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# Intersection of mitochondrial dysfunction and myelination: an overlooked aspect in neurodevelopmental disorders

**Ariel Nir Sade, Gal Wiener, Boaz Barak***

Neurodevelopmental processes represent a finely tuned interplay between genetic and environmental factors, shaping the dynamic landscape of the developing brain. A major component of the developing brain that enables this dynamic is the white matter (WM), known to be affected in neurodevelopmental disorders (NDDs) (Rokach et al., 2024). WM formation is mediated by myelination, a multifactorial process driven by neuro-glia interactions dependent on proper neuronal functionality (Simons and Trajkovic, 2006). Another key aspect of neurodevelopmental abnormalities involves neuronal dynamics and function, with recent advances significantly enhancing our understanding of both neuronal and glial mitochondrial function (Devine and Kittler, 2018; Rojas-Charry et al., 2021). Energy homeostasis in neurons, attributed largely to mitochondrial function, is critical for proper functionality and interactions with oligodendrocytes (OLs), the cells forming myelin in the brain's WM. We herein discuss the interplay between these processes and speculate on potential dysfunction in NDDs.

Mitochondria play a fundamental role in cellular energy supply, driving metabolic processes within cells (**Figure 1**). Neuronal mitochondria, strategically enriched at synapses, orchestrate energy production for synaptic activity, thereby influencing the connectivity of developing neural circuits (**Figure 1**). In NDDs, compromised neuronal mitochondrial function not only diminished neuronal performance, impairing brain development, but also disrupts energy-intensive neuro-glia interactions essential for myelination (**Figure 2**). Specifically, disruptions in neuronal mitochondrial function, particularly in adenosine triphosphate (ATP) production, directly influence myelin synthesis and maintenance by compromising the essential energy supply required in myelinating OLs for these processes (Saab and Nave, 2017; Meyer and Rinholm, 2021; **Figure 2**).

Three fundamental disruptions collaboratively jeopardize neuronal mitochondrial homeostasis and viability: oxidative stress, ATP reduction, and calcium overload (**Figure 2**). Additionally, iron dysregulation and accumulation in mitochondria further compromise these processes. This combination results in redox imbalance (the balance of reduction and oxidation reactions within cells), energy deficiency, and calcium dyshomeostasis, impacting both mitochondria and WM integrity, potentially leading to a pathogenic state (Court and Coleman, 2012; Emamnejad et al., 2024).

While neuronal mitochondria regulate energy supply and neuro-glia interaction, OL mitochondria are crucial for myelin synthesis and maintenance, ensuring axonal survival and function in the WM. Myelin, the insulating coating of axons, is crucial for neurodevelopment as it shapes neural circuits in the brain essential for cognitive and motor functions. The production and maintenance of myelin demand significant energy due to the complex cellular processes involved. Despite the essential roles, the functions of OL mitochondria remain poorly understood. It has been suggested that mitochondria play crucial roles in the lifecycle of OLs, serving as indispensable providers of carbon skeletons and energy crucial for lipid synthesis essential for myelin sheath development. More specifically, mitochondrial β-oxidation generates acetyl-CoA, a critical precursor for synthesizing lipids and cholesterol crucial for myelin formation (Fünfschilling et al., 2012; Morató et al., 2014). OL mitochondria respond uniquely to glutamate, enhancing their movement and displaying nuanced regulatory features involving calcium and ATP.

During OL development, significant metabolic changes occur that are crucial for their maturation and function. Initially, OL precursor cells primarily rely on glycolysis for energy, reflecting their need for rapid proliferation and migration. In the differentiation process from OL precursor cell into mature OL, there is a shift toward oxidative phosphorylation (OXPHOS) and increased mitochondrial biogenesis which is associated with an extensive network of tubular mitochondria, essential for ATP generation and facilitating the growth of the myelin sheath. These metabolic changes support the high energy demands associated with the synthesis of myelin. Mature OLs exhibit fewer and more fragmented mitochondria associated with a decrease in OXPHOS and an increase in glycolysis, as well as lactate release through the myelin sheath to the neurons. The myelin sheath contains mitochondria as well, albeit they are smaller and have a lower density (Meyer and Rinholm, 2021).

OL mitochondria are influenced by hormones and growth factors, which regulate mitochondrial biogenesis and energy metabolism through genomic and non-genomic pathways. Thyroid hormone, essential for mitochondrial function, can activate Akt/mTOR signaling, promoting mitochondrial function, reducing oxidative stress, and supporting processes like myelin production and repair. Additionally, non-canonical pathways triggered by thyroid hormone analogs may stimulate OL proliferation and remyelination, essential for neuroprotection. While mitochondrial biogenesis enhances cellular energy, thyroid hormone also mitigates oxidative damage by limiting reactive oxygen species production (Emamnejad et al., 2022).

