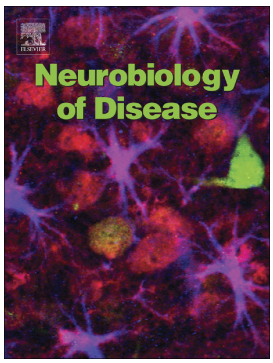

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Title

Mitochondrial Regulation of Adult Hippocampal Neurogenesis: Insights into Neurological Function and Neurodevelopmental Disorders

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Abstract (172 words)

Mitochondria are essential regulators of cellular energy metabolism and play a crucial role in the maintenance and function of neuronal cells. Studies in the last decade have highlighted the importance of mitochondrial dynamics and bioenergetics in adult neurogenesis, a process that significantly influences cognitive function and brain plasticity. In this review, we examine the mechanisms by which mitochondria regulate adult neurogenesis, focusing on the impact of mitochondrial function on the behavior of neural stem/progenitor cells and the maturation and plasticity of newborn neurons in the adult mouse hippocampus. In addition, we explore the link between mitochondrial dysfunction, adult hippocampal neurogenesis and genes associated with cognitive deficits in neurodevelopmental disorders. In particular, we provide insights into how alterations in the transcriptional regulator NR2F1 affect mitochondrial dynamics and may contribute to the pathophysiology of the emerging neurodevelopmental disorder Bosch-Boonstra-Schaaf optic atrophy syndrome (BBSOAS). Understanding how genes involved in embryonic and adult neurogenesis affect mitochondrial function in neurological diseases might open new directions for therapeutic interventions aimed at boosting mitochondrial function during postnatal life.

Keywords

Mitochondria; Nr2f1; BBSOAS; adult neural stem cells; dentate gyrus

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Introduction

Mitochondria are essential organelles in eukaryotic cells that play a central role in energy homeostasis, metabolism, signaling and apoptosis. Beyond their primary function in ATP production through oxidative phosphorylation of glycolysis and lipolysis products, mitochondria are involved in a plethora of cellular functions. They contribute to biosynthetic pathways and produce signaling molecules such as reactive oxygen species (ROS) and reactive metabolic intermediates, which are conveyed to the nucleus and modulate epigenetic regulation (Picard et al., 2016). Mitochondria are involved in calcium (Ca2+) buffering, a function that is particularly important in neurons for shaping synaptic responses (Devine et al., 2018). In addition, mitochondria undergo morphological transitions through processes involving fusion and fission that are tightly regulated and closely linked to cellular metabolism and function. Any changes in the metabolic state can affect mitochondrial fission, fusion, transport and degradation, whereas changes in mitochondrial morphology will impact cell energetics and various cellular functions, such as differentiation, plasticity and apoptosis (Picard et al., 2016).

During embryonic and adult neurogenesis mitochondria regulate essential functions of neural development (reviewed in Iwata and Vanderhaeghen, 2021; Khacho et al., 2019; Khacho and Slack, 2018) and accumulating evidence supports the idea that mitochondrial dysfunction might be a common factor in neurodevelopmental disorders (NDDs) (Garone et al., 2024; Ortiz-González, 2021; Rojas-Charry et al., 2021). NDDs include disorders such as intellectual disability (ID), autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), communication disorders, and motor disorders that occur in infancy or childhood (ICD-11 https://www.who.int/standards/classifications/classification-of-diseases) and often show comorbidity, suggesting common underlying mechanisms (Parenti et al., 2020). Additionally, schizophrenia, while not officially classified as an NDD, shares many characteristics with these disorders and can be influenced by a significant neurodevelopmental component (Lewis and Levitt, 2002).

Although the functional and cognitive impairments characteristic of NDDs are largely attributed to cerebral cortical defects, an increasing body of evidence suggests that the hippocampus, a brain region characterized by activity-dependent structural and functional plasticity (Li et al., 2019; Pons-Espinal et al., 2013), might also be central in NDDs. The hippocampus is crucial for information consolidation, which includes both short and long-term memory, as well as learning (Lizman et al., 2017). In addition, the ventral region of the hippocampus is involved in emotional regulation and anxiety (Strange et al., 2014). Furthermore, the hippocampus is responsive to experience, making it particularly vulnerable to disease, but also a highly promising therapeutic target in treating NDDs. In both NDDs patients and animal models, hippocampal dysfunction can lead to difficulties in spatial and episodic memory, as well as impaired learning and cognitive flexibility, which are often correlated to structural alterations (i.e. reduced hippocampal volume, abnormalities in

dendrite and synapse formation) (Penzes et al., 2011; Pizzarelli and Cherubini, 2011) and nonfunctional network connectivity, such as the hippocampal-prefrontal cortical circuit (HPC-PFC) (Ruggiero et al., 2023). Moreover, increasing evidence indicates that alterations in the process of adult neurogenesis occurring in the hippocampal dentate gyrus (DG), may contribute to the manifestation of NDDs symptoms, as altered neurogenesis has been reported in several animal models of neurodevelopmental disorders such as ID, including Rett, Fragile X and Down syndromes (Guo et al., 2011; Li et al., 2016; Smrt et al., 2007; Valenti et al., 2017). In light of these findings and the emerging role of mitochondrial dysfunction in NDDs, elucidating mitochondrial behavior and function in adult hippocampal neurogenesis under both physiological and pathological conditions becomes crucial to better characterize the pathogenic mechanisms underlying NDDs and to explore new therapeutic strategies to overcome disease-associated alterations.

In this review, we will discuss recent studies on mitochondria as multifaceted regulators of adult neurogenesis, focusing on the hippocampal neurogenic niche in the adult brain. We will also summarize cases of NDDs where mitochondrial dysfunction in adult neurogenesis correlates with cognitive deficits. Finally, we will discuss recent data linking mitochondrial dysfunction to the emerging NDD Bosch-Boonstra-Schaaf optic atrophy syndrome (BBSOAS), providing insights into the genetic basis of mitochondrial involvement in this disease for a better understanding of its physiopathology and a constructive contribution to a potential therapy.

1. Neurogenesis in the adult mammalian brain: focus on the hippocampal dentate gyrus

The majority of neurons are born during embryonic development; however, neurogenesis continues to occur in restricted regions of the mammalian brain in the postnatal/adult life. Adult neurogenesis is a multi-step process by which new functional neurons are generated from adult neural stem cells (NSCs) and functionally integrate into the pre-existing neural circuits throughout life. Under physiological conditions, neurogenesis in the adult mouse brain occurs within two distinct neurogenic microenvironments or 'niches': the subventricular zone of the lateral ventricle, which generates newborn neurons that migrate to the olfactory bulb, where they differentiate into diverse subtypes of inhibitory interneurons (Bonzano et al., 2016; Obernier and Alvarez-Buylla, 2019), and the subgranular zone of the dentate gyrus (DG) of the hippocampus, where glutamatergic DG granule neurons are generated (Kempermann et al., 2015; Ming and Song, 2011). Adult neurogenesis is tightly regulated by several cell-intrinsic factors and extrinsic cues from the environmental niche - which also involve different cellular types including astrocytes, ependymal cells and microglia (Bond et al., 2015; Cassé et al., 2018; Crisci et al., 2024; Denoth-Lippuner and Jessberger, 2021; Karakatsani et al., 2023; Urbán et al., 2019) - and both local and long-range neuronal circuits (Bao et al., 2017; Li et al., 2022; Song et al., 2016).

