, Jin MS, Youn SJ, Ryu YH, Mah S, Han SH, Lee H, Paik SG, Lee JO. Recognition of lipopeptide patterns by Toll-like receptor 2-Toll-like receptor 6 heterodimer. *Immunity.* 2009; 31(6):873–884.10.1016/j.immuni.2009.09.018 [PubMed: 19931471]
124. Renault VM, Rafalski VA, Morgan AA, Salih DA, Brett JO, Webb AE, Villeda SA, Thekkat PU, Guillerey C, Denko NC, Palmer TD, Butte AJ, Brunet A. FoxO3 regulates neural stem cell homeostasis. *Cell Stem Cell.* 2009; 5(5):527–539.10.1016/j.stem.2009.09.014 [PubMed: 19896443]
125. van der Vos KE, Eliasson P, Proikas-Cezanne T, Vervoort SJ, van Boxtel R, Putker M, van Zutphen IJ, Mauthe M, Zellmer S, Pals C, Verhagen LP, Groot Koerkamp MJ, Braat AK, Dansen TB, Holstege FC, Gebhardt R, Burgering BM, Coffey PJ. Modulation of glutamine metabolism by the PI(3)K-PKB-FOXO network regulates autophagy. *Nature Cell Biol.* 2012; 14(8):829–837.10.1038/ncb2536 [PubMed: 22820375]
126. Vazquez P, Arroba AI, Cecconi F, de la Rosa EJ, Boya P, de Pablo F. Atg5 and Ambra1 differentially modulate neurogenesis in neural stem cells. *Autophagy.* 2012; 8(2):187–199.10.4161/auto.8.2.18535 [PubMed: 22240590]
127. Wang C, Liang CC, Bian ZC, Zhu Y, Guan JL. FIP200 is required for maintenance and differentiation of postnatal neural stem cells. *Nat Neurosci.* 2013; 16(5):532–542.10.1038/nn.3365 [PubMed: 23542691]
128. Magri L, Cambiaghi M, Cominelli M, Alfaro-Cervello C, Cursi M, Pala M, Bulfone A, Garcia-Verdugo JM, Leocani L, Mini-cucci F, Poliani PL, Galli R. Sustained activation of mTOR pathway in embryonic neural stem cells leads to development of tuberous sclerosis complex-associated lesions. *Cell Stem Cell.* 2011; 9(5):447–462.10.1016/j.stem.2011.09.008 [PubMed: 22056141]
129. Anderl S, Freeland M, Kwiatkowski DJ, Goto J. Therapeutic value of prenatal rapamycin treatment in a mouse brain model of tuberous sclerosis complex. *Hum Mol Genet.* 2011; 20(23): 4597–4604.10.1093/hmg/ddr393 [PubMed: 21890496]
130. Goto J, Talos DM, Klein P, Qin W, Chekaluk YI, Anderl S, Malinowska IA, Di Nardo A, Bronson RT, Chan JA, Vinters HV, Kernie SG, Jensen FE, Sahin M, Kwiatkowski DJ. Regulable neural progenitor-specific Tsc1 loss yields giant cells with organellar dysfunction in a model of tuberous sclerosis complex. *Proc Natl Acad Sci USA.* 2011; 108(45):E1070–E1079.10.1073/pnas.1106454108 [PubMed: 22025691]
131. Zhou J, Shrikhande G, Xu J, McKay RM, Burns DK, Johnson JE, Parada LF. Tsc1 mutant neural stem/progenitor cells exhibit migration deficits and give rise to subependymal lesions in the lateral ventricle. *Genes Dev.* 2011; 25(15):1595–1600.10.1101/gad.16750211 [PubMed: 21828270]
132. Guertin DA, Sabatini DM. Defining the role of mTOR in cancer. *Cancer Cell.* 2007; 12(1):9–22.10.1016/j.ccr.2007.05.008 [PubMed: 17613433]
133. Csibi A, Fendt SM, Li C, Poulogiannis G, Choo AY, Chapski DJ, Jeong SM, Dempsey JM, Parkhitko A, Morrison T, Henske EP, Haigis MC, Cantley LC, Stephanopoulos G, Yu J, Blenis J.

