Impact of Metabolic Pathways and Epigenetics on Neural Stem Cells

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ABSTRACT: Balancing self-renewal with differentiation is crucial for neural stem cells (NSC) functions to ensure tissue development and homeostasis. Over the last years, multiple studies have highlighted the coupling of either metabolic or epigenetic reprogramming to NSC fate decisions. Metabolites are essential as they provide the energy and building blocks for proper cell function. Moreover, metabolites can also function as substrates and/or cofactors for epigenetic modifiers. It is becoming more evident that metabolic alterations and epigenetics rewiring are highly intertwined; however, their relation regarding determining NSC fate is not well understood. In this review, we summarize the major metabolic pathways and epigenetic modifications that play a role in NSC. We then focus on the notion that nutrients availability can function as a switch to modify the epigenetic machinery and drive NSC sequential differentiation during embryonic neurogenesis.

KEYWORDS: Neurogenesis, neural stem cells, cerebrospinal fluids, nutrients, lipid metabolism, glutamine, one carbon folate pathway, glycolysis, epigenetics

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Introduction

The mammalian cortex is composed of an incredible diversity of neurons and glial cells which arise from the differentiation of neural stem cells (NSC) during embryonic stages and the first postnatal weeks. During this process, the transition from NSC to fully differentiated neurons and glia is called neurogenesis and gliogenesis, respectively. While most of the specialized stem cells are capable of producing several different lineages, NSC produce different cell types sequentially and their potentiality decreases with time in a phenomenon called sequential fate restriction.[1,2] Indeed, NSC switch from proliferative symmetrical divisions to asymmetrical cell division to sequentially produce all cortical neurons which will populate the 6 different layers of the cortex. Finally, NSC switch to gliogenesis which persists after birth. The mechanisms regulating this temporal differentiation progression are not fully understood. In recent years, it has become clear that both extracellular factors as well as intracellular cues can control the proliferation/differentiation balance in NSC. Among the extracellular factors, nutrients modulate fundamental cellular processes including proliferation, secretion, and autophagy.[3] In addition to their bioenergetics intracellular function, recent work showed that extracellular nutrients and intracellular metabolites can influence cell state by acting as signaling molecules affecting both signaling pathways and gene expression particularly through their effect on chromatin modifications. Indeed, most chromatin-modifying enzymes require substrates or cofactors that are intermediates of cellular metabolism.[4] Thus, variation of these metabolic inputs will determine epigenome remodeling and transcription. This is of interest because epigenetics, which are defined as the heritable traits that involve chromatin changes rather than DNA sequence alterations, control gene expression which is at the heart of differentiation and development. In fact, long-term epigenetic silencing of key developmental genes that are associated with specific cell lineages is at the center of NSC fate restriction.[5]

Epigenetic landscape can be modified by DNA and histone modification enzymes following metabolic changes, and conversely, epigenetic mechanisms can regulate the cellular metabolome through modulating metabolic gene expression. Thus, understanding the interplay between metabolism and epigenetics has proven to be a difficult task. Extensive research during the past decades has focused on elucidating the roles of metabolic pathways in the control of stem cells fate decisions; however, the role they may play during neurogenesis has been largely understudied. In this review, we will summarize the recent research progress in the epigenetic and metabolic regulation of NSC cell fate and discuss how the understanding of the link between epigenetic and metabolism could identify new vintage points in the field of neurogenesis.

The Cerebrospinal Fluid and Neurogenesis

NSC are in permanent and direct contact with the cerebrospinal fluid (CSF) at the ventricular surface from the earliest stages of brain development. Indeed, the primitive cerebroventricular system emerges with the closure of the neural tube which entraps some of the amniotic fluid and serves as the initial CSF. The CSF is then actively regenerated throughout embryogenesis and adulthood from arterial blood by the choroid plexus tissues.[6] The CSF has been shown to have age-dependent effect on NSC proliferation suggesting that its composition is relevant to normal corticogenesis.[7] Due to the