In this review, we will focus on adult DG neurogenesis, as most studies addressing the role of mitochondria in adult neurogenesis are based on this system. In addition, adult-born neurons play different physiological roles in hippocampus-dependent functions such as learning, memory, pattern separation, and cognitive flexibility, which are particularly relevant in the context of NDDs. Within the subgranular zone of the adult hippocampal DG, adult NSCs are predominantly quiescent astroglial cells with a distinct radial morphology, called radial glia-like cells or type I cells (**Fig.1**). Once activated, radial glia-like cells divide either symmetrically, producing two radial glial-like cells, or asymmetrically, producing one identical radial glial-like cell for self-renewal and one neural progenitor cell with a different fate, also called intermediate progenitor or transiently amplifying progenitor (type 2 cell). Collectively, these two populations can be referred to as adult neural stem/progenitor cells. The intermediate progenitor cells undergo multiple rounds of cell division to expand the progenitor pool, eventually producing neuroblasts that exit the cell cycle to differentiate into immature granule cells in the early postmitotic phase and eventually mature into granule cells (**Fig.1**) (Bond et al., 2015; Kempermann et al., 2015). During immature stages, adult-born neurons pass through a critical period for survival: an early selection phase occurs in the first two weeks after birth, when newborn cells exit the cell cycle and start neuronal differentiation. In this first selection, only a small amount of newborn neurons survive (around 30/40%) in animals raised in standard housing (Encinas et al., 2011; Tashiro et al., 2007, 2006). The second phase consists of negative selection by competitive behaviors at synaptic levels, which involves synaptic competition among cohorts of age-matched adult-born granule cells as well as with pre-existing granule cells (Adlaf et al., 2017; McAvoy et al, 2016; Kleine Borgmann et al., 2016; Kochan et al., 2024; Toni et al., 2007): thus, only adult-born granule cells able to functionally connect and stably integrate into the pre-existing DG circuitry will survive for long-term (Kempermann et al., 2003). Granule neurons serve as the primary excitatory neurons in the DG: they receive inputs from the entorhinal cortex and project their axons along the mossy fiber pathway to the hippocampal CA3 region (**Fig. 1**). Within a few days after cell cycle exit, adult-born granule cells send their axon and establish functional synapses to CA3. In parallel to axonal elongation and targeting, the dendritic tree starts to grow in the DG molecular cell layer and massively develops within the first three weeks (Sun et al., 2013; Zhao et al., 2006). Retroviral labeling shows that the first dendritic spines appear in 17-day-old granule cells (Zhao et al., 2006), thus indicating that axon elongation and targeting to CA3 partially precedes spine formation on dendrites (Sun et al., 2013; Kempermann et al., 2015). Adult-born neurons integrating into the DG compete with resident mature granule cells for inputs and outputs, and they are transiently more excitable compared to pre-existing cells, making them more likely to be recruited by different behavioral experiences (Ge et al., 2007; Piatti et al., 2011; Tashiro et al., 2007). Overall, the addition of new neurons to the DG significantly enhances the structural and functional plasticity of the hippocampal circuit. Indeed, abnormal neurogenesis in the adult brain may contribute to alterations of hippocampal-DG-related spatial memory and pattern separation functions (reviewed in Fölsz et al., 2023; Toda et al., 2019). Interfering with the adult neurogenic pool through genetic

tools (i.e. inducible conditional models) but also through acute irradiation or environmental manipulations, can lead to deficiencies in hippocampal-dependent learning and memory tasks in rodents (Deng et al., 2009; Gu et al., 2012; Malloul et al., 2018; Saxe 2006; Snyder et al., 2005). On the other hand, running and/or exposure to an enriched environment, well-known to promote and boost neurogenesis, can have beneficial effects on hippocampal-dependent learning behaviors (Garthe et al., 2016; Valero et al., 2011; Van Praag et al., 1999).

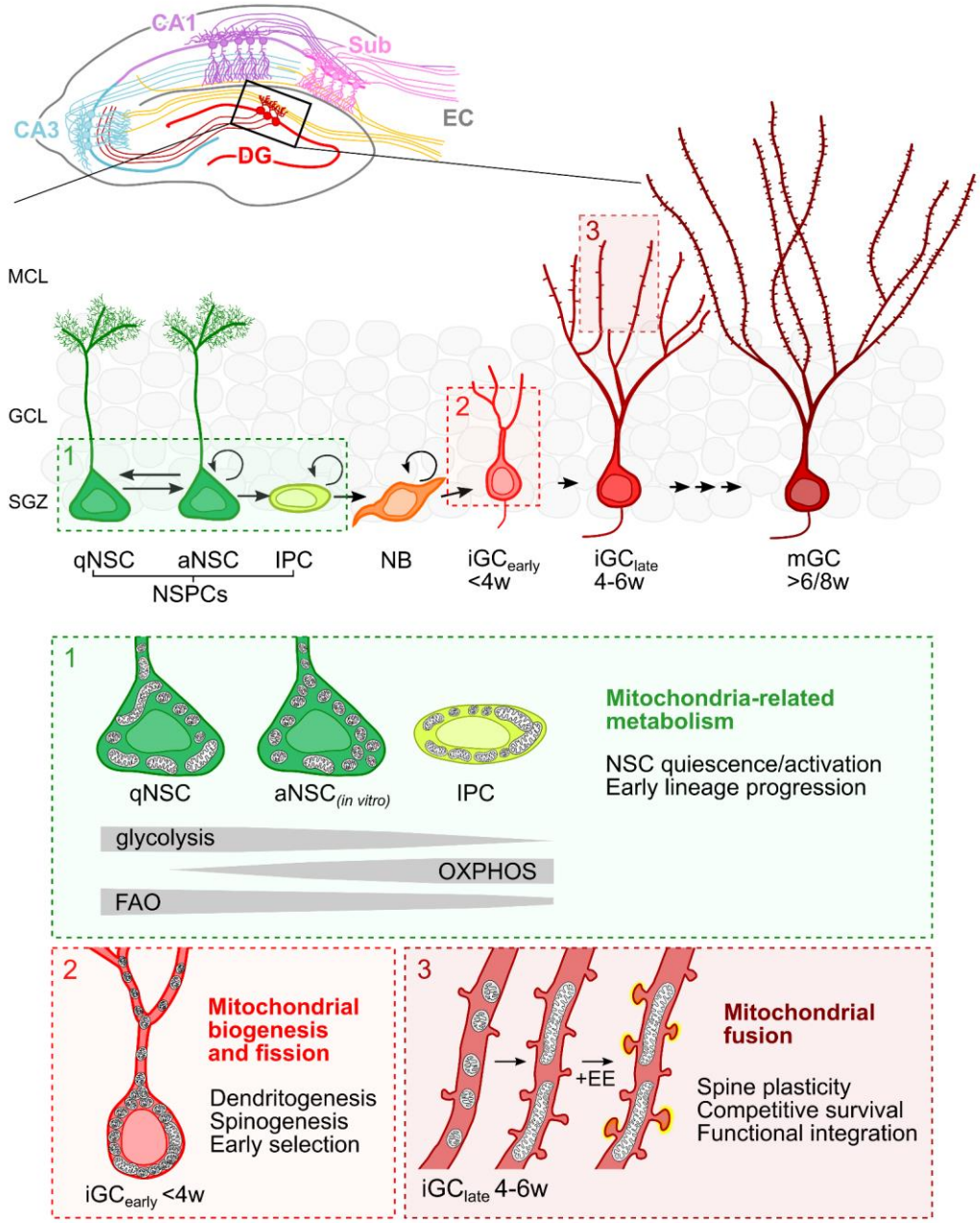

Figure 1. Schematic representation of the pleiotropic roles of mitochondria during adult neurogenesis in the mouse hippocampal dentate gyrus (DG). Abbreviations: CA, cornus ammonis; Sub, subiculum; EC, entorhinal cortex; MCL, molecular cell layer; GCL, granule cell layer; SGZ, subgranular zone; qNSC, quiescent neural stem cell; aNSC, active neural stem cell; NSC, neural stem cell; IPC, intermediate progenitor; NSPCs, neural stem

progenitor cells; NB, neuroblast; iGC, immature granule cell; mGC, mature granule cell; w, weeks (of cellular age); OXPHOS, oxidative phosphorylation; FAO, fatty acid beta-oxidation; EE, enriched environment.

Adult neurogenesis has been reported in most mammalian species, yet with interspecies differences, and its occurrence in the human brain remains a controversial topic with conflicting results (Simard et al., 2024; Tobin et al., 2019). Some reports have suggested that hippocampal neurogenesis in humans continues throughout physiological aging and can be severely impaired in patients with various neurological disorders (Boldrini et al., 2018; Moreno-Jiménez et al., 2019; Spalding et al., 2013; Wang et al., 2022), while others have proposed that this phenomenon ceases in early childhood (Sorrells et al., 2018) and is very rare or absent in the adult human DG (Seki et al., 2019; Sorrells et al., 2018; Zhou et al., 2022). Despite these divergences, one common element in human studies relates to the presence of "immature" neurons in the adult DG (Zhou et al., 2022; reviewed in Simard et al., 2024). Interestingly, beyond the canonical neurogenic niches, "immature" neurons have been described in several regions of the adult mammalian brain. In rodents, these neurons may "awake" and mature during adulthood and aging (Benedetti et al., 2023). These cells are particularly abundant in large-brained mammals and according to an emerging hypothesis they can represent a new form of structural plasticity in long-living species showing reduced rates of stem cell-driven neurogenesis (Bonfanti et al., 2023). Thus, while further studies are needed to ascertain whether the immature granule cells in the adult human hippocampus are generated during development or in adult life, it seems clear that they might serve plastic functions even in the absence of cell division.

