Regulatory roles of mitochondria and metabolism in neurogenesis
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Abstract
Neural stem cells (NSCs) undergo massive molecular and cellular changes during neuronal differentiation. These include mitochondria and metabolism remodelling, which were thought to be mostly permissive cues, but recent work indicates that they are causally linked to neurogenesis. Striking remodelling of mitochondria occurs right after mitosis of NSCs, which influences the postmitotic daughter cells towards self-renewal or differentiation. The transitioning to neuronal fate requires metabolic rewiring including increased oxidative phosphorylation activity, which drives transcriptional and epigenetic effects to influence cell fate. Mitochondria metabolic pathways also contribute in an essential way to the regulation of NSC proliferation and self-renewal. The influence of mitochondria and metabolism on neurogenesis is conserved from fly to human systems, but also displays striking differences linked to cell context or species. These new findings have important implications for our understanding of neurodevelopmental diseases and possibly human brain evolution.

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Introduction
Neurogenesis is a key event of neural development, by which neural stem/progenitor cells (NSPCs) stop self-renewing and dividing, to convert to postmitotic neurons. The delicate balance between self-renewal and differentiation of NSPCs is controlled by intrinsic and extrinsic cues, in particular transcription factors and morphogen signals (reviewed in [1,2]). However, recent evidence has uncovered the key influence of mechanisms once considered to be merely permissive: cell metabolism and mitochondria dynamics.

Mitochondria play essential roles in energy production, calcium homeostasis and cell signalling. These organelles constitute a network that is constantly remodelled through a process of fission or fusion or mitochondria dynamics [3]. Mitochondria dynamics have been associated with cell fate decisions in various systems [4]. It can influence stem cell renewal and differentiation in part through the direct or indirect production of metabolites that can modulate developmental pathways, in particular through post-translational modifications (PTMs), such as histone acetylation and methylation [5,6]. The impact of mitochondria on neuronal development and function has long been illustrated by the major neurological consequences of mitochondrial diseases (mostly caused by mutations in mitochondria-related genes, the most exemplative disease being Leigh syndrome), including motor and sensory hypofunction, epilepsy, autism spectrum behaviours and dementia [7], but their implication in early neural development and neurogenesis had remained mostly unexplored until recently.
Mitochondria dynamics is closely linked to the cell cycle, with increased fusion during G1/S phases followed by fission during G2 and mitosis [10], which allows for partitioning of mitochondria between the daughter cells. How then can mitochondrial dynamics be articulated with the progression of neurogenesis, which is by definition a postmitotic event? This was addressed with a novel in vitro tracking method to follow mitochondrial dynamics of cortical NSPCs throughout self-renewal and neuronal differentiation, from cell division to fate acquisition [9]. This confirmed that mitochondrial fission occurred during NSPC mitosis, as expected, but it also revealed a dichotomic behaviour of the daughter cells: those destined to remain NSPCs displayed high levels of mitochondrial fusion, whereas prospective neuronal cells maintained higher levels of mitochondrial fission (Figure 1). Moreover, the acute induction of mitochondria fusion shortly after mitosis (using fusion activator or fission inhibitor molecules) dramatically altered the balance of cell fate, leading most NSPCs to undergo self-renewal instead of neuronal differentiation (Figure 1). The impact of mitochondrial dynamics after NSPC mitosis was also assessed in vivo, using the FlashTag method to label mitotic cortical progenitors [11], confirming the positive impact of mitochondrial fusion on NSPC self-renewal [9]. These results demonstrate that mitochondrial dynamics have a profound influence on cortical neurogenesis. In addition, the timing of the events indicates that fate commitment is not irreversibly determined in postmitotic daughter cells but that there is a postmitotic critical period of plasticity of fate commitment. This finding extends the classical view of neuronal fate decision that is thought to occur before mitosis as early as G1 in the mother cell [12].

Could these findings be conserved beyond mouse corticogenesis? Human cortical progenitors display increased self-renewal potential that enables expansion of progenitors and ultimately increased neuronal output, which underlies the increase in cortical size in the human lineage [1]. The same tracking system of mitochondria and cell fate was applied to human cortical progenitors derived from pluripotent stem cells, revealing conserved relationships between mitochondria dynamics and neurogenesis [9]. However, mitochondrial dynamics was found to be able to influence cell fate for a much longer, doubled period after cell division, when compared with mouse cortical progenitors (Figure 1). The prolonged critical period of postmitotic fate plasticity in human cortical progenitors could be in line with their increased self-renewal potential, although this remains to be tested further [9].