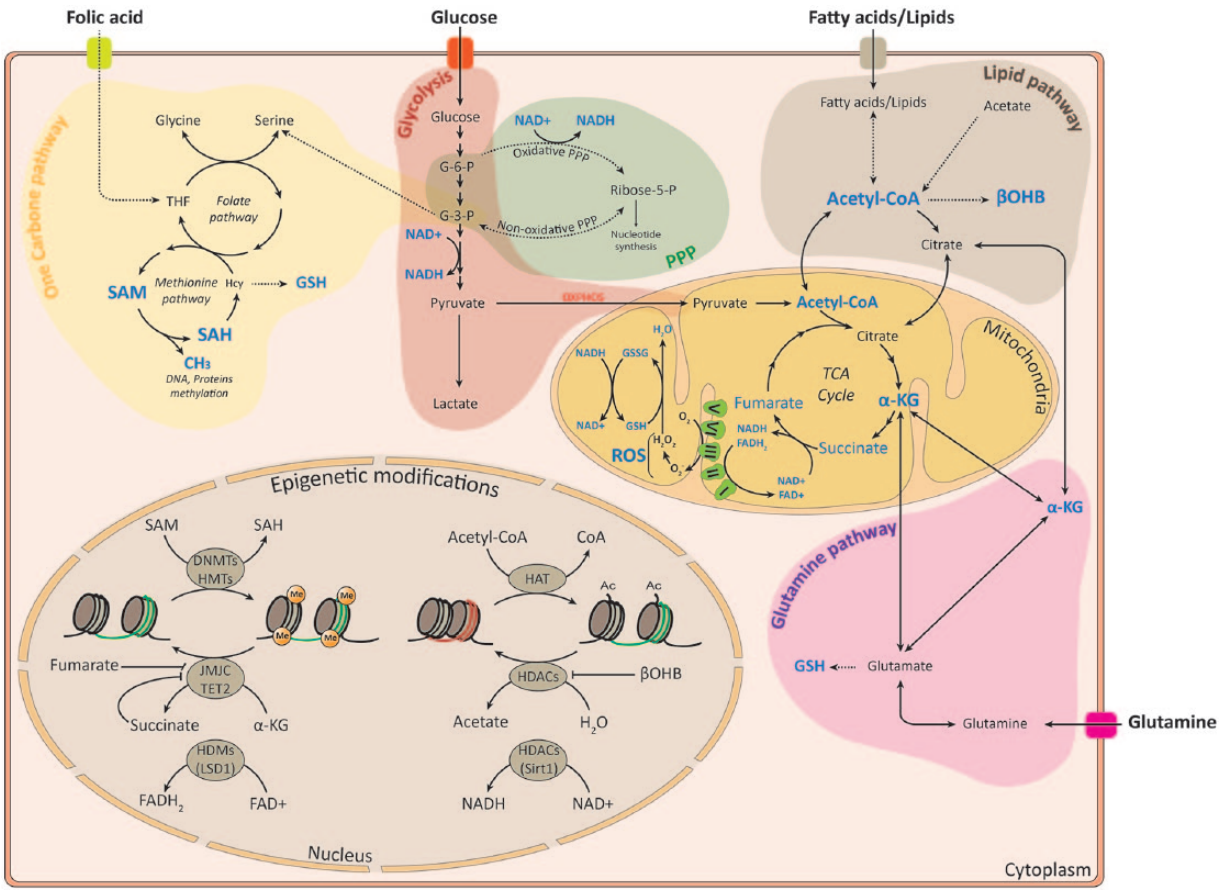

Figure 1. Overview of metabolic pathways implicated in epigenetic modifications in NSC. Metabolites that are used as substrates and cofactors for reactions that coordinate epigenetic status are highlighted in blue color. Epigenetic modificatons are represented as methylation and acetylation marks on histones. α-KG indicates α-ketoglutarate; βOHB, β-hydroxybutyrate; Ac, acetyl; CoA, co-enzyme; DNMT, DNA methyltransferase; FAD, flavine adenine dinucleotide; FADH2, flavin adenine dinucleotide dihydride; G-6-P, glucose-6-phosphate; G-3-P, glyceraldehyde-3-phosphate; GSH, glutathione; GSSG, glutathione disulfide; HAT, histone acetyltransferases; Hcy, homocysteine; HDM, histone demethylases; HDAC, histone deacetylase; HMT, histone methyltransferase; JMJC, Jumonji domain demethylase; LSD1, lysine-specific demethylase 1; Me, methyl; NAD+, nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide hydride; PPP, pentose phosphate pathway; P, phosphate; ROS, reactive oxygen species; SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine; TCA, tricarboxylic acid; TET2, ten-eleven translocation 2; THF, tetrahydrofolate.

advancement in proteomics, the highly dynamic CSF proteome starts to be characterized and have revealed similarities between human and rodent proteomes at different time points during corticogenesis.[8,9] While we are only beginning to uncover CSF composition, the range of factors present in the CSF known to be important for NSC already includes fibroblast growth factors (FGF), insulin-like growth factor (IGF), sonic hedgehog (Shh), and retinoic acid (RA). Interestingly, the presence of regulators of lipid metabolism, glucose, as well as folate and some of its derivatives has also been reported[10]; however, the metabolic profile of CSF during corticogenesis has yet to be established. Finally, whether variation of CSF composition can have great influence on NSC intracellular metabolites levels and how that will affect neurogenesis will require further investigation.

Metabolism and Epigenetic Modifications in NSC

Early pioneering studies have linked metabolic gradients to developmental patterning indicating that metabolic differences are intrinsically and functionally linked to cell differentiation in different developmental contexts.[11,12] Flexibility in energy metabolism supports stage-specific energetic demands. The most known metabolic rewiring is the glycolysis/oxidative phosphorylation (OXPHOS) switch where glycolysis maintains stemness through provision of energy and OXPHOS allows for more efficient energy production to match the needs of the differentiating progeny.