2. Pleiotropic role of mitochondria in adult neurogenesis

The generation of new neurons in the adult hippocampus follows a stereotypic developmental sequence involving intrinsic and extrinsic factors (reviewed in Kempermann, 2015; Urbán and Cheung, 2021). Among them, a metabolic switch from glycolysis to oxidative phosphorylation, together with mitochondrial remodeling, has emerged as a crucial player in adult neurogenesis (**Fig. 1**). In the following paragraphs we discuss recent evidence covering the importance of mitochondrial mass, morphology, distribution, function, and metabolism in regulating the balance of NSC proliferation, differentiation, and survival of adult-born neurons as well as their synaptic plasticity and functional integration.

2.1 Mitochondrial Metabolism in Adult NSCs: Impact on Activation and Early Lineage Progression

One of the most critical regulatory steps in adult neurogenesis is the decision of NSCs to remain quiescent or to enter an active state to eventually generate cell progeny. The

involvement of mitochondria in controlling stem cell behavior has been demonstrated in different systems (Bahat and Gross, 2019; Mandal et al., 2011; Wanet et al., 2015), including embryonic and adult neurogenesis (reviewed in Khacho et al., 2019; Khacho and Slack, 2018).

Adult NSCs in a quiescent state (qNSCs), like most somatic stem cells, are thought to primarily use glycolysis as their main metabolic pathway to produce energy. Glycolysis is a process in which glucose is broken down to pyruvate, producing a small amount of adenosine triphosphate (ATP) without requiring oxygen consumption, thus limiting the oxidative metabolism-dependent generation of reactive oxygen species (ROS) to prevent cell damage and ensure lifelong self-renewal (Beckervordersandforth, 2017). A shift in energy metabolism from glycolysis to oxidative phosphorylation (OXPHOS) early in the NSC fate transition has been supported by unbiased single-cell RNA sequencing (Shin et al., 2015). Specifically, as NSCs enter the cell cycle, there is a decreased expression of glycolytic genes and an upregulated expression of genes involved in OXPHOS, suggesting that oxidative metabolism becomes the primary energy source upon activation of adult NSCs. Furthermore, although adult NSCs show a stable expression of early mitochondrial respiratory chain complexes (complexes I, II, III and IV), the expression of genes involved in complex V (ATPase) increases over pseudo time (i.e., the reconstruction of molecular state transitions along continuous biological processes), suggesting a gradual completion of the full electron transport chain during early lineage progression (Shin et al., 2015). Further in-depth analysis revealed that the transition from NSCs to intermediate progenitor cells is associated with a gradual upregulation of tricarboxylic acid (TCA) cycle enzymes, which provide electron carriers to the electron transport chain (ETC), in parallel with an up-regulation of mitochondrial complex components. In addition, key enzymes of glycolysis, such as aldolase A and lactate dehydrogenase A, and mitochondrial uncoupling protein 2 (UCP2), which has been implicated in promoting aerobic glycolysis over OXPHOS in embryonic neural precursors (Khacho et al., 2016; Zheng et al., 2016), are downregulated around the time of NSC activation (Beckervordersandforth et al., 2017).

Some of the first functional evidence that proliferating NSCs/progenitors are highly dependent on functional ETCs and OXPHOS was provided by pharmacologically blocking the activity of ETCs and OXPHOS *in vitro*. Treatment of cultured adult hippocampal NSCs/progenitors with rotenone, which inhibits the transfer of electrons from mitochondrial complex I to the electron carrier ubiquinone, or oligomycin, which inhibits mitochondrial complex V, completely abolished cell proliferation and led to a dramatic increase in cell death (Beckervordersandforth et al, 2017). Further evidence came from genetic ablation of the mitochondrial transcription factor A (*Tfam*) in the adult hippocampal neurogenic lineage: TFAM regulates the expression of key components of the mitochondrial ETC/OXPHOS complexes (Larsson et al., 1998) and its inactivation in adult NSCs resulted in abnormal mitochondria with clumped morphology - also observed to a lesser extent in newborn neurons - and a complete loss of *Cox1* expression, a known target of TFAM transcriptional

activity (Beckervordersandforth et al., 2017). Remarkably, these changes were not associated with alterations in the total number of NSCs or the proportion of activated NSCs but induced severe defects in the progression of NSCs to the neurogenic lineage, ultimately leading to increased cell death of highly proliferative intermediate progenitor cells (Beckervordersandforth et al, 2017). Together, these data show that the shift from quiescent to activated NSCs is not strictly dependent on ETC and OXPHOS activity, which instead regulates intermediate progenitor cell expansion and early progression towards the neurogenic lineage.

Moreover, recent data are beginning to reveal a previously underestimated role for mitochondrial-related metabolism in adult NSCs (recently reviewed in Scandella et al., 2023). While somatic stem cells often show a simple mitochondrial structure characterized by immature spherical/round mitochondria with poorly formed cristae and low levels of mitochondrial DNA (Lisowski et al., 2018), radial glia-like NSCs in the adult mouse hippocampus have rather abundant mitochondria with a mixed tubular and spherical shape (Beckervordersandforth et al., 2017). Recent studies have shown that in the adult DG NSCs mitochondria are even more elongated than previously thought, both *in vivo* (Wani et al., 2022) and *in vitro* (Petrelli et al., 2023), suggesting their important role in NSC behavior. A study by Knobloch and colleagues has provided mechanistic evidence that oxidized fatty acids are required for energy production and serve as an alternative carbon source for adult NSCs indicating that glycolysis is not the sole source of energy for adult qNSCs. Indeed, qNSCs have high levels of mitochondrial fatty acid beta-oxidation (FAO) (Knobloch et al., 2017), the metabolic process of fatty acid degradation that occurs in the mitochondrial matrix. FAO is downregulated upon NSC activation, when *de novo* lipogenesis predominates. Consistently, qNSCs show the highest levels of SPOT14 transcript and protein (Knobloch et al., 2014; Shin et al., 2015), which negatively regulates *de novo* lipogenesis, and high levels of enzymes required for fatty acid degradation (e.g. ACSL3, ACSL6 and ACSBG1) (Shin et al., 2015). Instead, high levels of FAO are required to maintain quiescence in adult DG NSCs, as pharmacological or genetic inhibition of this pathway leads to massive disturbances in NSC/ progenitor behavior both *in vivo* and *in vitro*. Inhibition of FAO *in vitro* leads to increased cell death of qNSCs, but also reduces their entry into the cell cycle. Similarly, conditional deletion of carnitine palmitoyltransferase 1 (*Cpt1a*) - the rate-limiting enzyme for FAO - impairs the activation of adult NSCs, resulting in fewer and smaller cell clusters as assessed by *in vivo* clonal analysis (Knobloch et al., 2017). High levels of FAO during quiescence are, at least in part, regulated at the transcriptional level. Expression of peroxisome proliferator-activated receptor alpha (*Pparα*), a known transcriptional regulator of genes involved in FAO, and its target genes are highly upregulated in quiescent NSCs/progenitors compared to proliferating NSCs/progenitors (Knobloch et al., 2017). Nevertheless, why mitochondrial FAO is so important for adult qNSCs still remains largely unknown (Scandella et al., 2023). Mitochondrial pyruvate metabolism, which requires the activity of the mitochondrial pyruvate carrier (MPC), is another factor influencing the maintenance of quiescence in adult

NSCs, as demonstrated in a recent study by Petrelli et al (2023). The MPC is highly expressed in adult NSCs/progenitors, and its loss of function leads to the activation of qNSCs and enhances neurogenesis, both *in vivo* and *in vitro*, thereby exhausting the NSC pool. These data show that mitochondrial metabolism involving FAO and glucose-derived pyruvate plays a key role in the maintenance of quiescence in adult NSCs. It remains to be determined whether quiescent NSCs require these substrates solely for energy production or also for modulating the availability of TCA intermediates and regulating mitochondria-to-nucleus retrograde signaling (Scandella et al., 2023).