- The mTORC1 pathway stimulates glutamine metabolism and cell proliferation by repressing SIRT4. *Cell*. 2013; 153(4):840–854.10.1016/j.cell.2013.04.023 [PubMed: 23663782]
134. Ricoult SJ, Manning BD. The multifaceted role of mTORC1 in the control of lipid metabolism. *EMBO reports*. 2013; 14(3):242–251.10.1038/embor.2013.5 [PubMed: 23399656]
 135. Lamming DW, Sabatini DM. A Central role for mTOR in lipid homeostasis. *Cell Metabol*. 2013; 18(4):465–469.10.1016/j.cmet.2013.08.002
 136. Wang BT, Ducker GS, Barczak AJ, Barbeau R, Erle DJ, Shokat KM. The mammalian target of rapamycin regulates cholesterol biosynthetic gene expression and exhibits a rapamycin-resistant transcriptional profile. *Proc Natl Acad Sci USA*. 2011; 108(37):15201–15206.10.1073/pnas.1103746108 [PubMed: 21876130]
 137. Morrisett JD, Abdel-Fattah G, Hoogeveen R, Mitchell E, Ballantyne CM, Pownall HJ, Opekun AR, Jaffe JS, Oppermann S, Kahan BD. Effects of sirolimus on plasma lipids, lipo-protein levels, and fatty acid metabolism in renal transplant patients. *J Lipid Res*. 2002; 43(8):1170–1180. [PubMed: 12177161]
 138. Semenza GL. HIF-1 mediates metabolic responses to intratumoral hypoxia and oncogenic mutations. *J Clin Invest*. 2013; 123(9):3664–3671.10.1172/JCI67230 [PubMed: 23999440]
 139. Simon MC, Keith B. The role of oxygen availability in embryonic development and stem cell function nature reviews. *Mol Cell Biol*. 2008; 9(4):285–296.10.1038/nrm2354
 140. Adelman DM, Maltepe E, Simon MC. Multilineage embryonic hematopoiesis requires hypoxic ARNT activity. *Genes Dev*. 1999; 13(19):2478–2483. [PubMed: 10521392]
 141. Takubo K, Goda N, Yamada W, Iriuchishima H, Ikeda E, Kubota Y, Shima H, Johnson RS, Hirao A, Suematsu M, Suda T. Regulation of the HIF-1 α level is essential for hematopoietic stem cells. *Cell Stem Cell*. 2010; 7(3):391–402.10.1016/j.stem.2010.06.020 [PubMed: 20804974]
 142. Jang YY, Sharkis SJ. A low level of reactive oxygen species selects for primitive hematopoietic stem cells that may reside in the low-oxygenic niche. *Blood*. 2007; 110(8):3056–3063.10.1182/blood-2007-05-087759 [PubMed: 17595331]
 143. Zhu XH, Yan HC, Zhang J, Qu HD, Qiu XS, Chen L, Li SJ, Cao X, Bean JC, Chen LH, Qin XH, Liu JH, Bai XC, Mei L, Gao TM. Intermittent hypoxia promotes hippocampal neurogenesis and produces antidepressant-like effects in adult rats. *J Neurosci*. 2010; 30(38):12653–12663.10.1523/JNEUROSCI.6414-09.2010 [PubMed: 20861371]
 144. Tsai YW, Yang YR, Wang PS, Wang RY. Intermittent hypoxia after transient focal ischemia induces hippocampal neurogenesis and c-Fos expression and reverses spatial memory deficits in rats. *PLoS One*. 2011; 6(8):e24001.10.1371/journal.pone.0024001 [PubMed: 21887361]
 145. Zhu LL, Zhao T, Li HS, Zhao H, Wu LY, Ding AS, Fan WH, Fan M. Neurogenesis in the adult rat brain after intermittent hypoxia. *Brain Res*. 2005; 1–2:1–6.10.1016/j.brainres.2005.04.075
 146. Chen X, Tian Y, Yao L, Zhang J, Liu Y. Hypoxia stimulates proliferation of rat neural stem cells with influence on the expression of cyclin D1 and c-Jun N-terminal protein kinase signaling pathway in vitro. *Neuroscience*. 2010; 165(3):705–714.10.1016/j.neuroscience.2009.11.007 [PubMed: 19909792]
 147. Zhu LL, Wu LY, Yew DT, Fan M. Effects of hypoxia on the proliferation and differentiation of NSCs. *Mol Neurobiol*. 2005; 31(1–3):231–242.10.1385/MN:31:1-3:231 [PubMed: 15953824]
 148. Mu J, Krafft PR, Zhang JH. Hyperbaric oxygen therapy promotes neurogenesis: where do we stand? *Med Gas Res*. 2011; 1(1):14.10.1186/2045-9912-1-14 [PubMed: 22146131]
 149. Milosevic J, Adler I, Manaenko A, Schwarz SC, Walkinshaw G, Arend M, Flippin LA, Storch A, Schwarz J. Non-hypoxic stabilization of hypoxia-inducible factor α (HIF- α): relevance in neural progenitor/stem cells. *Neurotox Res*. 2009; 15(4):367–380.10.1007/s12640-009-9043-z [PubMed: 19384570]
 150. Yeung SJ, Pan J, Lee MH. Roles of p53, MYC and HIF-1 in regulating glycolysis - the seventh hallmark of cancer. *CMLS*. 2008; 65(24):3981–3999.10.1007/s00018-008-8224-x [PubMed: 18766298]
 151. Chen C, Pore N, Behrooz A, Ismail-Beigi F, Maity A. Regulation of glut1 mRNA by hypoxia-inducible factor 1. Interaction between H-ras and hypoxia. *J Biol Chem*. 2001; 276(12):9519–9525.10.1074/jbc.M010144200 [PubMed: 11120745]

