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Lorenz, C., Prigione, A.

This is the final version of the accepted manuscript. The original article has been published in final edited form in:

Current Opinion in Cell Biology
2017 DEC ; 49: 71-76
2017 DEC 22 (first published online: final publication)
doi: 10.1016/j.ceb.2017.12.004

Publisher: Elsevier

Mitochondrial metabolism in early neural fate and its relevance for neuronal disease modeling

Authors and affiliations:

Carmen Lorenz[1,2], Alessandro Prigione[1§]

[1]Max Delbrueck Center for Molecular Medicine (MDC), 13125 Berlin, Germany

[2]Berlin Institute of Health (BIH), 10178 Berlin, Germany

[§]**Contact information**:

Alessandro Prigione, M.D. Ph.D. Robert-Roessle-Str. 10, 13125 Berlin, Germany. Phone: 0049-30-9406-2871, Fax: 0049-30-9406-3696, Email: alessandro.prigione@mdc-berlin.de.

Keywords: metabolism; neural stem cells; neurogenesis; mitochondria; neurodegeneration; mitochondrial disease

Abstract

Modulation of energy metabolism is emerging as a key aspect associated with cell fate transition. The establishment of a correct metabolic program is particularly relevant for neural cells given their high bioenergetic requirements. Accordingly, diseases of the nervous system commonly involve mitochondrial impairment. Recent studies in animals and in neural derivatives of human pluripotent stem cells (PSCs) highlighted the importance of mitochondrial metabolism for neural fate decisions in health and disease. The mitochondria-based metabolic program of early neurogenesis suggests that PSC-derived neural stem cells (NSCs) may be used for modeling neurological disorders. Understanding how metabolic programming is orchestrated during neural commitment may provide important information for the development of therapies against conditions affecting neural functions, including aging and mitochondrial disorders.

Within the nervous system, stem cells need to generate both neurons and glia [1–3]. Their derivation -collectively defined here as neurogenesis - requires the careful orchestration of cell type-specific epigenetic signatures. These signatures may be influenced by the metabolic state of the cells, given that metabolites can act as epigenetic regulators [4]. At the same time, the transcriptional reorganization associated with neural specification generates distinct metabolic programs that may also be cell type-specific and may in turn contribute to the correct establishment of the needed cellular identity.

Here, we discuss recent literature addressing how the metabolic programs of neurons and glia are constructed. The works have been conducted both in animals and in neural derivatives of human pluripotent stem cells (PSCs). It is important to point out that the generation of neural cells *in vitro* can be influenced by the culture conditions, including signaling molecules and oxygen levels [5]. Therefore, the metabolism of *in vitro* derived human neural cells may not necessarily mirror that of the actual neural cells residing in the human brain. Nonetheless, the use of human PSC neural derivatives is allowing for the first time to investigate the metabolic regulation of human brain cells.

Some of the recent findings that we will discuss here, generated from *in vivo* and *in vitro* experiments, have challenged the conventional idea associated with the metabolic remodeling of neurogenesis. The picture emerging is that metabolism is more plastic than previously expected and that it can be fine-tuned at different levels during neural commitment. We also comment on clinically relevant opportunities that are starting to be translated from these basic studies. We believe that this renewed interest in the metabolic contribution to neural specification may bring important insights for the study of diseases affecting the nervous system, including neurodegeneration and mitochondrial disorders.

Glycolytic metabolism and neurogenesis

The metabolic programs of neurons and glia are considered to be very divergent. Neurons are dependent on mitochondrial-based oxidative phosphorylation (OXPHOS) while glia rely on glycolysis [6,7]. Both cell types are generated from multipotent neural stem cells (NSCs), which appear to share some of the features of glial cells, including the reliance on glycolytic metabolism [2,8]. Given that the modulation of metabolism may be instrumental during neural commitment [9], it becomes critical to investigate how the cell type-specific metabolic programs are regulated.