Further evidence for an instructive role of mitochondrial metabolism in adult NSCs comes from a study on the role of intracellular L-arginine homeostasis in modulating glycolysis and mitochondrial activity in adult DG neurogenesis. Adult mice lacking the mitochondrial urea metabolism enzyme Arginase II (ARG-II) exhibit NSC overactivation, leading to accelerated NSC pool depletion and reduced hippocampal neurogenesis over time. Mechanistically, *Arg-II* deficiency resulted in increased L-arginine levels and the induction of a metabolic shift from glycolysis to OXPHOS caused by impaired hexokinase-I binding to mitochondria, without overall changes in mitochondrial dynamics and function. Notably, selective inhibition of OXPHOS improved NSC overactivation and reversed abnormal neurogenesis in *Arg-II*-deficient mice (Xu et al., 2023). Finally, *in vitro* studies have revealed that reversible changes in the mitochondrial proteome of NSCs/progenitors occur during the transition from proliferation to quiescence, without significant changes in mitochondrial mass or membrane potential. This ”metabolic flexibility” is regulated by mitochondrial protease activity. Using a combination of unbiased -omics approaches and conditional mouse models, Bergami and colleagues identified the i-AAA protease YME1L as a key player in dynamically shaping the mitochondrial proteome of NSCs/progenitors (Wani et al., 2022). Indeed, deletion of *Yme1l* in adult NSCs shifts them away from high FAO rates, resulting in defective self-renewal and premature differentiation, and ultimately leading to exhaustion of the NSCs/progenitors pool (Wani et al., 2022). Strikingly, deletion of *Yme1l* at the single clone level *in vivo* resulted in a phenotype reminiscent of genetic ablation of the FAO rate-limiting enzyme *Cpt1a*, which drives NSCs/progenitors exit from quiescence and enhances terminal neurogenic symmetric divisions at the expense of neurogenic asymmetric self-renewal (Knobloch et al., 2017). This novel and unexpected role of the protease YME1L in maintaining the self-renewal potential of adult NSCs/progenitors appears to be independent of its role in balancing mitochondrial dynamics via OPA1 processing (Ohba et al., 2020; Kochan et al., 2024), and demonstrates that YME1L-specific effects go beyond changes in mitochondrial morphology. Importantly, these findings add a key layer of regulation to the mechanisms that govern the metabolic state transitions of NSCs/progenitors, beyond the potential changes in the transcriptome profiles. Finally, they support an emerging concept in NSC/progenitor biology, i.e. 'metabolic adaptation’, which is the ability of the mitochondrial proteome to dynamically adjust its protein composition to support NSC/progenitor proliferation and maintain their stemness over time.

2.2. Mitochondrial Biogenesis, Subcellular Compartmentalization and Dynamics: Implication for Maturation and Functional Integration of Adult-born DG Neurons

The morphological development of adult-born hippocampal granule cells *in vivo* is accompanied by substantial remodeling of mitochondrial networks. This includes a marked increase in mitochondrial mass, indicative of mitochondrial biogenesis, and extensive changes in mitochondrial distribution and shape (Kochan et al., 2024; Steib et al., 2014).

Several signaling pathways and transcription factors control mitochondrial biogenesis (Hock and Kralli, 2009). Among these, proliferator-activated receptor co-activator 1 (PGC-1α) acts as a master regulator by cooperating with other transcription factors such as nuclear respiratory factor 1 (NRF1) and estrogen-related receptors (EERs). These factors regulate the expression of nuclear genes encoding mitochondrial proteins, such as *Tfam*. Altered expression of these factors not only causes mitochondrial dysfunction, but also leads to changes in neuronal morphology. For example, adenovirus-mediated knockdown of PGC-1α in DG hippocampal neurons *in vivo* reduces dendritic spine density without altering dendritic arborization, suggesting a role for PGC-1α in synapse maintenance in DG neurons (Cheng et al., 2012). Furthermore, deletion of *Tfam* specifically in DG proliferating neuronal precursors by stereotaxic injection of a Cre recombinase-encoding retrovirus into *Tfam* -floxed mice resulted in newborn neurons with mildly shortened dendritic length and reduced dendritic complexity, suggesting that *Tfam* loss-of-function impairs differentiation/maturation of adult-born neurons (Beckervordersandforth et al., Neuron 2017).

Neurons rely on localized and compartmentalized mitochondria to meet spatially heterogeneous metabolic demands (Misgeld and Schwarz, 2017). This is also reflected by changes in mitochondrial shape in different cellular subcompartments, as evidenced by the distinct morphological features that characterize the mitochondrial network between axons and dendrites (Misgeld and Schwarz, 2017; Rangaraju et al, 2019a). In general, axonal mitochondria are shorter and less complex in morphology, whereas dendritic mitochondria are longer, often tubular and typically more elaborate. This is also true for DG granule cells, as demonstrated by serial section electron microscopy (Faitg et al., 2021). In granule cell dendrites, mitochondria are complex in structure and particularly enriched in the proximity of dendritic spines, likely to meet regional energy demands and contribute to local Ca2+ buffering, whereas axonal mitochondria are simpler than dendritic ones (Faitg et al., 2021).

Interestingly, changes in mitochondrial morphology and content occur during the differentiation and maturation of adult-born DG neurons. Using retroviral-mediated labeling of mitochondria in the adult DG, Steib and colleagues provided the first evidence of changes in the distribution and shape of mitochondria at different days post-viral injection (dpi) during the development of newborn neurons. At early time points (3-7 dpi), mitochondria are predominantly located in the soma and the initial segment of processes, forming large tubular structures. Subsequently (16-42 dpi), mitochondria in the soma and dendritic shaft become

more fragmented, exhibiting a mixed tubular and globular shape, which is maintained in mature adult granule cells (106 dpi) in the soma. At this stage, somatic mitochondria form interconnected networks that extend into the dendritic shaft, with dendritic mitochondria evenly distributed throughout the dendritic arbor (Steib et al., 2014). A further comprehensive characterization of the shape of the mitochondrial network in the dendritic compartment during the maturation of adult-born neurons has been recently carried out by the Bergami lab (Kochan et al., 2024). Their data show that during the first three weeks of DG granule cell development, dendritic mitochondria are short and irregularly spaced. However, by the fourth week, they become more elongated and more even distributed along the dendrites (Kochan et al., 2024). These findings are consistent with a significant reduction in the sphericity index of individual mitochondria starting from the fourth week. Moreover, mitochondria elongation coincides with a significant increase in mitochondrial occupancy along the dendrites at four weeks, exceeding 50% of the dendritic volume, compared to less than 40% at earlier stages (Kochan et al., 2024). Overall, these data indicate that adult-born granule cells undergo extensive remodeling of their dendritic mitochondria during the fourth week of life, when adult-born neurons transition from an immature to a more mature phenotype (Toni et al., 2007; Zhao et al., 2006), highlighting the role of mitochondrial dynamics in the maturation of newborn neurons.

Mitochondrial dynamics are governed by a concerted action of GTPases and cofactors that regulate mitochondrial fission and fusion adapting mitochondrial shape and mass to cellular and metabolic demands (Seager et al., 2020). Mitochondrial fusion is controlled by mitofusins 1 and 2 (MFN1 and MFN2) in the outer mitochondrial membrane and OPA1 in the inner mitochondrial membrane, whereas mitochondrial fission is primarily mediated by the soluble dynamin-related protein DRP1 (Giacomello et al., 2020). Notably, mitochondrial fission is crucial for the efficient distribution of new mitochondria to the growing dendritic trees, as observed in cultured neurons (Li et al., 2004). *In vivo* genetic inhibition of DRP 1 by stereotaxic injection of a retroviral vector encoding a dominant-negative form of DRP1 (dnDRP1) significantly reduces the survival of immature DG newborn cells. The remaining surviving neurons exhibit depleted mitochondria and impaired dendrite extension (Steib et al., 2014). Additional evidence supporting the importance of DRP1-mediated mitochondrial fission in modulating dendritic growth of adult-born neurons came from a study on the ganglioside GD3, which binds to Drp1 to positively regulate its turnover (Tang et al., 2021). Adult-born granule cells in GD3 synthase-knockout (*GD3S*-KO) mice undergo a huge mitochondrial fragmentation - due to enhanced DRP1 levels - paralleled to decreased mitochondrial mass particularly in the dendritic arbors. GD3-deficient adult-born DG neurons show reduced total length and decreased complexity of dendrites at 28-42 dpi, further indicating that fine-tuning DRP1 protein levels is crucial for dendritogenesis in adult-born neurons.

The role of mitochondrial fusion in adult-born granule cells maturation has been recently addressed. Adult-born neurons lacking either MFN1 or MFN2 (or both) show a marked mitochondrial fragmentation throughout their cell body and dendritic tree with a greater

depletion of mitochondrial mass at more distally located dendritic regions (Kochan et al.,2024). Analysis of newborn GC survival disclosed no alterations in any of the examined genotypes at 3 weeks of cell age, when the mitochondrial network in wild-type granule cells is still largely fragmented (Steib et al., 2014; Kochan et al., 2024), suggesting that disrupting mitochondrial fusion has no effect in the first critical time window of newborn cell selection. However, by 6 weeks, the survival of *Mfn1*-cKO, *Mfn2*-cKO, and *Mfn1/2*-cKO granule cells was reduced by about 50% as compared with wild-type granule cells, indicative of compromised survival at later time points. Nevertheless, the remaining surviving fraction of mutant granule cells appears viable without signs of degeneration and exhibit a modest reduction in their total dendritic lengths and mild-to-moderate impairments in the overall complexity of dendrites. Notably, while *Mfn1* or *Mfn2* single KO granule cells show limited changes in the overall complexity of the apical dendrite, *Mfn1/2*-double mutant granule cells exhibited a stronger impairment of distal dendritic regions, suggesting that complete ablation of mitochondrial fusion may interfere with the growth of more distal dendritic branches (Kochan et al., 2024).