152. Riddle SR, Ahmad A, Ahmad S, Deeb SS, Malkki M, Schneider BK, Allen CB, White CW. Hypoxia induces hexokinase II gene expression in human lung cell line A549. *Am J Physiol Lung Cell Mol Physiol*. 2000; 278(2):L407–L416. [PubMed: 10666126]
153. Simsek T, Kocabas F, Zheng J, Deberardinis RJ, Mahmoud AI, Olson EN, Schneider JW, Zhang CC, Sadek HA. The distinct metabolic profile of hematopoietic stem cells reflects their location in a hypoxic niche. *Cell Stem Cell*. 2010; 7(3):380–390.10.1016/j.stem.2010.07.011 [PubMed: 20804973]
154. Metallo CM, Gameiro PA, Bell EL, Mattaini KR, Yang J, Hiller K, Jewell CM, Johnson ZR, Irvine DJ, Guarente L, Kelleher JK, Vander Heiden MG, Iliopoulos O, Stephanopoulos G. Reductive glutamine metabolism by IDH1 mediates lipogenesis under hypoxia. *Nature*. 2012; 481(7381):380–384.10.1038/nature10602 [PubMed: 22101433]
155. Sun RC, Denko NC. Hypoxic regulation of glutamine metabolism through HIF1 and SIAH2 supports lipid synthesis that is necessary for tumor growth. *Cell Metab*. 2014; 19(2):285–292.10.1016/j.cmet.2013.11.022 [PubMed: 24506869]
156. Haigis MC, Guarente LP. Mammalian sirtuins—emerging roles in physiology, aging, and calorie restriction. *Genes Dev*. 2006; 20(21):2913–2921.10.1101/gad.1467506 [PubMed: 17079682]
157. Finkel T, Deng CX, Mostoslavsky R. Recent progress in the biology and physiology of sirtuins. *Nature*. 2009; 460(7255):587–591.10.1038/nature08197 [PubMed: 19641587]
158. Rodgers JT, Lerin C, Haas W, Gygi SP, Spiegelman BM, Puigserver P. Nutrient control of glucose homeostasis through a complex of PGC-1 α and SIRT1. *Nature*. 2005; 434(7029):113–118.10.1038/nature03354 [PubMed: 15744310]
159. Lee IH, Cao L, Mostoslavsky R, Lombard DB, Liu J, Bruns NE, Tsokos M, Alt FW, Finkel T. A role for the NAD-dependent deacetylase Sirt1 in the regulation of autophagy. *Proc Natl Acad Sci USA*. 2008; 105(9):3374–3379.10.1073/pnas.0712145105 [PubMed: 18296641]
160. Zhong L, D'Urso A, Toiber D, Sebastian C, Henry RE, Vady-sirisack DD, Guimaraes A, Marinelli B, Wikstrom JD, Nir T, Clish CB, Vaitheesvaran B, Iliopoulos O, Kurland I, Dor Y, Weissleder R, Shirihai OS, Ellisen LW, Espinosa JM, Mostoslavsky R. The histone deacetylase Sirt6 regulates glucose homeostasis via Hif1 α . *Cell*. 2010; 140(2):280–293.10.1016/j.cell.2009.12.041 [PubMed: 20141841]
161. Finley LW, Carracedo A, Lee J, Souza A, Egia A, Zhang J, Teruya-Feldstein J, Moreira PI, Cardoso SM, Clish CB, Pandolfi PP, Haigis MC. SIRT3 opposes reprogramming of cancer cell metabolism through HIF1 α destabilization. *Cancer Cell*. 2011; 19(3):416–428.10.1016/j.ccr.2011.02.014 [PubMed: 21397863]
162. Jing E, Emanuelli B, Hirsche MD, Boucher J, Lee KY, Lombard D, Verdin EM, Kahn CR. Sirtuin-3 (Sirt3) regulates skeletal muscle metabolism and insulin signaling via altered mitochondrial oxidation and reactive oxygen species production. *Proc Natl Acad Sci USA*. 2011; 108(35):14608–14613.10.1073/pnas.1111308108 [PubMed: 21873205]
163. Someya S, Yu W, Hallows WC, Xu J, Vann JM, Leeuwenburgh C, Tanokura M, Denu JM, Prolla TA. Sirt3 mediates reduction of oxidative damage and prevention of age-related hearing loss under caloric restriction. *Cell*. 2010; 143(5):802–812.10.1016/j.cell.2010.10.002 [PubMed: 21094524]
164. Qiu X, Brown K, Hirsche MD, Verdin E, Chen D. Calorie restriction reduces oxidative stress by SIRT3-mediated SOD2 activation. *Cell Metab*. 2010; 12(6):662–667.10.1016/j.cmet.2010.11.015 [PubMed: 21109198]
165. Brown K, Xie S, Qiu X, Mohrin M, Shin J, Liu Y, Zhang D, Scadden DT, Chen D. SIRT3 reverses aging-associated degeneration. *Cell Rep*. 2013; 3(2):319–327.10.1016/j.celrep.2013.01.005 [PubMed: 23375372]
166. Haigis MC, Mostoslavsky R, Haigis KM, Fahie K, Christodoulou DC, Murphy AJ, Valenzuela DM, Yancopoulos GD, Karow M, Blander G, Wolberger C, Prolla TA, Weindrich R, Alt FW, Guarente L. SIRT4 inhibits glutamate dehydrogenase and opposes the effects of calorie restriction in pancreatic beta cells. *Cell*. 2006; 126(5):941–954.10.1016/j.cell.2006.06.057 [PubMed: 16959573]
167. Lombard DB, Alt FW, Cheng HL, Bunkenborg J, Streeper RS, Mostoslavsky R, Kim J, Yancopoulos G, Valenzuela D, Murphy A, Yang Y, Chen Y, Hirsche MD, Bronson RT, Haigis M, Guarente LP, Farese RV Jr, Weissman S, Verdin E, Schwer B. Mammalian Sir2 homolog