The glycolytic nature of NSCs is usually explained by the fact that glycolysis is the preferred metabolic route of stemness [10]. Accordingly, PSC-derived neural progenitor cells (NPCs) have been found to depend on glycolytic metabolism [11]. Moreover, metabolic profiling of cells exiting pluripotency *in vitro* indicates that the metabolic switch towards OXPHOS does not occur uniformly for all germ layers, as ectodermal lineage and NPC induction still require the maintenance of a high glycolytic flux [12].

The picture becomes more complicated when we consider the proliferative rate of stem cells. In the case of PSCs, for example, the glycolytic metabolism is suggested to be a consequence of their elevated level of proliferation [13,14]. Highly proliferative cells like cancer cells prefer indeed glycolysis, since it provides the precursor molecules for biomass generation via the pentose phosphate pathway (PPP) that emerges from the upstream branches of glycolysis [15]. In the case of hematopoietic stem cells (HCS), however, glycolysis is considered to be chosen over OXPHOS due to the fact that HSCs do not actively proliferate and therefore do not have high bioenergetic needs [16,17]. These findings raise the question of why stem cells would prefer glycolysis regardless of their rate of proliferation. The relationship between proliferation and stem cell metabolism may be particularly important in the context of the nervous system. NSCs *in vivo* can in fact rapidly divide during development but become quiescent in adult age [18].

One possibility is that the stem cell reliance on glycolysis is linked to the regulation of redox metabolism. The use of glycolysis may reduce the intracellular levels of reactive oxygen species (ROS) generated as OXPHOS by-products and at the same time it may enhance the production of the antioxidant glutathione through the PPP-mediated generation of the NADPH [19]. ROS can also function as second messengers. The regulation of redox homeostasis may play a crucial role in the self-renewal of NSCs [20]. The physiological effect of ROS may contribute to the induction of neurogenesis *in vivo* [21]. Intermittent generation of ROS in proliferative NPCs in the developing cortex *in vivo* negatively influences their rate of proliferation [22], suggesting that low ROS levels are indeed beneficial for NPCs. Recent *in vivo* findings demonstrated that mouse embryonic NSCs exhibit reduced amount of ROS, while committed NPCs increase ROS production to promote differentiation [23]. NPC differentiation *in vivo* may be induced following a transcriptional program activated by the nuclear factor erythroid 2-related factor 2 (NRF2) [23]. NRF2 is indeed known to stimulate the expression of genes involved in redox signaling, thereby supporting neuronal differentiation by protecting against toxic insults [24].

The induction of glycolysis in NSCs might also be influenced by the level of oxygen and by the activation of hypoxia inducible factors (HIFs) [25]. This was found to be the case in the context of PSCs [26,27]. The oxygen sensing response can in fact be controlled by cellular ROS rather than by OXPHOS metabolism per se [28]. Nevertheless, the glycolytic metabolic state of *ex vivo* mouse NSCs has been found to be not dependent on HIFs [29]. At the same time, HIFs may be important in the *in vitro* derivation of NPCs from human PSCs, as the level of oxygen has been suggested to modulate whether NPCs can differentiate more efficiently into neurons or glia [30]. Therefore, the importance of HIF-mediated response in neurogenesis requires further investigations.

Another possibility for explaining the reliance on glycolysis of NSCs and glia and the reliance on OXPHOS in the case of neurons may be that these metabolic programs may contribute to the epigenetic regulation of the respective cell fate. The process of establishing a cell fate identity requires a complex integration between environmental cues and transcriptional states [13]. In this scenario, cellular metabolism may represent the mechanism through which a cell responds to both exogenous stimuli and gene expression programs [4]. Within the complex regulation of epigenetics during neural cell commitment [31], however, the importance of metabolism still remains largely unexplored.

Mitochondrial metabolism and dynamics during neurogenesis

An important aspect that has been recently challenged of the classical view of metabolism in neurogenesis relates to the time point in which the oxidative metabolic program is activated and to the respective morphology of mitochondria.