Overall, these data strongly suggest that mitochondria remodelling plays a crucial instructive role in neurogenesis, raising the question of the downstream mechanisms. Mitochondria fission and fusion are tightly

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**Figure 1**

**Mitochondria dynamics regulate neurogenesis during a postmitotic critical period.** The mouse cortical NSC/RGC has tubular mitochondria during interphase and undergoing mitochondrial fission during mitosis. After mitosis, both daughter cells display fragmented mitochondria. However, the cells that undergo mitochondrial fusion in the next hours will remain NSCs, whereas those that keep fragmented mitochondria will become neurons. During this critical period, which is double in human NSCs compared with mouse NSCs, the fate of the cells can be changed by manipulating mitochondrial dynamics.
linked to mitochondria activity, in part through the regulation of mitochondria cristae in which oxidative phosphorylation (OXPHOS) molecular effectors and the electron transport chain (ETC) are concentrated [3]. Indeed OXPHOS is essential for proper neurogenesis, whether in NSCs themselves or during the neurogenesis transition, as explained in the following.

Glycolysis to OXPHOS metabolic shifts during neurogenesis

Glycolysis in the cytosol and OXPHOS in the mitochondria are the two main processes that generate ATP within cells (reviewed in [13]) (Figure 2a). The glycolytic pathway leads to pyruvate generation, which can be converted into lactate. Cytoplasmic pyruvate can also enter mitochondria to feed the tricarboxylic acid (TCA) cycle, which generates the fuels for OXPHOS to generate ATP via the ETC. Glycolysis generates much less ATP than OXPHOS does, but its kinetics is overall faster, and it feeds in most biosynthetic pathways to support cell growth and proliferation [13]. Therefore, highly proliferative cells tend to rely mostly on glycolysis, even in the presence of high oxygen levels, a process known as aerobic glycolysis, once thought to be a landmark property of cancer cells [13]. On the other hand, mitochondria respiration through OXPHOS is the most efficient way for the cell to generate ATP, which is therefore heavily used in energy-demanding differentiated cells such as neurons. Indeed, metabolic analyses of NSPCs and their neuronal progeny in many systems and species have shown that NSPCs rely predominantly on glycolysis over OXPHOS, whereas differentiated neurons exhibit higher mitochondrial respiration [8,14–19]. But do these pathways play a role in the...
neurogenic transition? A first direct implication of glycolysis–OXPHOS metabolic balance in neurogenesis was provided by genetic disruption of mitochondrial OXPHOS-related genes in the *Drosophila* brain: OXPHOS genes were shown to be required at the end of neurogenesis to reduce the size of NSPCs and induce their cell cycle exit towards neuronal fate acquisition [14] (Figure 2). These data indicate that glycolysis to OXPHOS metabolic shift is a likely cause and not a mere consequence of neuronal differentiation. On the other hand, the disruption of OXPHOS genes in fly neuroblasts has also consequences in NSPCs themselves, including reduced proliferation rates and altered temporal patterning, that is, temporal changes in their identity, which also perturb the transition to cell cycle exit [20]. Consistent with these findings, genetic disruption in the mouse apoptosis-inducing factor (AIF), a mitochondrial protein essential for OXPHOS, results in impaired self-renewal capacity of cortical NSPCs together with impaired cell cycle exit and neuronal differentiation, ultimately leading to microcephaly [21]. The impact of mitochondria on neurogenesis has also been studied in the context of adult neurogenesis in the mouse hippocampus [22]. In this case, mitochondria activity is required for the amplification and differentiation of neurogenic precursors, but notably, the NSC mitochondria display a mostly fragmented shape, and progressive fusion takes place in neurogenic precursors and differentiated neurons [22]. This suggests that the relationships between mitochondria morphology, dynamics and function depend on the cell context, which should be investigated further. Finally, the requirement of OXPHOS for human neurogenesis was explored recently in the context of mitochondrial disease modelling, using pluripotent stem cell–derived NSCs bearing pathogenic mutations in the mitochondria EC assembly gene SURF1 (causative for Leigh syndrome), which displayed reduced neuronal fate acquisition and maturation [23].