- SIRT3 regulates global mitochondrial lysine acetylation. *Molecular Cell Biol.* 2007; 27(24): 8807–8814.10.1128/MCB.01636-07
168. Schlicker C, Gertz M, Papatheodorou P, Kachholz B, Becker CF, Steegborn C. Substrates and regulation mechanisms for the human mitochondrial sirtuins Sirt3 and Sirt5. *J Mol Biol.* 2008; 382(3):790–801.10.1016/j.jmb.2008.07.048 [PubMed: 18680753]
 169. Saharan S, Jhaveri DJ, Bartlett PF. SIRT1 regulates the neurogenic potential of neural precursors in the adult subventricular zone and hippocampus. *J Neurosci Res.* 2013; 91(5):642–659.10.1002/jnr.23199 [PubMed: 23404532]
 170. Prozorovski T, Schulze-Toppoff U, Glumm R, Baumgart J, Schroter F, Ninnemann O, Siegert E, Bendix I, Brustle O, Nitsch R, Zipp F, Aktas O. Sirt1 contributes critically to the redox-dependent fate of neural progenitors. *Nature Cell Biol.* 2008; 10(4):385–394.10.1038/ncb1700 [PubMed: 18344989]
 171. Hisahara S, Chiba S, Matsumoto H, Tanno M, Yagi H, Shimohama S, Sato M, Horio Y. Histone deacetylase SIRT1 modulates neuronal differentiation by its nuclear translocation. *Proc Natl Acad Sci USA.* 2008; 105(40):15599–15604.10.1073/pnas.0800612105 [PubMed: 18829436]
 172. Rafalski VA, Ho PP, Brett JO, Ucar D, Dugas JC, Pollina EA, Chow LM, Ibrahim A, Baker SJ, Barres BA, Steinman L, Brunet A. Expansion of oligodendrocyte progenitor cells following SIRT1 inactivation in the adult brain. *Nature Cell Biol.* 2013; 15(6):614–624.10.1038/ncb2735 [PubMed: 23644469]
 173. Houtkooper RH, Pirinen E, Auwerx J. Sirtuins as regulators of metabolism and healthspan. *Nat Rev Mol Cell Biol.* 2012; 13(4):225–238.10.1038/nrm3293 [PubMed: 22395773]
 174. Baudino TA, McKay C, Penderville-Samain H, Nilsson JA, Maclean KH, White EL, Davis AC, Ihle JN, Cleveland JL. c-Myc is essential for vasculogenesis and angiogenesis during development and tumor progression. *Genes Dev.* 2002; 16(19):2530–2543.10.1101/gad.1024602 [PubMed: 12368264]
 175. van Bokhoven H, Celli J, van Reeuwijk J, Rinne T, Glaudemans B, van Beusekom E, Rieu P, Newbury-Ecob RA, Chiang C, Brunner HG. MYCN haploinsufficiency is associated with reduced brain size and intestinal atresias in Feingold syndrome. *Nature Gene.* 2005; 37(5):465–467.10.1038/ng1546
 176. Hirvonen H, Makela TP, Sandberg M, Kalimo H, Vuorio E, Alitalo K. Expression of the myc proto-oncogenes in developing human fetal brain. *Oncogene.* 1990; 5(12):1787–1797. [PubMed: 2284098]
 177. Kerosuo L, Piltti K, Fox H, Angers-Loustau A, Hayry V, Eilers M, Sariola H, Wartiovaara K. Myc increases self-renewal in neural progenitor cells through Miz-1. *J Cell Sci.* 2008; 121(Pt 23):3941–3950.10.1242/jcs.024802 [PubMed: 19001505]
 178. Knoepfler PS, Cheng PF, Eisenman RN. N-myc is essential during neurogenesis for the rapid expansion of progenitor cell populations and the inhibition of neuronal differentiation. *Genes Dev.* 2002; 16(20):2699–2712.10.1101/gad.1021202 [PubMed: 12381668]
 179. Wey A, Knoepfler PS. c-myc and N-myc promote active stem cell metabolism and cycling as architects of the developing brain. *Oncotarget.* 2010; 1(2):120–130. [PubMed: 20651942]
 180. Wey A, Martinez Cerdeno V, Pleasure D, Knoepfler PS. c- and N-myc regulate neural precursor cell fate, cell cycle, and metabolism to direct cerebellar development. *Cerebellum.* 2010; 9(4): 537–547. [PubMed: 20658325]
 181. Wilson A, Murphy MJ, Oskarsson T, Kaloulis K, Bettess MD, Oser GM, Pasche AC, Knabenhans C, Macdonald HR, Trumpp A. c-Myc controls the balance between hematopoietic stem cell self-renewal and differentiation. *Genes Dev.* 2004; 18(22):2747–2763.10.1101/gad.313104 [PubMed: 15545632]
 182. Moumen M, Chiche A, Deugnier MA, Petit V, Gandarillas A, Glukhova MA, Faraldo MM. The proto-oncogene Myc is essential for mammary stem cell function. *Stem Cells.* 2012; 30(6):1246–1254.10.1002/stem.1090 [PubMed: 22438054]
 183. Zinin N, Adameyko I, Wilhelm M, Fritz N, Uhlen P, Ernfors P, Henriksson MA. MYC proteins promote neuronal differentiation by controlling the mode of progenitor cell division. *EMBO Rep.* 2014; 15(4):383–391.10.1002/embr.201337424 [PubMed: 24599748]