As mentioned above, the NSC state is believed to be linked with glycolytic metabolism coupled to non-fused mitochondrial morphology, which is considered typical for glycolytic stem cells [32]. In the neural lineage, OXPHOS metabolism is usually associated only with differentiated neurons [7,33], which exhibit a tubular mitochondrial network. This has been confirmed in several recent works investigating the mitochondrial state of neurons derived *in vitro* from human PSCs [11,34,35]. Proteomics analysis further underscored the increase of OXPHOS-related proteins in differentiating neurons both *in vitro* and *in vivo* [36,37].

In contrast to the assumptions about the mitochondrial state of NSCs, recent findings demonstrated that mouse embryonic NSCs exhibit elongated mitochondria *in vivo* while remaining glycolytic [23]. At the same time, proliferative NPCs *in vivo* displayed non-fused fragmented mitochondria [23]. Mouse adult NSCs *in vivo* have been found to possess mitochondria with a mixed globular and tubular shape that becomes consistently more elongated in proliferative intermediate progenitor cells (IPCs) [38]. Consequently, single cell transcriptomics identified the up-regulation of OXPHOS components and the down-regulation of glycolytic enzymes during the transition between NSCs and IPCs *in vivo* [38].

In agreement with a potential activation of the oxidative metabolic program in early neural fate commitment, NPCs derived *in vitro* from human PSCs have been found to display tubular mitochondria and a reduction of glycolytic metabolism when compared to PSCs [39]. The apparent disagreement of these latter findings with other published works on PSC-derived NPCs [11,12], may perhaps be explained by the type of signaling molecules used for the derivation of NPCs *in vitro*. Glycolytic NPCs were cultivated using basal FGF [11], which may be per se associated with enhanced glycolysis [40]. Conversely, oxidative NPCs were grown with LIF [39], which promotes mitochondrial metabolism [41]. Collectively, these data indicate that activation of the OXPHOS program during neurogenesis may occur earlier than expected [42] and that it may be influenced by signaling and environmental cues **(Figure 1)**.

This novel concept of how metabolic programs are orchestrated during neural commitment underscores the metabolic plasticity associated with the cell fate transitions. In this emerging picture, it will be relevant to dissect the state of mitochondrial metabolism and dynamics of glia cells. Astrocytes are considered to be dependent on glycolytic metabolism, as they can produce glycolysis-derived lactate that is then secreted and used to fuel neurons [6]. Oligodendrocytes also rely on glycolysis [43], further supporting the metabolic compartmentalization of the central nervous system. Nonetheless, the lactate produced by astrocytes and oligodendrocytes can also be obtained from pyruvate generated from malate coming from the mitochondrial tricarboxylic acid (TCA) cycle [44]. Hence, mitochondrial metabolism might also be potentially relevant for glial cells. Accordingly, glioblastoma cells forced to increase OXPHOS and mitochondrial biogenesis efficiently differentiate into astrocytes [45].

Understanding the relevance of mitochondria for glia cells might be important for facilitating the reprogramming of astrocytes into neurons [46], given that metabolism represents a critical roadblock in this process [47]. The investigation of astrocytic mitochondria may also provide essential clues to explain the phenomenon of mitochondrial transfer between astrocytes and neurons that has been reported to occur *in vivo* in mice following ischemic insults [48].

Targeting mitochondria for improving neurogenesis in neurological diseases

Mitochondrial defects are a known pathogenetic mechanism involved in conditions causing neurological impairment, including aging-associated neurodegeneration [49]. At the same time, mitochondrial disorders due to OXPHOS mutations usually cause symptoms at the level of the nervous system [50]. The findings discussed above open new avenues in our understanding of these human diseases and in the development of therapies.