[13] For instance, in drosophila, this metabolic switch was shown to trigger neuroblasts terminal differentiation during metamorphosis.[14] However, in mammals, while most studies have focused on the role of metabolites in adult NSC,[15–17] much less is known regarding their function in embryonic NSC. Transcriptomic approaches have highlighted the temporal changes in both NSC metabolic gene expression and NSC epigenetic landscape during sequential generation of the different neuronal subtypes hinting toward their important role in corticogenesis.[18,19] Given the fact that metabolism intermediates are often used as cofactors and substrates for epigenetic modifying enzymes (Figure 1), we focus

on the link between the major metabolic pathways and NSC fate.

One-carbon pathway

One-carbon (1C) metabolism consists of a series of complex cyclical reactions in which a single carbon unit is transferred from donors to acceptors. It comprised 2 intertwined pathways: the folate and methionine pathways. The folate pathway is involved in DNA synthesis with the production of purine and pyrimidine via the metabolism of tetrahydrofolate (THF). However, the methionine pathway is involved in methylation reactions as it converts methionine to S-adenosyl methionine (SAM), which is a methyl donor.[20] 1C metabolism is implicated in NSC self-renewal and differentiation as its deficiency inhibited the proliferation of both embryonic NSC in vitro and adult hippocampal NSC.[21,22] Furthermore, in vitro folate supplementation increases NSC proliferation and neuronal differentiation by enhancing DNA methyltransferases (DNMT).[23,24] Finally, folate supplementation during pregnancy facilitates oligodendrocyte differentiation.[25] Recent work from us has shown that inhibition of the folate pathway induced a depletion of embryonic NSC in vivo.[26] NSC depletion was correlated to decreased methylation on lysine 4 of histone 3 (H3K4me3) at the promoter of key progenitor genes. Furthermore, we have identified a link between 1C metabolism and the cell-cell communication pathway Eph-Ephrins. This is of interest as it identifies metabolites of the folate pathway as signaling molecules connecting extracellular signals to cellular gene expression. Whether 1C metabolism–driven epigenetic alterations are involved throughout embryonic neurogenesis or are required at a specific stage to drive NSC specification warrants future investigation.