184. Dang CV. MYC, metabolism, cell growth, and tumori-genesis. Cold Spring Harbor perspectives in medicine. 2013; 3(8):10.1101/cshperspect.a014217
185. Wise DR, DeBerardinis RJ, Mancuso A, Sayed N, Zhang XY, Pfeiffer HK, Nissim I, Daikhin E, Yudkoff M, McMahon SB, Thompson CB. Myc regulates a transcriptional program that stimulates mitochondrial glutaminolysis and leads to glutamine addiction. Proc Natl Acad Sci USA. 2008; 105(48):18782–18787.10.1073/pnas.0810199105 [PubMed: 19033189]
186. Dang CV. MYC on the path to cancer. Cell. 2012; 149(1):22–35.10.1016/j.cell.2012.03.003 [PubMed: 22464321]
187. Kim JW, Zeller KI, Wang Y, Jegga AG, Aronow BJ, O'Donnell KA, Dang CV. Evaluation of myc E-box phylogenetic footprints in glycolytic genes by chromatin immunoprecipitation assays. Mol Cell Biol. 2004; 24(13):5923–5936.10.1128/MCB.24.13.5923-5936.2004 [PubMed: 15199147]
188. David CJ, Chen M, Assanah M, Canoll P, Manley JL. HnRNP proteins controlled by c-Myc deregulate pyruvate kinase mRNA splicing in cancer. Nature. 2010; 463(7279):364–368.10.1038/nature08697 [PubMed: 20010808]
189. Masui K, Tanaka K, Akhavan D, Babic I, Gini B, Matsutani T, Iwanami A, Liu F, Villa GR, Gu Y, Campos C, Zhu S, Yang H, Yong WH, Cloughesy TF, Mellinghoff IK, Cavenee WK, Shaw RJ, Mischel PS. mTOR complex 2 controls glycolytic metabolism in glioblastoma through FoxO acetylation and upregulation of c-Myc. Cell Metab. 2013; 18(5):726–739.10.1016/j.cmet.2013.09.013 [PubMed: 24140020]
190. van Lookeren Campagne M, Gill R. Tumor-suppressor p53 is expressed in proliferating and newly formed neurons of the embryonic and postnatal rat brain: comparison with expression of the cell cycle regulators p21Waf1/Cip1, p27Kip1, p57Kip2, p16Ink4a, cyclin G1, and the proto-oncogene Bax. J Comp Neurol. 1998; 397(2):181–198. [PubMed: 9658283]
191. Murase S, Poser SW, Joseph J, McKay RD. p53 controls neuronal death in the CA3 region of the newborn mouse hippocampus. Eur J Neurosci. 2011; 34(3):374–381.10.1111/j.1460-9568.2011.07758.x [PubMed: 21714817]
192. Meletis K, Wirta V, Hede SM, Nister M, Lundberg J, Frisen J. p53 suppresses the self-renewal of adult neural stem cells. Development. 2006; 133(2):363–369.10.1242/dev.02208 [PubMed: 16368933]
193. Kippin TE, Martens DJ, van der Kooy D. p21 loss compromises the relative quiescence of forebrain stem cell proliferation leading to exhaustion of their proliferation capacity. Genes Dev. 2005; 19(6):756–767.10.1101/gad.1272305 [PubMed: 15769947]
194. Forsberg K, Wuttke A, Quadrato G, Chumakov PM, Wizenmann A, Di Giovanni S. The tumor suppressor p53 fine-tunes reactive oxygen species levels and neurogenesis via PI3 kinase signaling. J Neurosci. 2013; 33(36):14318–14330.10.1523/JNEUROSCI.1056-13.2013 [PubMed: 24005285]
195. Bensaad K, Tsuruta A, Selak MA, Vidal MN, Nakano K, Bartrons R, Gottlieb E, Vousden KH. TIGAR, a p53-inducible regulator of glycolysis and apoptosis. Cell. 2006; 126(1):107–120.10.1016/j.cell.2006.05.036 [PubMed: 16839880]
196. Bensaad K, Cheung EC, Vousden KH. Modulation of intracellular ROS levels by TIGAR controls autophagy. EMBO J. 2009; 28(19):3015–3026.10.1038/emboj.2009.242 [PubMed: 19713938]
197. Li T, Kon N, Jiang L, Tan M, Ludwig T, Zhao Y, Baer R, Gu W. Tumor suppression in the absence of p53-mediated cell-cycle arrest, apoptosis, and senescence. Cell. 2012; 149(6):1269–1283.10.1016/j.cell.2012.04.026 [PubMed: 22682249]
198. Sablina AA, Budanov AV, Ilyinskaya GV, Agapova LS, Kravchenko JE, Chumakov PM. The antioxidant function of the p53 tumor suppressor. Nat Med. 2005; 11(12):1306–1313.10.1038/nm1320 [PubMed: 16286925]
199. Matoba S, Kang JG, Patino WD, Wragg A, Boehm M, Gavrilova O, Hurley PJ, Bunz F, Hwang PM. p53 regulates mitochondrial respiration. Science. 2006; 312(5780):1650–1653.10.1126/science.1126863 [PubMed: 16728594]
200. Suzuki S, Tanaka T, Poyurovsky MV, Nagano H, Mayama T, Ohkubo S, Lokshin M, Hosokawa H, Nakayama T, Suzuki Y, Sugano S, Sato E, Nagao T, Yokote K, Tatsuno I, Prives C.