In vitro studies have highlighted the importance of dendritic mitochondria in the morphogenesis of spines in hippocampal neurons (Bapat et al., 2024; Li et al., 2004; Rangaraju et al., 2019). In general, interfering directly with mitochondrial dynamics decreases mitochondrial mass in the dendritic arbor in adult-born DG neurons (Tang et al., 2021; Andraini et al. 2023; Kochan et al., 2024). Morphometric analyses of dendritic spines showed that adult-born granule cells in either *GD3S*-KO mice or *Opa1*-heterozygous mice had fewer dendritic spines (including mushroom ones) than those in controls, suggesting that enhanced mitochondrial fragmentation impairs dendritic spine formation (Tang et al., 2021; Andraini et al. 2023). Nevertheless, cell-autonomous deletion of either Mfn1 or Mfn2 in adult-born DG neurons, which dramatically reduced mitochondrial occupancy in dendrites, fails to induce changes in the number of total dendritic protrusions, but selectively reduces the abundance of mushroom spines, suggesting compromised dendritic spine maturation and/or synaptic plasticity (Kochan et al., 2024).

Overall, these data indicate that balanced mitochondrial fission/fusion plays a role in controlling dendrite and spine morphogenesis in adult-born DG granule cells, potentially influencing their synaptic integration into the hippocampal circuitry. Furthermore, these findings demonstrate the importance of precise regulation of mitochondrial morphology in the survival of adult-born neurons. They also suggest a causal relationship between mitochondrial morphology/distribution and synaptogenesis, which may be particularly relevant to synaptic plasticity as discussed in the following section.

2.3. The Role of Mitochondrial Dynamics in Neuronal Plasticity of Adult-born Granule Cells

Voluntary wheel running and environmental enrichment are widely used experimental methods to enhance brain plasticity in mouse models. Several studies have shown that

running acts as a strong modifier of adult hippocampal neurogenesis by increasing the proliferation of neuronal precursors and by accelerating neuronal maturation in terms of dendrite outgrowth, complexity and spine formation (Piatti et al., 2011; Van Praag et al., 1999; Zhao et al., 2006). Exposure of animals to an enriched environment instead stimulates the functional integration of adult-born neurons by promoting enhanced synaptic plasticity (Bergami et al., 2015; Alvarez et al., 2016). Interestingly, running triggers mitochondrial remodeling in adult-born granule cells, inducing a profound increase in mitochondrial content and a change in their distribution among the different cellular compartments (Steib et al., 2014). In particular, exercise-induced dendritic development in immature neurons is paralleled by increased mitochondrial content, more abundant globular mitochondria in the dendritic shaft, and enhanced distribution of mitochondria to the dendritic arbor. Thus, aerobic exercise could accelerate dendritic maturation at least in part through the modulation of mitochondrial biogenesis, morphology, and distribution (Steib et al., 2014).

As discussed in the previous section, the mitochondrial fission factor DRP1 plays a key role in dendritogenesis. Although retroviral-mediated *Drp1* overexpression results in the redistribution of mitochondria from the soma and dendritic shaft to the dendritic arbor, it is not sufficient to enhance dendritic development of adult-born granule cells under basal conditions. However, it enhances running-induced acceleration of neuronal maturation by promoting dendritogenesis, spinogenesis and premature expression of the postmitotic marker calbindin (Steib et al., 2014), suggesting a role for mitochondrial fission in neuronal plasticity responses.

Clear evidence that interfering with mitochondrial fusion dramatically impairs synaptic plasticity in adult-born DG neurons *in vivo* comes from an elegant study conducted by Bergami's lab (Kochan et al., 2024). In this study, they demonstrated that mitochondria undergo a surge in fusion during the differentiation of adult-born granule cells, leading to the formation of stable and larger mitochondrial domains in dendrites which are needed to sustain synaptic plasticity at spines. The increase in mitochondrial fusion is transient and occurs particularly during the fourth week of neuronal life, a critical period of increased synaptic plasticity for newborn granule cells (Ge et al., 2007). This high level of synaptic plasticity is crucial for maturing granule cells to functionally integrate through a mechanism involving synaptic competition among cohorts of newborn neurons of similar cellular age. Focusing on MFN2-mediated mitochondrial fusion, they demonstrated that *Mfn2*-cKO granule cells fail to induce mushroom spines when mice are exposed to environmental enrichment for 4 weeks, in contrast to wild-type granule cells and to *Mfn2*-cKO granule cells upon MFN2 re-expression, which almost doubled mushroom spines. Thus, Mfn2-mediated mitochondrial fusion is necessary for supporting experience-dependent synaptic plasticity in adult-born DG neurons. On the other hand, disrupting mitochondrial fusion leads to decreased survival of adult-born granule cells lacking mitochondrial fusion dynamics. This impaired survival occurs in absence of hallmarks of degeneration or major mitochondrial dysfunction, while the ultrastructure of dendritic spines and synapses remains normal. As

competition in maturing adult-born granule cells is largely regulated at the synaptic level, the transiently heightened synaptic plasticity of newborn granule cells has been suggested to facilitate their integration into pre-existing circuits (Adlaf et al., 2017; Ge et al., 2007; Tashiro et al., 2007), and Kochan and colleagues demonstrate the involvement of mitochondrial fusion in this process. Indeed, disruption of mitochondrial fusion impairs the competitive survival of adult-born neurons of similar cellular ages, resulting in a general decrease in the incorporation of adult-born granule cells lacking mitofusins. Notably, those that survive and integrate into the neuronal network show altered connectivity on local hippocampal inputs in response to experience (Kochan et al., 2024). This suggests that adult-born neurons lacking functional mitochondrial fusion undergo changes in structural connectivity, likely reflecting impaired synaptic plasticity. Moreover, MFN2-deficient adult-born granule cells also show typical signs of functional alteration at the circuit level, as revealed by alterations in neuronal recruitment (examined as decreased c-fos induction) in a recently formed memory trace in response to an enriched environment (Kochan et al.,2024). Although in their study Kochan and colleagues never observed signs of axonal degeneration or retraction in mitofusins-depleted adult-born granule cells, whether and how synaptic transmission at axonal boutons and pre-synaptic plasticity relies on mitochondrial fusion dynamics is still an open question that needs further investigations.

Altogether, these findings indicate that a transient increase in mitochondrial fusion stabilizes elongated mitochondria in dendrites to fuel synaptic plasticity necessary for achieving functional integration of adult-born DG neurons. This latter role is also supported by *in vitro* evidence showing that the establishment of large and stable mitochondrial domains in hippocampal neurons is critical for maintaining protein synthesis during structural plasticity at spines (Li et al., 2004; Rangaraju et al., 2019a). *In vitro* manipulation of mitochondrial content in dendrites can induce changes in spine density, suggesting a direct influence of mitochondrial function on synapse formation and plasticity (Rangaraju et al., 2019b).