Lipids pathway

Lipids, which have been often considered as membrane components, can also function as signal transduction molecules.[27] Lipids can act either by binding specific receptors and/or modulating the environment of receptors associated with lipid rafts; thus, lipid metabolism is important for the interaction between adult NSC and their niche.[28] Lipid production is upregulated in adult NSC through the fatty acid synthase (FASN)-dependent de novo lipogenesis which is essential for NSC proliferation as well as neurogenesis.[29] While lipid metabolism has been shown to regulate the relative proportions of asymmetric/symmetric divisions in adult NSC, not much is known on its role in NSC at the embryonic stages. Recent evidences have linked lipids breakdown through the fatty acid oxidation (FAO) to NSC activity during development. Indeed, FAO inhibition led to a reduced NSC pool due to their increased differentiation and reduced self-renewal.[30] Lipid metabolism has also been associated with epigenetic reprogramming. Histone acetyltransferases (HAT) use lipid-derived acetyl-CoA as a major source for histone acetylation and have been shown to drive cellular growth by promoting histone acetylation and expression of growth-related genes.[31] Furthermore, acetyl-CoA can be reduced to produce beta-hydroxybutyrate (βOHB) which is an endogenous inhibitor of histone deacetylases (HDAC).[32] Finally, pharmacological inhibition of histone deacetylation promoted neuronal differentiation while decreasing astrocyte differentiation in vitro.[33] While the tight connection between lipid metabolism and epigenetic regulations of gene expression has been consolidated in different stem cells as well as adult neurogenesis, whether it can exert similar functions in embryonic NSC remains to be elucidated.

Glutamine pathway

Glutamine (GLN) is the most abundant amino acid in plasma, up to 60% of the total free amino acid pool, and is the primary nutrient for maintaining and promoting cellular function.[34] The function of GLN goes beyond that of a simple metabolic fuel or protein precursor as it is actively involved in several cell-specific processes including nucleotide synthesis, cell survival/proliferation, redox homeostasis, and fatty acid synthesis.[35] In NSC, the GLN pathway is essential for their growth and long-term maintenance and is upregulated in astrocytic lineages.[36,37] Moreover, removal of GLN from growth culture medium impairs the spontaneous differentiation of cortical neurons in vitro.[38] Glutamate, which is produced by GLN hydrolysis, is a precursor in the synthesis of reduced glutathione and thus regulates NSC redox balance. This balance is important to control reactive oxygen species (ROS) levels which play a role in maintaining the proliferation of adult progenitor cells within this neurogenic niche.[39]

GLN undergoes deamination to produce α-ketoglutarate (α-KG) through 2 pathways, namely, Glutaminase I and II pathways, which is a tricarboxylic acid cycle (TCA)-Cycle intermediate and a substrate for demethylases that modify both proteins and DNA. Indeed, α-KG is used as a substrate by Jumonji-C domain containing histone demethylases (JMJC) and Tet-DNA demethylases. High α-KG levels promote naïve pluripotency by suppressing the accumulation of repressive histone modifications and DNA methylation in mouse embryonic stem cells.[39] Even though many studies have highlighted the importance of GLN metabolism in stem cell maintenance and differentiation, its function in embryonic NSC needs to be further characterized.

Glycolysis and pentose phosphate pathway

Glucose is imported into cells via glucose transporters (GLUT) and is a pivotal source of fuel that is used in different metabolic pathways. Glucose is metabolized into pyruvate (glycolysis) which can either be fermented into lactate or shuttled into the mitochondria to be used in the tricarboxylic acid (TCA) cycle (OXPHOS).[17] Glycolysis is critical for the function of