Phosphate-activated glutaminase (GLS2), a p53-inducible regulator of glutamine metabolism and reactive oxygen species. *Proc Natl Acad Sci USA*. 2010; 107(16):7461–7466.10.1073/pnas.1002459107 [PubMed: 20351271]

201. Hu W, Zhang C, Wu R, Sun Y, Levine A, Feng Z. Glutaminase 2, a novel p53 target gene regulating energy metabolism and antioxidant function. *Proc Natl Acad Sci USA*. 2010; 107(16): 7455–7460.10.1073/pnas.1001006107 [PubMed: 20378837]
202. Stambolic V, MacPherson D, Sas D, Lin Y, Snow B, Jang Y, Benchimol S, Mak TW. Regulation of PTEN transcription by p53. *Molecular Cell*. 2001; 8(2):317–325. [PubMed: 11545734]
203. Yan H, Parsons DW, Jin G, McLendon R, Rasheed BA, Yuan W, Kos I, Batinic-Haberle I, Jones S, Riggins GJ, Friedman H, Friedman A, Reardon D, Herndon J, Kinzler KW, Velculescu VE, Vogelstein B, Bigner DD. IDH1 and IDH2 mutations in gliomas. *New Eng J Med*. 2009; 360(8): 765–773.10.1056/NEJMoa0808710 [PubMed: 19228619]
204. Tefferi A, Lasho TL, Abdel-Wahab O, Guglielmelli P, Patel J, Caramazza D, Pieri L, Finke CM, Kilpivaara O, Wadleigh M, Mai M, McClure RF, Gilliland DG, Levine RL, Pardanani A, Vannucchi AM. IDH1 and IDH2 mutation studies in 1473 patients with chronic-, fibrotic- or blast-phase essential thrombocythemia, polycythemia vera or myelofibrosis. *Leukemia*. 2010; 24(7):1302–1309.10.1038/leu.2010.113 [PubMed: 20508616]
205. Dang L, White DW, Gross S, Bennett BD, Bittinger MA, Driggers EM, Fantin VR, Jang HG, Jin S, Keenan MC, Marks KM, Prins RM, Ward PS, Yen KE, Liao LM, Rabinowitz JD, Cantley LC, Thompson CB, Vander Heiden MG, Su SM. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. *Nature*. 2009; 462(7274):739–744. [PubMed: 19935646]
206. Figueroa ME, Abdel-Wahab O, Lu C, Ward PS, Patel J, Shih A, Li Y, Bhagwat N, Vasanthakumar A, Fernandez HF, Tallman MS, Sun Z, Wolniak K, Peeters JK, Liu W, Choe SE, Fantin VR, Paietta E, Lowenberg B, Licht JD, Godley LA, Delwel R, Valk PJ, Thompson CB, Levine RL, Melnick A. Leukemic IDH1 and IDH2 mutations result in a hypermethylation phenotype, disrupt TET2 function, and impair hematopoietic differentiation. *Cancer Cell*. 2010; 18(6):553–567.10.1016/j.ccr.2010.11.015 [PubMed: 21130701]