3. Adult Neurogenesis as a Model to Investigate Mitochondrial Involvement in Neurodevelopmental Disorders

Alterations in adult neurogenesis have been reported in animal models of several NDDs including ASD, Fragile X, Rett and Down syndromes as well as schizophrenia (**Table 1**). In parallel, accumulating evidence supports a role for mitochondrial dysfunction in the pathogenesis of these disorders. For instance, in Rett syndrome caused by mutations in the X-linked gene *Mecp2,* mitochondrial involvement has been demonstrated in human-derived neurons (Li et al., 2013) and astrocytes (Sun et al., 2023). Moreover, the results of a systemic transcriptomic and proteomic study on *Mecp2* mutant mice indicate that mutations in *Mecp2* cause a systemic disorder affecting lipid and mitochondrial metabolism (Zlatic et al., 2023). Similarly, a recent systematic review and meta-analysis of biomarkers in individuals with ASD

presents evidence that mitochondria are central to this NDD, contributing to abnormalities in brain development, cognition, and comorbidities such as immune and gastrointestinal dysfunction and neurodevelopmental regression (Frye et al., 2024). Given the key role of mitochondria in adult neurogenesis, investigating their implication in the generation, maturation and/or function of DG neurons in adult murine models of NDDs may be very informative to dissect the underlying mechanisms which may contribute to the pathophysiology of these disorders. However, at present only a few reports have begun to document an association of mitochondrial dysfunction with adult neurogenesis in NDD animal models (**Table 1**). For instance, a possible mechanistic link between altered mitochondrial dynamics and defective adult neurogenesis has been explored *in vitro* using the Ts65Dn Down syndrome mouse model (Valenti et al., 2017). In this study, by culturing hippocampal NPCs from adult Ts65Dn mice, deficits in mitochondrial bioenergetics and biogenesis with deregulation of fusion-fission processes were rescued by treatment with mitochondrial division inhibitor-1 (Mdivi-1), ultimately improving NPC proliferation and neuronal differentiation (Valenti et al., 2017). Another study reported direct evidence linking Fragile X mental retardation protein (FMRP) deficiency to mitochondrial dysfunction in adult DG neurogenesis *in vivo* in Fragile X syndrome mouse models (Shen et al., 2019, **Table 1**). Fragile X syndrome is a genetic disorder caused by an X-linked mutation in the Fragile X mental retardation (*FMR1*) gene that results in intellectual disability along with pervasive neurological symptoms, including autism, motor dysfunction, and an increased risk of epilepsy (Salcedo-Arellano et al., 2020). In their study, Shen and colleagues show that FMRP-deficient immature DG neurons exhibit altered mitochondrial gene expression, fragmented mitochondria, impaired mitochondrial function, and increased oxidative stress associated with impaired dendritic maturation. Notably, the authors also identify huntingtin as a critical mediator of FMRP regulation of mitochondria in newborn neurons and demonstrate that these abnormalities can be partially rescued by enhancing mitochondrial fusion. These findings highlight mitochondrial dysfunction as a key contributor to the impaired dendritic maturation of FMRP-deficient neurons (Shen et al., 2019). More recently, research on adult DG neurogenesis has provided insights into mitochondrial dysfunction in a rare neurodevelopmental syndrome caused by mutations in the nuclear receptor subfamily 2 group F member 1 (*NR2F1*) gene, which has not previously been associated with mitochondrial function (Bonzano et al., 2023). In the following sections, we will introduce the neurodevelopmental disorder caused by *NR2F1* mutations, summarize the studies supporting mitochondrial dysfunction in this condition, and present data revealing a novel role for NR2F1 in regulating mitochondria within the adult DG neurogenic niche.

NDDs	Animal models	Adult Hippocampal Neurogenesis (AHN)	Mitochondrial Deficits associated to AHN

Autism Spectrum Disorder (ASD)	*Shank3*+/ΔC	Reduction of radial glia-like NSCs and immature neurons in the ventral DG of the hippocampus (Cope et al., 2016).	No data
	Cntnap2−/−		
	Pten-cKO	Higher proliferation rate and accelerated differentiation of the NSPCs; depletion of the NSC pool and increased differentiation toward the astrocytic lineage (Amiri et al., 2012).	
	Valproic Acid prenatal exposure in rats	Long-term effect impairing adult neurogenesis in the DG associated with cognitive functional impairments; voluntary running increases DG neurogenesis and partly recovers cognitive functions (Juliandi et al., 2015); dose-dependent increased proliferation in the DG of VPA-treated offspring (Kinjo et al., 2019).	
	R451C Neuroligin3 knock-in (*Nlgn3*-KI)	Adult born neuron numbers, but not the size of the NSPC pool, are reduced in the ventral DG and rescued by fluoxetine treatment (Gioia et al., 2023).	
Fragile X Syndrome (FXS)	*Fmr1*-KO	Increased NSC proliferation and glial differentiation associated with decreased neurogenesis and cognitive impairment (Luo et al., 2010; Li et al., 2016; Li et al., 2018); inhibition of GSK3b rescues adult hippocampal neurogenesis (Guo et al., 2012).	No data
	Fmr1-icKO	Altered cell proliferation, specification and differentiation of aNSCs upon selective deletion of FMR1 under the Nestin promoter associated with deficits in hippocampal-dependent learning are rescued by FMR1 restoration (Guo et al., 2011); FMRP-deficient immature neurons (Dcx-CreERT2*FMRP flfl mice) exhibit impaired dendritic maturation that is partially rescued by treatment with M1, a Mitochondrial Fusion Promoter (Shen et al., 2019).	Altered expression of mitochondrial genes, fragmented mitochondria, impaired mitochondrial function, and increased oxidative stress in FMRP deficient immature neurons (Shen et al., 2019).
Rett Syndrome (RTT)	*Mecp2*-KO	Immature neurons in the DG of KO mice exhibit deficits in their ability to transition into later mature stages of development, including altered expression of presynaptic proteins and reduced dendritic spine density (Smrt et al., 2007); MeCP2 regulates maturation of adult-born neurons by repressing several microRNAs (i.e. miR137), decreased proliferation and increased differentiation of NSCs (Szulwach et al., 2010).	No data
	Foxg1-icKO	FOXG1 regulates postnatal development of the DG by maintaining a balance between progenitor proliferation and differentiation and is involved in the survival and maturation of postmitotic neurons (Thian et al., 2012).	

Down Syndrome (DS)	Ts65Dn	Reduced cell proliferation in DG, running fails to induce increased neurogenesis (Llorens-Martín et al., 2010); fluoxetine treatment restores DG neurogenesis (BrdU-labelled cells) (Clark et al., 2007; Bianchi et al., 2010).	Dysfunctional mitochondria in NSPCs (in vitro). Treatment with Mdivi-1 (inhibitor of Drp-1) decreases mitochondrial fission, restores mitochondrial network, prevents mitochondrial dysfunctions, and stimulates NPC proliferation and neural differentiation (Valenti et al., 2017).
	Ts1Cje Ts2Cje	Decreased BrdU-labeled proliferating cells and DCX-positive neuroblasts in the DG (Ishihara et al., 2010).	No data
Angelman Syndrome (AS)	*Ube3am-/p+*	Reduced progenitor proliferation and newborn neuron generation in the DG, partly rescued by fluoxetine (Godavarthi et al., 2015).	No data
Bosch Boonstra Schaaf Optic Atrophy Syndrome (BBSOAS)	*Nr2f1*-icKO *Nr2f1-cKO* *Nr2f1*-HET	Switch in NSPC cell fate: increased astrogliogenesis over neurogenesis in the DG, no difference in survival during early neuronal maturation (Bonzano et al., 2018); functional impairment of DG adult-born granule neurons integration and long-term survival, alteration in dendritic complexity and reduction of dendritic spine density in DG adult-born granule (Bonzano et al., 2023).	Decreased mitochondrial mass and increased mitochondria fragmentation in adult-born DG GCs; deregulation of key mitochondrial protein expression (Bonzano et al., 2023).
X-linked intellectual disability disorders (XLID)	*Ophn-1 −/y* KO	Reduction in the number of newborn neurons in the DG, altered density of DG dendritic protrusions and altered axonal growth; fasudil treatment (ROCK/PKA inhibitor) restores spine density to control levels, and enhances the long-term survival of adult-born neurons (Allegra et al., 2017).	No data
Schizopherenia	*DISC1-cKD* *DISC1 mutants*	Alteration in morphogenesis and migration of adult-born neurons, including increased soma size, ectopic dendrites (i.e.,multiple primary dendrites and/or basal dendrites and enhanced dendritic complexity), accelerated functional maturation (increase in synapse formation) and ectopic positioning (Duan et al., 2007). Homozygous DISC1-Q31L mutation reduces cell proliferation and the homozygous DISC1-L100P mutation induces deficits in the generation, positioning, and morphological maturation (i.e. decreased dendrite complexity) of adult-born neurons (Chandran et al., 2014).	No data

Table 1. Animal Models of NDDs with Reported Alterations in Adult Hippocampal Neurogenesis. This table summarizes animal models of NDDs (primarily mice, unless otherwise specified) where alterations in adult neurogenesis have been observed. It also includes cases where mitochondrial defects have been associated with adult neurogenesis. The table aims to provide an overview of selected studies, illustrating the multiple levels of effects on adult neurogenesis and the interplay between neurogenesis and mitochondrial function in the context of NDDs, where data are available. Please note that the table is not exhaustive. DG, dentate gyrus; GCs, granule cells; NSPCs, NSCs/progenitors; NSCs, neural stem cells.