Collectively, these data indicate that OXPHOS is required at multiple steps of neurogenesis, from NSC self-renewal to neuronal fate acquisition. How about glycolysis? Disruption of glycolysis does not appear to affect neurogenesis in fly neuroblasts [20], but recent evidence suggests that active regulation of glycolysis can participate in mouse cortical neurogenesis (Figure 2) [24–26]. The TP53-inducible glycolysis and apoptosis regulator (TIGAR), an endogenous inhibitor of glycolysis, is upregulated in neurons, whereas its disruption leads to decreased mouse cortical neurogenesis in *vitro* [25]. Moreover, a specific glycolysis metabolite, methylglyoxal (MGO), can influence NSPC self-renewal while regulating glycolytic rates [26] (Figure 2). Increased levels of MGO lead to decreased self-renewal capacity of NSPCs in the developing mouse cortex [26,27]. MGO acts by binding to the key glycolysis enzyme GAPDH, which diverts GAPDH from its enzymatic activity towards another function, as an RNA-binding protein [28]. GAPDH was found to bind the mRNA of Notch1, a crucial regulator of NSPC self-renewal, leading to Notch1 decreased translation and thereby increased neurogenesis [26]. These data suggest that glycolytic metabolites such as MGO can coordinate metabolism with neurogenesis, through direct post-translational interactions between key effectors of glycolysis and developmental pathways. The modulation of PTM by specific metabolites is indeed an emerging theme linking metabolism with cell fate control: an increasing number of metabolites have been found to serve as rate-limiting substrates for PTM, in particular for histones but also other proteins, or modulators of PTM effector enzymes such as sirtuin deacetylases [5,29]. As we shall see further in the following, this is likely to be the case for neurogenesis as well.

**Links between mitochondria OXPHOS and neurogenesis: ROS and sirtuins**

The data abovementioned implicate mitochondria-dependent OXPHOS to promote neurogenesis, but what could be the underlying mechanisms? Cellular reactive oxygen species (ROS), which are produced not only by mitochondrial OXPHOS via ETC activity but also by Nox enzymes at the plasma membrane, can have a physiological impact on cell behaviour and fate [30]. ROSs were initially found to increase NSPC self-renewal and proliferation [31], but more recent data indicate pleiotropic, context-dependent effects. In adult mouse neurogenesis, high levels of ROS have been associated with NSPC quiescence [32], whereas in the embryonic cortex, ROS increase during the conversion from NSPCs to neurons [8]. In this case, ROS appears to act through one of its physiological targets, the transcription factor NRF2, leading to upregulation of the BOTCH gene, a Notch inhibitor, thereby favouring the transition towards neuronal fate [8]. ROS production during neurogenesis has been reported upstream or downstream of various other classes of transcription factors [33–36], providing additional levels of complexity between ROS levels and transcriptional regulation during neurogenesis, which remain to be explored.

Another main consequence of OXPHOS activity is the change in REDOX (reduction–oxidation) balance, in particular through the pair formed by the oxidised and reduced form of NAD (NAD$^+$ and NADH). NAD$^+$/NADH ratios are influenced by glycolysis–OXPHOS balance and have been implicated in many aspects of neuronal fate acquisition and differentiation, mostly through the activity of the NAD$^+$-dependent deacetylase sirtuin family [37]. In particular, sirtuin-1 (Sirt1) is required for cell fate determination of NSPCs during embryonic development [38–40]. In mouse cortical
development, Sirt1 is recruited to selective DNA targets by the transcription repressor factor Bcl6 and induces selective epigenetic repression of neighbouring genes by histone deacetylation [39]. Interestingly, BCL6 acts by repressing key genes of the Notch, Wnt, SHH and FGF pathways, all of which promote NSPC self-renewal and proliferation: their repression by the BCL6/Sirt1 complex thus leads to cell cycle exit and neuronal differentiation [40].