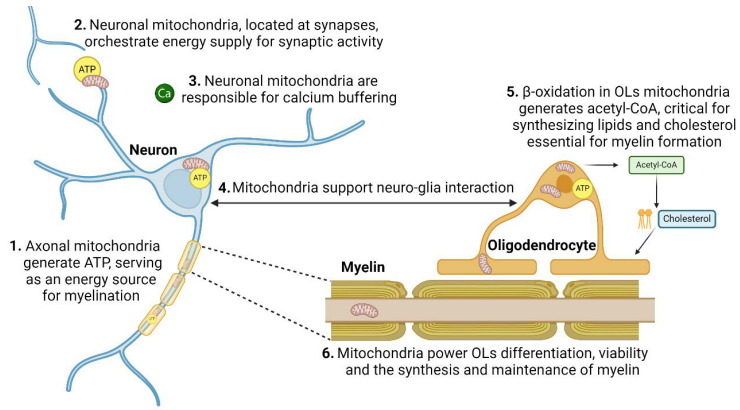


**Figure 1** | **Mitochondria and myelin interplay in the healthy brain.**
Neuronal mitochondria provide essential energy and metabolic support, influencing the differentiation, viability, and myelination process of OLs. This dynamic interaction sheds light on the critical role of mitochondrial cooperation in maintaining the integrity of the myelin sheath in the central nervous system. Created with BioRender.com. acetyl-CoA: Acetoacetyl coenzyme A; ATP: adenosine triphosphate; OLs: oligodendrocytes.

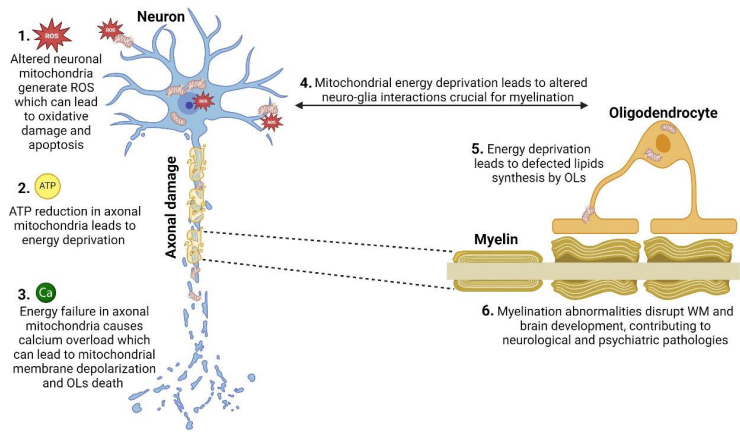


**Figure 2** | **Abnormal mitochondria affect myelination and may lead to pathological conditions and NDDs.**
Dysfunction in both neuronal and OL mitochondria significantly impacts myelin formation and WM integrity, contributing to pathologies and NDDs. These abnormalities disrupt normal brain development, highlighting the critical role of mitochondria in maintaining the complex processes essential for WM structure and function. Created with BioRender.com. ATP: Adenosine triphosphate; NDDs: neurodevelopmental disorders; OLs: oligodendrocytes; ROS: reactive oxygen species; WM: white matter.

Live imaging of mouse brain slices revealed that OL mitochondria exhibit lower mobility compared to those in neurons and astrocytes, potentially associated with shorter processes and reduced OXPHOS activity in OLs. This reduced mobility may impact fusion and content exchange, contributing to mitochondrial heterogeneity within Ols (Rinholm et al., 2016; Meyer and Rinholm, 2021).

OLs exhibit heightened vulnerability to energy deprivation so that their differentiation, viability, and ability to form myelin structures are all dependent on proper mitochondrial function (Morató et al., 2014). Part of the OLs' vulnerability comes from the fact that mitochondria are known to act as buffers for calcium or trigger apoptosis in case of calcium-overload-induced pathology, conditions that may take action upon energy deprivation such as ischemia. Mitochondria are also highly susceptible to iron imbalance. Iron accumulation in mitochondria promotes reactive oxygen species production through the Fenton reaction, directly damaging mitochondrial DNA. Additionally, excess iron disrupts the formation of iron-sulfur clusters, essential for cellular respiration and mitochondrial enzyme function. These effects result in impairing the synthesis of key proteins necessary for OXPHOS and ATP production (Emamnejad et al., 2024).