3.1. Mitochondrial dysfunction in the emerging neurodevelopmental disorder BBSOAS

Bosch-Boonstra-Schaaf Optic Atrophy Syndrome (BBSOAS OMIM# 615722; ORPHA 401777) is an autosomal dominant neurodevelopmental disorder caused by *de novo* mutations in the *NR2F1* gene, or deletions encompassing *NR2F1* on chromosome 5q15 (Bosch et al., 2014; Chen et al., 2016). *NR2F1*, also known as *COUP-TFI* (chicken ovalbumin upstream promoter transcription factor I) encodes a highly conserved orphan nuclear receptor protein that acts as transcriptional regulator with a key role in brain development (reviewed in Bertacchi et al., 2022 and Tocco et al., 2021). Numerous studies in mouse models have demonstrated a pleiotropic function for NR2F1, ranging from cortical patterning (Alfano et al., 2014a; Armentano et al., 2007) and hippocampal development (Flore et al., 2017; Parisot et al., 2017), regulation of NSC/progenitor proliferation and specification (Bonzano et al., 2018; Naka-Kaneda et al., 2014; Naka et al., 2008), and eye and optic nerve development (Bertacchi et al., 2019; Jurkute et al., 2021). Since the initial description of the first six patients in 2014 (Bosch et al., 2014) there has been a rapid increase in diagnosed cases, with more than 110 *NR2F1* variants reported in the literature so far (Bertacchi et al., 2022; Billiet et al., 2021). The clinical phenotype associated with BBSOAS is characterized by a combination of optic nerve atrophy (OA) (but also optic nerve hypoplasia and/or cortical visual impairment) along with global developmental delay (DD) and mild-to-moderate intellectual disability (ID). In addition, BBSOAS cases share other common features, such as epilepsy, autism spectrum disorder (ASD) or autistic traits, attention deficit/hyperactivity disorder (AD/HD), and hypotonia, among others (Bertacchi et al., 2022; Bosch et al., 2014; Chen et al., 2016; Rech et al., 2020). Analysis of the various clinical profiles related to *NR2F1* mutation sites suggests the existence of a genotype-phenotype correlation (Rech et al., 2020). Most pathogenic BBSOAS point mutations in humans occur within two main conserved functional domains: the zinc finger DNA-binding domain (DBD), responsible for interaction with target gene regulatory sequences, and the ligand-binding domain (LBD), essential for dimerization and co-factor binding, with DBD mutations being associated with the most severe phenotypes (reviewed in Bertacchi et la., 2022).

Interestingly, mitochondrial involvement has been reported in two case studies of BBSOAS patients. In the first case, a heterozygous de novo missense mutation in *NR2F1* resulted in a pathogenic variant in the DBD domain (Martín-Hernandez et al., 2018). Clinical presentations exhibited by this patient, in addition to OA, DD and ID, included hypotonia, stroke-like episodes (acute neurological episodes without epileptic events), hemiparesis, and deficiency of complex IV of the mitochondrial respiratory chain in skeletal muscle - symptoms commonly associated with mitochondrial disorders (DiMauro and Schon 2008). Intriguingly, the authors also reported a slight elevation of lactate peak in basal ganglia, measured by Magnetic Resonance Spectroscopy (MRS), further suggesting a mitochondrial phenotype in brain tissue (Martín-Hernandez et al., 2018). In another study, a *NR2F1* truncation was found in a patient with new-onset psychosis with clinical symptoms comprising ID, autism, epilepsy, bilateral OA, and hypotonia associated with deficiency in complex I that were initially interpreted as

secondary to a mitochondrial encephalopathy. However, whole-genome sequencing identified a heterozygous *de novo* pathogenic nonsense mutation in *NR2F1*, leading to the diagnosis of BBSOAS (Hobbs et al., 2020). In both clinical cases, mitochondrial DNA (mtDNA) analysis revealed no deletions or pathological variants.

Whether the observed mitochondrial phenotype in the skeletal muscle of BBSOAS patients is caused by muscle intrinsic defects or by a secondary phenomenon originating in the nervous system remains unknown. However, a recent study in adult mice provides data supporting that NR2F1 may play a critical role in regulating mitochondrial function, at least in the brain (Bonzano et al., 2023), suggesting that mitochondrial dysfunction in BBSOAS patients may be directly caused by dysregulated expression of nuclear mitochondrial genes as a consequence of *NR2F1* mutations. Specifically, over the 2119 putative binding sites identified by genome-wide analysis of NR2F1 occupancy using chromatin immunoprecipitation followed by deep sequencing (ChIP-seq), Gene Ontology (GO) term annotation revealed that the mitochondrion and several mitochondrial-associated processes were the top enriched categories in both the GO cellular compartment and biological process ones (Bonzano et al., 2023). Notably, some well-known components of the core network controlling the expression of mitochondrial genes in the nucleus, are direct genomic targets for NR2F1 and show altered expression following *Nr2f1* haploinsufficiency. Among them, the Nrf1 gene, which encodes one of the major activators for the expression of metabolic nuclear genes required for respiration, as well as mitochondrial DNA transcription and replication, and the *Esrra* gene coding the estrogen-related receptor alpha (ERRα), which regulates an array of nuclear genes devoted to mitochondrial functions and numerous mitochondrial DNA genes (Hock and Kralli, 2009). Furthermore, a gene set enrichment analysis (GSEA) integrating ChIP-seq data from this study with previously published transcriptome data from the hippocampi of adult mice heterozygous for *Nr2f1* (*Nr2f1*-HET) (Chen et al., 2020), a validated BBSOAS mouse model (Tocco et al., 2021), showed that a significant number (82 out of 1053) of nuclear encoded mitochondrial proteins bound by NR2F1 show altered expression in the hippocampi of the *Nr2f1*-HET mice (Bonzano et al., 2023; **Fig.2**). GO term annotation of these genes further confirmed the central and direct role of NR2F1 in fine-tuning the expression of a network of highly interconnected mitochondrial proteins involved in the mitochondrial organization and biogenesis, regulation of mitochondrial gene expression and translation, and control of cellular respiration and metabolism (Bonzano et al., 2023; **Fig.2**). Notably, some of these genes have been implicated in human disease. For example, biallelic variants in *OXA1L* gene, encoding a multifunctional protein insertase that facilitates protein transport, assembly, and stability at the inner mitochondrial membrane (reviewed in Homberg et al., 2023), causes a profoundly decreased level of mitochondrial OXPHOS leading to severe illness and premature death of a patient with hypotonia, grave encephalopathy, and developmental delay (Thompson et al., 2018). Mutations in the mitochondrial citrate carrier *SLC25A1* are associated with impaired neuromuscular transmission (Chaouch et al., 2014), while its overexpression has been linked to ASD (RIgby et al., 2022). Deficiency of ECHS1, an enzyme

involved in the second step of the FAO, is associated with clinical symptoms such as infantile-onset severe developmental delay, seizures, elevated lactate levels and brain MRI abnormalities consistent with Leigh syndrome (Masnada et al., 2020).

A role for NR2F1 in the mitochondrial gene expression regulatory network is also supported by data from a genome-wide analysis of COUP-TF1/NR2F1 targets in neonatal mouse inner ear tissue, revealing a dataset of 182 candidate targets, including nuclear genes encoding mitochondrial proteins such as *Slc25a1*, *Echs1*, *Mrpl45*, *Timm23*, *Sod1* among others (Montemayor et al., 2010).