Recently, the relationship between Sirt1 activity and mitochondrial function/dynamics was assessed during neuronal fate determination [9] (Figure 3). This revealed that the pharmacological increase of the ETC activity using Carbonyl cyanide m-chlorophenyl hydrazone (CCCP), a proton ionophore, which is expected to lead to increased NAD+/NADH ratios [41], could promote cortical neurogenesis in a Sirt1-dependent manner. Conversely, the induction of NSPC self-renewal induced by mitochondria fusion (Figure 1) could be blocked by sirtuin activation. Finally, manipulation of either sirtuin activity or mitochondria fusion, during the neurogenic conversion, could lead to acute changes in acetylation patterns of histone H4 lysine 16 (H4K16), a main target of Sirt1/Bcl6 (Figure 3). Collectively, these data suggest that mitochondrial influence on neuronal fate determination involves the redox-sensitive Sirt1 activity, which could lead to chromatin remodelling, favouring neuronal fate acquisition. However, it remains to be determined how the changes in mitochondrial morphology actually lead to increased mitochondrial NAD+ levels and how this can then affect Sirt1 activity in the nucleus [42]. Moreover, it will be important to understand how the observed histone acetylation changes actually lead to selective transcriptional responses required for neurogenesis and to explore whether other mitochondria-derived metabolites can drive PTM of histones or other relevant proteins [5,6]. Finally, it will be interesting to study modulation of sirtuins by mitochondrial activity in other cell fate conversions in which OXPHOS is implicated, such as direct neuronal reprogramming and neural tumorigenesis [43,44].

**Beyond and between glycolysis and OXPHOS: TCA and lipid metabolism in neurogenesis**

Although these data illustrate the key influence of OXPHOS on neurogenesis, other mitochondria-dependent metabolic functions have been implicated, in particular in link with the TCA cycle and lipid metabolism (Figure 4).

Primary microcephaly (MCPH) is a genetic neurodevelopmental disorder (NDD) characterised by highly reduced brain size, in particular of the cerebral cortex [45]. One of the causative genes, microcephalin 1 (MCPH1), was previously involved in NSPC proliferation and survival through the regulation of chromatin segregation during mitosis [45]. Recently, however, the MCPH1-encoded protein was detected at the level of mitochondria outer membranes [46]. MCPH1 was found to interact with and activate mitochondrial calcium channels linking the endoplasmic reticulum (ER) to mitochondria (Figure 4). Deletion of MCPH1 in mouse cortical NSPCs leads to a reduced intramitochondrial calcium level, which can affect the activity of TCA cycle key enzymes including α-ketoglutarate dehydrogenase (KGDH) [47], which is required for neurogenesis in fly neuroblasts [14]. MCPH1 deficiency could also be linked to decreased expression of mitochondrial phosphoenolpyruvate carboxykinase (PEPCK-M or PCK2). PCK2 can promote glycolysis and glutaminolysis in tumour growth through pyruvate regeneration, to feed acetyl-CoA to the TCA cycle [48]. These results point to potential roles of MCPH1 in neurogenesis through regulation of the mitochondrial calcium level and metabolic activity. Interestingly, several gene mutations associated with other forms of microcephaly have been linked to the TCA cycle, in particular at the level of glutaminolysis (Figure 4). These include SLC25A19 (solute carrier family 25 member 19), the mitochondrial thiamine pyrophosphate transporter [49], the deletion of which leads to early neural defects in the mouse and to a reduction in activity of KGDH through a depletion of mitochondrial thiamine pyrophosphate [50], KGDH itself [51] and glutamate pyruvate transaminase 2 (GPT2) [52]. Finally, ARHGAP11B (Rho GTPase-activating protein 11B), a human-specific gene that drives proliferation of cortical NSPCs, was also localised to mitochondria [53], where its gain of function can lead to blockade of the mitochondrial permeability transition pore (mPTP), thereby leading to increased calcium levels. The expansion of mouse cortical NSPCs induced by ARHGAP11B overexpression could be blocked by pharmacological inhibition of glutaminolysis, which could also reduce the number of proliferative NSPCs in *ex vivo* cultures of the human fetal cortex [53]. It is intriguing that both MCPH1 and ARHGAP11B appear to control mitochondrial calcium levels, albeit through different mechanisms. It will be interesting to test further the impact of mitochondrial calcium on neurogenesis, as it can influence cell fate in cardiomyogenesis through Notch pathway modulation [54].