If OXPHOS metabolism is relevant not only for fully differentiated neurons but also for proliferative neural precursors, diseases impairing mitochondria could also affect neurogenesis and targeting mitochondrial function may represent a strategy for improving neural defects [51]. Accordingly, piracetam-mediated activation of mitochondrial respiration promoted neurogenesis *in vivo* in aged mice [38]. Furthermore, mitochondrial dysfunctions due to PINK1 deficiency caused defective neurogenesis in a mouse model of Parkinson's disease [52]. Enhanced mitochondrial function upon modulation of microRNA-210 led to improved NSC proliferation and differentiation *in vitro* following inflammatory insults [53].

The findings also suggest that iPSC-derived NPCs may represent a viable model for investigating neurological diseases. NPCs from patients affected by schizophrenia have been found to exhibit disease-associated phenotypes [54]. The use of NPCs may particularly be important for mitochondrial disorders that are caused by mutations in the mitochondrial DNA (mtDNA) and for which there is a lack of viable modeling systems [55]. iPSC-derived NPCs from patients affected by Leigh syndrome carrying a mtDNA mutation in the gene *MT-ATP6* have been used for the establishment of a drug discovery platform [39]. Leigh syndrome NPCs displayed a defect in calcium homeostasis that was observed in neurons but not in other peripheral cells [39]. The observed NPC defects might imply that Leigh syndrome also affects neurogenesis. Interestingly, hypoxia stimulation was recently shown to significantly improve the life-span of a mouse model of Leigh syndrome [56]. The mechanisms underlying the beneficial effect of hypoxia in the Leigh syndrome mice remain unclear. However, given the above-mentioned importance of redox metabolism and HIFs signaling for NSCs and their glycolytic state, it is perhaps possible that hypoxic exposure may be beneficial to Leigh syndrome mice because it promotes NSC proliferation and neurogenesis.

In conclusion, the recent data addressing how the metabolic programs of neural cells are established *in vitro* and *in vivo* is challenging the traditional view of neurogenesis and is opening new ways to approach and cure disorders of the nervous system. A deeper understanding of the metabolic programming occurring upon neural fate commitment will shed new lights on how brain cells are generated and how we can develop strategies to restore their function during disease states.

Acknowledgements

The authors declare no competing financial or commercial interests. We acknowledge financial support from the German Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF) (e:Bio Young Investigator grant #AZ.031A318), the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) (PR1527/1-1), and the Berlin Institute of Health (BIH).