embryonic NSC as neural tube abnormalities are detected in diabetic pregnancies.[40] Neuronal differentiation from human embryonic stem cells–derived NSC is accompanied by metabolic reprogramming from aerobic glycolysis to neuronal OXPHOS.[41] The TCA cycle provides several intermediates that are used in numerous other reactions. Among these intermediates, acetyl-CoA and α-KG are described above, as well as the reducing agents nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$). FAD, the oxidized form of $FADH_2$, is a cofactor for the lysine-specific demethylase (LSD1) that regulates NSC proliferation in adult hippocampal dentate gyrus through modulation of histone methylation.[42] Moreover, LSD1 repressed the expression of HEYL through demethylation of H3K4me3 to promote neuronal differentiation of human fetal NSC.[43] NADPH is important to manage oxidative stress and ROS by maintaining reduced glutathione levels.[44] Increase in NAD+, the oxidized form of NADH, to NADH ratio activates SIRT1, a NAD+-dependent deacetylase which has been shown to inhibit adult hippocampal NSC self-renewal and promote embryonic NSC neuronal differentiation.[45,46] However, activation of SIRT1 by resveratrol to mimic early neural developmental stress triggered OCT6 deacetylation and increased neural tube defects in mouse embryos.[47] Thus, tight regulation of NAD+/NADH ratio is essential for neurogenesis. Finally, fumarate and succinate which are TCA intermediates have been shown to inhibit α-KG-dependent histone and DNA demethylases.[48] Several TCA intermediates are exported out of the mitochondria and contribute to epigenetic regulation of transcription (eg, α-KG, NADH, $FADH_2$); however, the role of glycolysis as a whole in regulating embryonic gene expression is not well studied.

Glucose-6-phosphate (G-6-P), a glycolytic intermediate, is used either for glycolysis or the pentose phosphate pathway (PPP). PPP is divided into 2 branches, oxidative PPP and non-oxidative PPP. The oxidative PPP uses the G-6-P to produce the reducing agent NADH. In the non-oxidative PPP branch, ribose-5-phosphate and/or xylulose-5-phosphate are produced, which function as signaling molecules that regulate transcription.[49] In vitro studies have shown the reliance of NSC on the PPP which is stimulated during neuronal differentiation.[50] Furthermore, PPP dysfunction contributes to impaired adult hippocampal neurogenesis.[51] Whether PPP is linked to embryonic neurogenesis and NSC epigenetic remodeling remains to be elucidated.

Concluding Remarks

While human brain maturation continues throughout life, the first 1000 days is a unique period where the foundation of optimum growth and neurodevelopment are established.[52] Maternal malnutrition or placenta insufficiency leads to intrauterine growth restriction (IGUR) as the fetus fails to reach its genetic potential size. In IGUR, blood is redirected preferentially toward brain at the expense of other vital organs highlighting the importance of brain nutrition during the early developmental stages. While "brain-sparing" refers to the relative protection of the brain, it does not guarantee its normal development as recent studies have shown child behavioral problems and altered neurotransmitters' profiles.[53,54] Thus, understanding how nutrition and metabolites affect NSC proliferation and differentiation during embryonic neurogenesis has profound impacts not only in understanding basic processes of brain development but also in the field of neurological disorders.

Work in the past decade has uncovered the complexity of the connections between metabolism and chromatin dynamics and how that influences neurogenesis, mostly in the adult. Metabolites are now considered as signaling molecules that provide a link between the cellular environment and nuclear transcription. While systems biology approaches are helping to understand this complexity at an unprecedented pace, technological challenges are present that must be overcome to unravel the mystery at the next level. Most studies have focused on expression levels of each metabolic enzyme inside cells, but these may not completely reflect the actual level of enzymatic activity. To move forward, it is crucially important to understand how metabolic profiles shift within NSC during embryonic neurogenesis. We have highlighted in this review the recent discoveries as well as the gaps in our understanding of the process of metabolic reprogramming in embryonic neurogenesis. Future studies investigating the epigenetic landscape of NSC should include analyses of intracellular metabolites as a deeper understanding of this connection may help shed light on how NSC adapt to their environment to coordinate brain construction as well as the etiology of a variety of complex diseases.

Author Contributions

MF and AD conceived and designed the article. MF wrote the manuscript. MF and AD edited the manuscript.

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