Overall, these studies highlight the importance of the TCA cycle and related pathways in embryonic cortical neurogenesis across species. It will be important to determine whether these effects contribute to NSPC proliferation through the generation of ATP and TCA-dependent metabolism (Figure 4).
The model of the links between mitochondrial dynamics and sirtuin signalling during neurogenesis. After mitosis, NSCs that display high levels of mitochondria fusion (following fusion activation/fission inhibition (a) or physiologically (b)) will remain NSCs, through the action of activated genes that promote self-renewal. On the other hand, the cells that maintain high levels of fission will convert into neurons (c), in part through the action of NAD⁺-dependent sirtuins that deacetylate histones, thereby maintaining self-renewal genes in a repressed mode. The same impact on neuronal fate acquisition and histone remodelling can be obtained with treatment of the cells with the OXPHOS activator CCCP (d), even with mitochondria in a fused state.
anabolism, through the feeding of OXPHOS, or whether they control NSPC biology in a more instructive fashion through TCA-derived signalling metabolites, such as α-KG that could promote histone H3 demethylation, which is required for neurogenesis [55,56].

Finally, another important aspect of mitochondria function related to neurogenesis is fatty acids (FAs) metabolism (Figure 4). In mammalian cells, FAs are obtained either by direct exogenous uptake or by de novo synthesis from acetyl-CoA in the cytoplasm, in this latter case catalysed by fatty acid synthase (FASN). A first direct implication of FA metabolism in neuronal fate determination was shown in the context of mouse adult neurogenic niches, where proliferating NSCs show high FASN activity, and its genetic disruption leads to reduced proliferation and neurogenesis [57]. Conversely, a gain-of-function mutation in the same gene (FASN-R1819W, leading to enhanced FASN activity) leads to intellectual disability [58], whereas mutant mice bearing the same mutation also display reduced adult hippocampal neurogenesis [59]. Interestingly, although FASN-R1819W–mutant mice show seemingly normal embryonic cortical development, human cerebral organoids carrying the patient’s mutation show reduced proliferation of NSPCs [59]. These results suggest that the impact of FA metabolism is cell type–specific, but could also be linked to species differences.

On the other hand, FAs are converted back to acetyl-CoA via mitochondrial β-oxidation (FAO), which is also implicated in adult and embryonic neurogenesis [60,61] (Figure 4). In adult neurogenesis, the key FAO enzyme, carnitine palmityltransferase 1a (Cpt1a), is required for the maintenance of quiescence of NSCs [60]. In the mouse embryonic cortex, downregulation of FAO by knockdown of Cpt1a, or of trimethyllysine hydroxylase, epsilon (TMLHE, involved in FAO through carnitine biosynthesis), leads to decreased self-renewal and apoptosis of cortical NSPCs [60,61]. These data indicate the importance of FA metabolism in neurogenesis, although as for TCA, it will be important to determine the underlying downstream mechanisms, permissive and/or instructive.

Conclusions and perspectives
Mitochondria and related metabolism have emerged as a crucial source of cues required for proper neurogenesis, from NSC self-renewal to neuronal fate commitment, but many open questions are still standing. Among these, it remains unclear how mitochondria dynamics and function are actually linked to one another during neurogenesis, and by which upstream mechanisms they are controlled, in synergy with developmental signals. Conversely, it will be important to find out which downstream mechanisms are involved in each effect of mitochondria on neurogenesis, whether through permissive regulation of metabolite production or through more instructive signalling modes, such as metabolism-driven PTMs.

On the other hand, the finding that mitochondria dynamics–dependent neuronal fate acquisition displays striking timing differences between mouse and human species suggests that metabolism could be causally linked to species-specific properties relevant to brain evolution, perhaps in link with recently uncovered species differences in protein turnover related to developmental timing in other systems [62,63].

Finally, although mitochondrial defects have long been thought to strike preferentially the brain because of its high energy needs, the new findings reviewed here invite to revisit the mechanisms of mitochondria-linked NDD, exploring early neural defects as well as direct links with known neurodevelopmental pathways.

Conflict of interest statement
Nothing declared.
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