207. Losman JA, Looper RE, Koivunen P, Lee S, Schneider RK, McMahon C, Cowley GS, Root DE, Ebert BL, Kaelin WG Jr. (R)-2-hydroxyglutarate is sufficient to promote leukemogenesis and its effects are reversible. *Science*. 2013; 339(6127):1621–1625.10.1126/science.1231677 [PubMed: 23393090]
208. Chowdhury R, Yeoh KK, Tian YM, Hillringhaus L, Bagg EA, Rose NR, Leung IK, Li XS, Woon EC, Yang M, McDonough MA, King ON, Clifton IJ, Klose RJ, Claridge TD, Ratcliffe PJ, Schofield CJ, Kawamura A. The oncometabolite 2-hydroxyglutarate inhibits histone lysine demethylases. *EMBO Rep*. 2011; 12(5):463–469.10.1038/embor.2011.43 [PubMed: 21460794]
209. Xu W, Yang H, Liu Y, Yang Y, Wang P, Kim SH, Ito S, Yang C, Xiao MT, Liu LX, Jiang WQ, Liu J, Zhang JY, Wang B, Frye S, Zhang Y, Xu YH, Lei QY, Guan KL, Zhao SM, Xiong Y. Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of alpha-ketoglutarate-dependent dioxygenases. *Cancer Cell*. 2011; 19(1):17–30.10.1016/j.ccr.2010.12.014 [PubMed: 21251613]
210. Lu C, Ward PS, Kapoor GS, Rohle D, Turcan S, Abdel-Wahab O, Edwards CR, Khanin R, Figueroa ME, Melnick A, Wellen KE, O'Rourke DM, Berger SL, Chan TA, Levine RL, Mellinghoff IK, Thompson CB. IDH mutation impairs histone demethylation and results in a block to cell differentiation. *Nature*. 2012; 483(7390):474–478.10.1038/nature10860 [PubMed: 22343901]
211. Sasaki M, Knobbe CB, Munger JC, Lind EF, Brenner D, Brustle A, Harris IS, Holmes R, Wakeham A, Haight J, You-Ten A, Li WY, Schalm S, Su SM, Virtanen C, Reifemberger G, Ohashi PS, Barber DL, Figueroa ME, Melnick A, Zuniga-Pflucker JC, Mak TW. IDH1(R132H) mutation increases murine haematopoietic progenitors and alters epigenetics. *Nature*. 2012; 488(7413):656–659.10.1038/nature11323 [PubMed: 22763442]
212. Rohle D, Popovici-Muller J, Palaskas N, Turcan S, Grommes C, Campos C, Tsoi J, Clark O, Oldrini B, Komisopoulou E, Kunii K, Pedraza A, Schalm S, Silverman L, Miller A, Wang F, Yang H, Chen Y, Kernysky A, Rosenblum MK, Liu W, Biller SA, Su SM, Brennan CW, Chan TA, Graeber TG, Yen KE, Mellinghoff IK. An inhibitor of mutant IDH1 delays growth and promotes differentiation of glioma cells. *Science*. 2013; 340(6132):626–630.10.1126/science.1236062 [PubMed: 23558169]