OL mitochondria face a unique challenge. To meet the energy demands of myelin formation, these mitochondria navigate through a complex system of cytoplasmic channels within the myelin sheath, requiring a high degree of functionality. Consequently, disruption in OL mitochondrial homeostasis can harm this crucial process, potentially leading to impaired myelin formation, maintenance, or repair.

Dysfunction in neuronal and OL mitochondria can contribute to the emergence of NDDs and disrupt the complex processes underlying WM formation. In our prior findings, we identified multiple myelination dysfunctions in a mouse model of the genetic NDD Williams syndrome, highlighting disruptions in myelin integrity and its impact on neural function (Barak et al., 2019). Additionally, our recent findings indicated the presence of various neuronal mitochondrial abnormalities in the same model (Nir Sade et al., 2023). Growing recognition of the impact of mitochondrial dynamics and function on myelin formation highlights mitochondrial recovery as a promising and innovative therapeutic target for a multitude of NDDs.

Similarly, several mitochondrial diseases share characteristics of axonal damage, hinting at a possible link between clinical progression, severity, and mitochondrial function (Morató et al., 2014). The interplay between disrupted mitochondrial processes and WM pathology reveals a compelling narrative, underscoring the need for a deeper exploration of the underlying mechanisms. We believe there is a pressing need for an in-depth exploration of how mitochondria affect myelination in NDDs such as autism, Williams syndrome, Rett syndrome, Fragile X syndrome, Down syndrome, and more.

To do so, one promising avenue is single-cell RNA sequencing from post-mortem human brain samples of individuals with NDDs. By examining gene expression at a single-cell level, researchers could gain insights into how mitochondrial dynamics in neurons may impact other cells within the brain, including OLs. Moreover, by testing these transcriptional alterations in different developmental phases along neurodevelopment, valuable information on the molecular underpinnings of mitochondrial involvement in myelination in these disorders can be achieved.

Additionally, to better study mitochondrial properties associated with these NDDs, investigating organoids related to neuro-glia interactions in humans with NDDs can shed light on the complex interplay between glial cells, neurons, and mitochondria in the context of neurodevelopmental conditions. The utilization of 3D dynamics, coupled with state-of-the-art microscopy and molecular biomarkers for labeling and monitoring mitochondrial physiology in live imaging, empowers researchers to advance the field. Furthermore, generating induced pluripotent stem cells from individuals with NDDs and differentiating them into neurons and glial cells (Pas, 2018), can help study mitochondrial function and myelination in these patient-derived cells to capture disease-specific characteristics. These platforms can also serve as a foundation for evaluating the safety and efficacy of potential drugs—whether repurposed FDA-approved drugs or newly developed ones—in mitigating mitochondrial dysfunction in NDDs.

A profound investigation of mitochondrial DNA and nuclear DNA mutations in individuals with NDDs is also needed, as understanding these may reveal specific mutations or variations that may lead to the consequent impaired myelination (Morató et al., 2014). Complimentary to that will be the employment of electron microscopy to examine ultrastructural abnormalities in mitochondria of neurons and glial cells in postmortem human brain tissue during different stages of development in NDDs.

As we navigate the evolving landscape of NDDs, questions arise regarding the interplay between mitochondrial abnormalities and myelin formation:
• To what extent do mitochondrial abnormalities in early neurodevelopmental stages influence the progression of myelin dysfunction? Is mitochondrial abnormality alone sufficient to initiate abnormal brain development and myelin formation in NDDs, or does it necessitate additional malicious processes?
• Can addressing mitochondrial issues alone potentially repair brain development failures and consequently NDDs?
• Given recent studies highlighting the early occurrence of mitochondrial dysfunction in comparison to myelin loss, how significant is this when devising therapeutic options for NDDs, considering the potential narrow therapeutic window?
• What preclinical outcome parameters prove meaningful in clinical trials evaluating potential therapeutics for addressing myelin dysfunction in NDDs?

Collectively, these inquiries underscore the critical need to understand the relationship between mitochondrial dysfunction and myelin formation, paving the way for innovative therapeutic approaches that could revolutionize the treatment of NDDs.

**Ariel Nir Sade, Gal Wiener, Boaz Barak***
Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel (Sade AN, Wiener G, Barak B)
School of Psychological Sciences, Tel Aviv University, Tel Aviv, Israel (Barak B)
***Correspondence to:** Boaz Barak, PhD, boazba@tauex.tau.ac.il.
https://orcid.org/0000-0001-9724-4578 (Boaz Barak)
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