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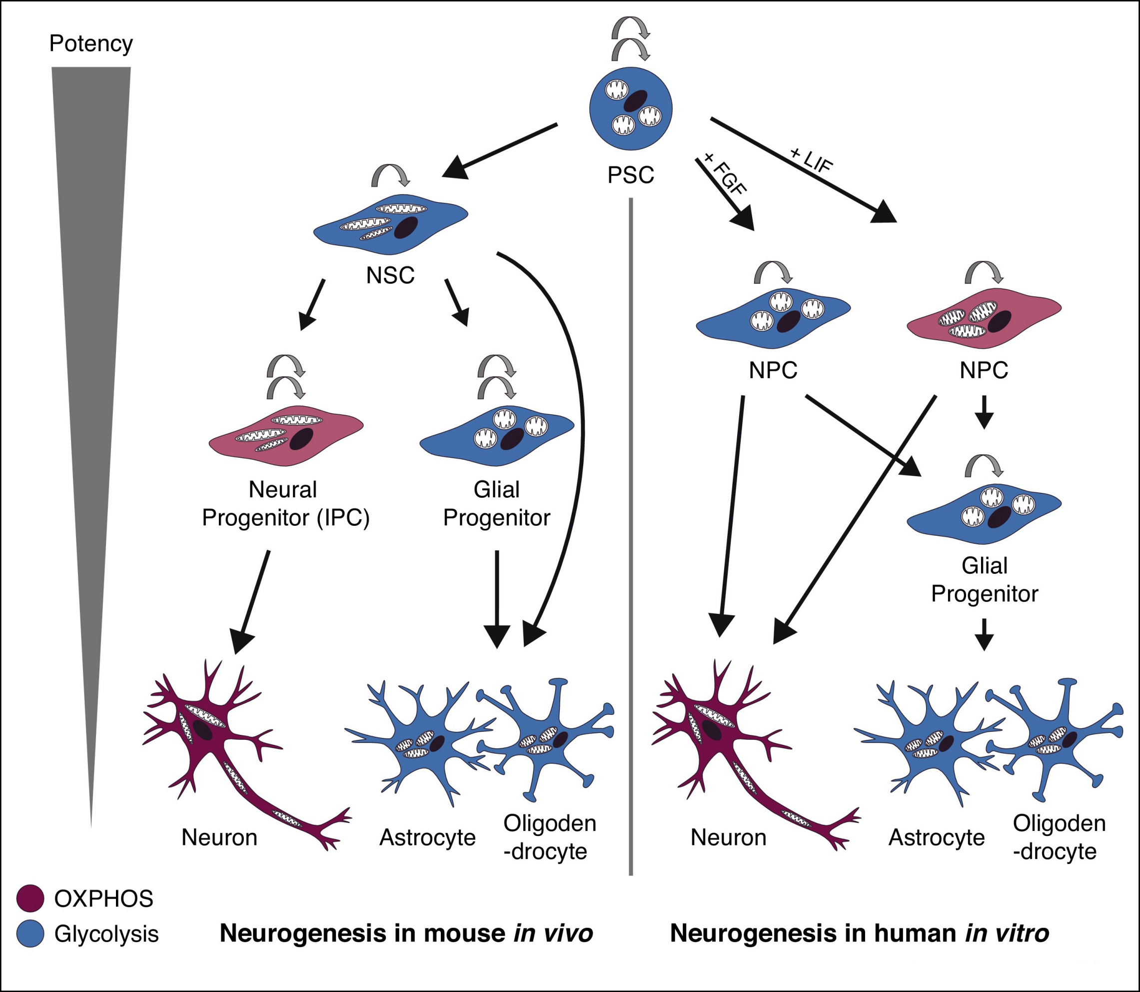
****This work identified the hypoxia response as a suppressor of mitochondrial dysfunction. The authors demonstrated that chronic hypoxia treatment significantly improved the pathogenesis and life span in a mouse model of the mitochondrial disease Leigh syndrome.**

Figure legends

Figure 1. Mitochondrial metabolism and dynamics during neurogenesis. Cartoon depicting the orchestration of metabolic programs and mitochondrial states during the generation of neurons and glia based on the studies conducted in mouse *in vivo* and in PSC derivatives *in vitro*. The color code refers to the energy metabolism of the cells: blue for glycolysis (in PSCs, NSCs, astrocytes, oligodendrocytes, and PSC-derived NPCs grown with basal FGF), light red for intermediate OXPHOS metabolism (in proliferative IPCs and PSC-derived NPCs cultured with LIF), and dark red for marked OXPHOS metabolism (in mature neurons). The grey arrows above the cells refer to the reported proliferative rates. The morphology of mitochondria is simplified and shown as non-fused roundish organelles with sparse cristae (in PSC, glycolytic NPCs, and glial progenitors), as partly elongated organelles (in NSCs, IPCs, oxidative NPCs, and astrocytes and oligodendrocytes), and as strongly elongated organelles (in mature neurons). Abbreviations: PSC= pluripotent stem cell; NSC= neural stem cell; NPC= neural progenitor cell; IPC= intermediate progenitor cell; OXPHOS= oxidative phosphorylation.


Potency
PSC
+ FGF
+ LIF
NSC
Neural Progenitor (IPC)
Glial Progenitor
Neuron
Astrocyte
Oligoden -drocyte
NPC
NPC
Glial Progenitor
Neuron
Astrocyte
Oligoden -drocyte
OXPHOS
Glycolysis
Neurogenesis in mouse in vivo
Neurogenesis in human in vitro