213. Ben-Shaanan TL, Ben-Hur T, Yanai J. Transplantation of neural progenitors enhances production of endogenous cells in the impaired brain. *Mol Psychiatry*. 2008; 13(2):222–231.10.1038/sj.mp.4002084 [PubMed: 17876325]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Fig. 1. Schematic model of the adult NSPC niche and intracellular mechanism in NSPCs under hypoxic environment. a SVZ type B cells in this region are neural stem cells, which give rise to type C transit-amplifying cells. In turn, type C cells generate migrating neuroblasts (type A cells) destined for the olfactory bulb. Ependymal cells line the walls of the lateral ventricle. SGZ type 1 radial astrocytes give rise to type 2 transit-amplifying cells than type 3 migrating neuroblasts. Although direct measurements from oxygen tension in the SVZ have never been performed, NSCs are considered to reside in hypoxic areas of the brain. b Under the hypoxic environment, the role of HIF-1 is important. HIF-1α protein is maintained as low level under normoxia, as a result of prolyl hydroxylation-mediated degradation.

However, low oxygen tension inhibits this degradation and stabilized HIF-1 α translocates to the nucleus and activates gene transcription after heterodimerization with HIF-1 β . Upon activation of the Notch receptor in NSCs, the Notch intracellular domain (NICD) is accumulated in the nucleus and HIF-1 α potentiates Notch-dependent activation of target genes through interaction with the NICD. HIF-1 α increases activation of TCF/LEF and enhances b-catenin dependent Wnt signaling. High oxygen interferes with BMP signaling. Many other signals are translated as intracellular signaling and accompanying gene expression and metabolic adaptation

Fig. 2.

Molecular pathway of glycolysis in NSPCs. After glucose is taken up through glucose transporter (GLUT), it is converted to pyruvate by glycolysis. In turn, the pyruvate enters the energy-generating TCA cycle. HIF-1 α contributes to glycolysis via turning on the expression of Glut and hexokinase (HK2). Also, HIF-1 α increases the expression of pyruvate dehydrogenase kinase (PDK), which blocks the entry of pyruvate into the TCA cycle. MYC cooperates with HIF in activating several glycolytic genes. FoxO mediates glycolysis via activating transcription of glycolytic enzymes (Pgd, Pdk4) as well as ROS-detoxifying genes. The PI3K–AKT axis stimulates glycolysis by directly regulating glycolytic enzymes and by activating mTOR. The p53 suppresses glycolysis through TP53-induced glycolysis and apoptosis regulator (TIGAR) and increases mitochondrial metabolism via SCO2. *G-6-P* glucose-6-phosphate, *PEP* phosphoenolpyruvate, α -*KG* α -ketoglutarate, *OAA* Oxaloacetate, *PPP* Pentose Phosphate Pathway. The *dashed lines* indicate loss of p53 function

Fig. 3.

Molecular pathway of glutaminolysis in NSPCs. After glutamine is taken up into the cells, it is converted to glutamate by the action of glutaminase (GLS). Glutamine metabolism is important for redox balance control through GSH biosynthesis. Cellular uptake and export of glutamine is the rate-limiting step of mTOR activation. mTORC1 regulates glutamine anaplerosis. mTORC1 inhibits CREB-mediated Sirt4 transcription via proteasomal degradation of CREB2. Mitochondria-localized SIRT4 inhibits the activity of glutamate dehydrogenase (GDH, GLUD). Several transcription factors (FoxO, MYC, CREB, p53) regulate glutaminolysis through target gene activation

Table 1

Metabolic pathways in NSPCs

Pathways	Regulated by	Functions in NSPCs	References
Glycolysis	FoxO, TSC/mTOR, HIF-1, Sirtuin, MYC, p53	Regulate development, proliferation and differentiation Pivotal for cellular bioenergetics, biosynthesis, and redox homeostasis	[76, 150–153, 158–161, 184–189, 195–199]
Pentose phosphate pathway	FoxO, p53	Maintain reduced glutathione levels and suppress cellular oxidative stress by generating NADPH Necessary for proliferation, growth, and migration	[76, 77, 195, 196]
Glutamine metabolism	FoxO, TSC/mTOR, HIF-1, Sirtuin, MYC, p53	Maintain redox homeostasis Regulate growth and proliferation Necessary for epigenetic modifications	[76, 80–84, 125, 133, 166–168, 184, 185, 200, 201]
One-carbon metabolism		Regulate self-renewal and differentiation	[2, 85, 87]
Lipid metabolism	TSC/mTOR, HIF-1 α , MYC	Regulate proliferation and neurogenesis	[4, 132–138, 154, 155, 184]