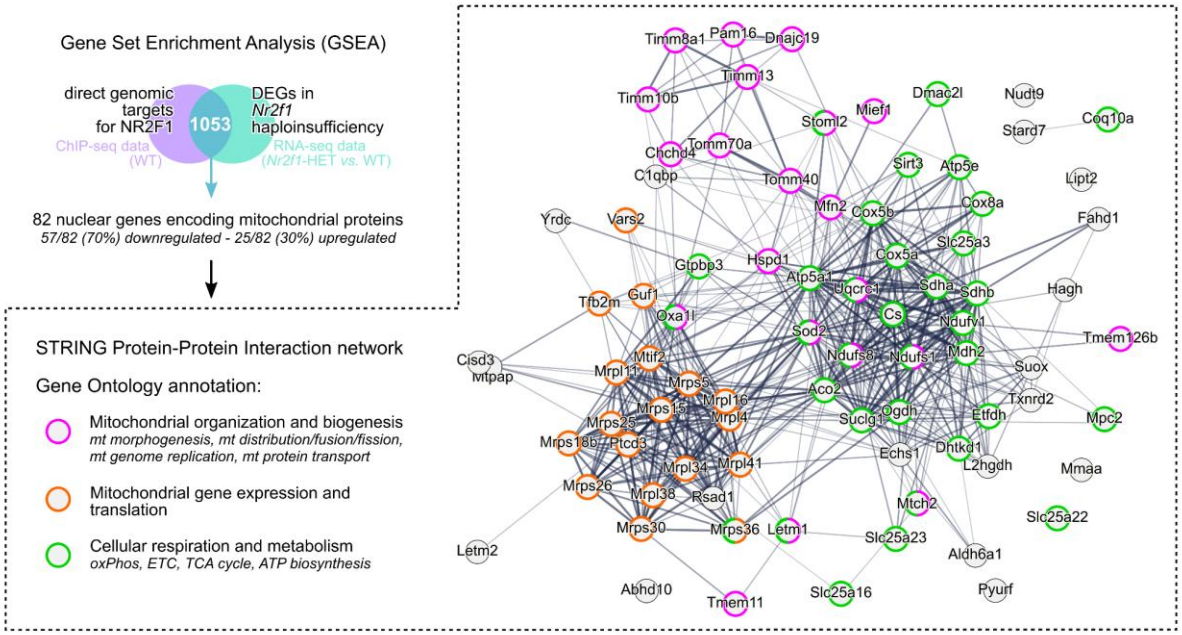

Figure 2. Gene set enrichment analysis (GSEA) revealed that of the nuclear genes directly bound by NR2F1 in their promoters and whose expression changes in the hippocampi of adult constitutive heterozygous (*Nr2f1*-HET) mice, almost 8% (82 out of 1053) encode mitochondrial proteins. On the right, STRING Protein-Protein interaction (PPI) graph of the 82 genes bound by NR2F1 and differentially expressed in *Nr2f1*-HET hippocampi. Nodes are colored according to the GO biological process annotation term listed on the left. DEGs=differentially expressed genes. Modified from Bonzano et al., 2023.

3.2. Exploring Adult Hippocampal Neurogenesis to Unveil a Novel Role for NR2F1 in Mitochondria Regulation and BBSOAS physiopathology

The pleiotropic role of NR2F1 during brain development has been extensively investigated (Naka et al., 2008; Alfano et al., 2014a; Armentano et al., 2006; reviewed in Bertacchi et al., 2019), while relatively few studies addressed its function in the postnatal/adult brain where *Nr2f1* expression is maintained in multiple neural cell types (Bonzano et al., 2018; Bovetti et al., 2013; Dye et al., 2011; Llorens-Bobadilla et al., 2015). In the mouse, NR2F1 drives the activity-dependent expression of tyrosine hydroxylase in olfactory dopaminergic neurons (Bovetti et al., 2013) and controls neuronal-astroglial cell fate decisions in the neurogenic

niche of the DG (Bonzano et al., 2018). In the adult DG, *Nr2f1* is widely expressed in NSCs/progenitors and their neurogenic lineage, but at different levels: neuronal progenitors show higher *Nr2f1* expression compared to NSCs/progenitors (Artegiani et al., 2017; Bonzano et al., 2018) which correlates with an overall increase in mitochondrial mass observed along the neurogenic lineage (Beckervordersandforth et al., 2017; Steib et al., 2014). Interestingly, *in vivo* conditional *Nr2f1* loss-of-function using the Cre-loxP system targeting the adult NSCs/progenitor lineage, combined with retroviral-mediated labeling of mitochondria with the fluorescent protein DsRed (RV-mitoDsRed), revealed an overall reduction in mitochondrial mass and changes in their architecture in adult-born hippocampal neurons. This was particularly clear in their dendritic arbors, where mitochondrial mass was reduced by half as a result of both decreased dendritic mitochondrial abundance and marked fragmentation (Bonzano et al., 2023). This mitochondrial phenotype observed in *Nr2f1*-depleted neurons is reminiscent of that observed due to the depletion or altered expression and function of mitochondrial fusion proteins (Chan, 2020; Fang et al., 2016; Kochan et al., 2024). Accordingly, the mitochondrial proteins MFN2 and OPA1 are reported to be downregulated not only in the brains of *Nr2f1*-HET mice but also cell-autonomously in *Nr2f1*-depleted adult-born DG neurons (Bonzano et al., 2023). NR2F1 binds to an active promoter region close to the transcription start site (TSS) of the *Mfn2* gene, strongly supporting direct positive regulation. However, *Opa1* did not appear among the direct putative targets of NR2F1. Considering the extensive network of nuclear-encoded mitochondrial factors potentially controlled by NR2F1, OPA1 downregulation may result from indirect mechanisms affecting its expression (i.e. by Nrf1/ERRalpha deregulation), protein stability and/or import into the inner mitochondrial membrane (due to altered expression of the mitochondrial Tim/Tom import machinery; **Fig. 2**). Reduced levels of OPA1 in BBSOAS models is particularly intriguing given that *Opa1* haploinsufficiency is the major genetic pathological mechanism of autosomal dominant optic atrophy in humans (Lenaers et al, 2021) and optic atrophy is a common clinical feature in BBSOAS patients. In light of these findings, the mitochondrial abnormalities observed in the optic nerve and retina of constitutive *Nr2f1*-knockout/*Nr2f1*-HET mice (Bertacchi et al., 2019) may be a direct consequence of altered NR2F1 function, and possibly contributing to the OA observed in BBSOAS mouse models. Several ETC/OXPHOS components, including both direct and indirect NR2F1 targets, were found to be defective in the brain mitochondria of *Nr2f1* haploinsufficient mice and in *Nr2f1*-deficient DG newborn neurons. These neurons were also found to have moderate changes in the architecture of the dendritic arbor with an overall reduced dendritic arbor length and complexity, with fewer dendritic spines. This was associated with impaired expression of the immediate early gene Zif268, implying altered recruitment of those neurons in the hippocampal circuitry, and reduced long-term survival (Bonzano et al., 2023). Based on the recent evidence demonstrating that a transient enhancement of mitochondrial fusion during the differentiation of adult-born granule cells is crucial to sustaining synaptic plasticity at spines *in vivo* (Kochan et al.,2024), it is likely that cellular phenotypes observed in adult-born granule cells lacking NR2F1 might be derived by an aberrant formation of mitochondrial domains in

dendrites as a consequence of altered mitochondrial fusion. Finally, in light of the direct involvement of NR2F1 in the mitochondrial gene expression regulatory network, it is tempting to speculate that a mitochondrial phenotype may also contribute to the imbalance in neuronal-astroglial cell fate observed upon deletion of *Nr2f1* in adult DG NSCs/progenitors (Bonzano et al., 2018). Future investigations will dissect the contribution of such mechanisms.

Taken together, these data from animal models indicate that in addition to their effects on neurodevelopment during embryonic stages (Armentano et al., 2007; Alfano et al., 2014a; Flore et al., 2017; Parisot et al., 2017), NR2F1 alterations also impact postnatal/adult neuronal systems by perturbing the mitochondrial network in neurons, which in turn affects neuronal maturation and/or plasticity (Stei et al., 2014; Kochan et al., 2024), thereby potentially interfering with cognitive functions. Given the high homology between human and mouse NR2F1 - particularly in the DNA binding domain, with 100% amino acid sequence homology (Alfano et al., 2014b) - its functions and targets are also likely to be conserved in both species. This strongly supports the role of mitochondrial abnormalities in BBSOAS and highlights the need for further investigation to clarify their relative contribution to the development of various clinical phenotypes associated with BBSOAS that are compatible with mitochondrial dysfunction (e.g. OA, hypotonia, ASD, seizures). Ultimately, this could also lead to the introduction of targeted therapeutic interventions to improve mitochondrial function in postnatal/adult life (e.g. diet, exercise and pharmacological therapy) (Bottani et al., 2020; Murphy and Hartley, 2018), which could alleviate symptoms and positively impact on the life of BBSOAS patients.

Concluding Remarks

In recent years, our understanding of adult neurogenesis and the multiple roles of mitochondria in neuronal development, function and plasticity has expanded significantly. The study of adult DG neurogenesis in models of NDDs provides a comprehensive framework of postnatal neuroplasticity. This approach not only gives insights into the underlying mechanisms of human disorders, but also opens new directions for therapeutic interventions aimed at improving cognitive function by targeting mitochondria during postnatal life.

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Highlights

- Mitochondrial dysfunction in the pathogenesis of neurodevelopmental disorders.
- The pleiotropic function of mitochondria in adult neurogenesis and brain plasticity.
- Adult neurogenesis as a model to study the role of mitochondria in neurodevelopmental disorders.
- NR2F1 regulates mitochondria in adult hippocampal neurogenesis.
- Involvement of brain mitochondrial dysfunction in BBSOAS.