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Neuromuscular Junction as A Potential Therapeutic Target in Mitochondrial Disease

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Abstract

The development of therapies for mitochondrial disease (MD) remains a major challenge given the extensive heterogeneity inherent of these disorders, which are characterized by multi-organ involvement and occurrence in all age groups. Muscle weakness, linked to damage to both skeletal muscles and peripheral nerves, is a predominant feature of MD. Recent scientific evidence has highlighted that the neuromuscular junction (NMJ), the peripheral synaptic connection between motor neurons (MNs) and skeletal muscle fibers, is involved in the pathogenesis of various MD. The intricate interplay between mitochondrial function and the integrity of NMJ is critical for proper neuromuscular function. Investigating the role of NMJs in MD may facilitate the development of more precise and effective therapeutic strategies. In summary, targeting the NMJ may represent a promising avenue for research and therapeutic development of MD.

A deeper understanding of the molecular mechanisms involved in NMJ dysfunction associated with MD could potentially lead to innovative treatment strategies aimed at preserving NMJ function and ameliorating the symptoms of these complex and heterogeneous disorders. The study of CHCHD10, a mitochondrial protein involved in both mitochondrial processes and NMJ integrity, may provide insights into its role in maintaining NMJ structure and function. Understanding the molecular mechanisms by which CHCHD10 is involved in the NMJ may open avenues for the development of targeted therapeutic strategies for MD associated with NMJ dysfunction.

Keywords: CHCHD10; Mitochondrial Disease; Motor Neuron; Neuromuscular Junction; Skeletal Muscle

Abbreviations: AChR: Acetylcholine Nicotinic Receptor; ALS: Amyotrophic Lateral Sclerosis; CHCHD10: Coiled-coil-Helix-Coiled-coil-Helix Domain containing 10; FTD: Frontotemporal Dementia; MD: Mitochondrial Disease; MN: Motor Neuron; NMJ: Neuromuscular Junction.

Introduction

Mitochondrial diseases (MD) are rare disorders impacting approximately 1 in 5000 individuals. Their clinical manifestation is notably heterogeneous, involving multiple organs and exhibiting onset at various ages [1]. These disorders are characterized by a deficit in the activity of the respiratory chain, resulting in the disruption of energy production. Clinical presentations encompass a range of symptoms, frequently implicating the central nervous system and peripheral muscles. Treatment of MD is mainly symptomatic and does not substantially modify the course of the disease.

A major characteristic of MD is muscle weakness, linked to damage to the skeletal muscles and peripheral nerve. Recent scientific evidence has highlighted the involvement of neuromuscular junction (NMJ), a peripheral synaptic connection between motor neurons (MNs) and skeletal muscle fibers, in the pathogenesis of various MD. NMJ abnormalities have been documented across a spectrum of mitochondrial disorders including nuclear or mitochondrial gene defects. Nonetheless, a comprehensive understanding of the mechanistic interplay between NMJ dysfunction and the initiation and progression of MD remains incomplete, impeding therapeutic advancements. Preserving NMJ emerges as an important element in counteracting muscle atrophy.

NMJs are specialized synapses in the peripheral nervous system that facilitate signal transmission between the motor nerve terminal and skeletal muscle fibers, ultimately leading to muscle contraction. The NMJ comprises three essential components: the presynaptic region (motor nerve end), the intrasynaptic space

(synaptic basal lamina), and the postsynaptic region (motor end plate of muscle cell). Mitochondria play a pivotal role in NMJs by contributing to ATP production, regulating calcium levels, buffering oxidative stress, and maintaining the overall energy balance necessary for proper muscle contraction and function [2]. Disruptions in mitochondrial function can adversely impact the efficiency of NMJ, affecting the transmission of signals between MNs and skeletal muscles, and finally contributing to muscle-related disorders. Mitochondria are notably enriched at NMJs, present in both presynaptic motor nerve terminals and postsynaptic junction folds. On the one hand, presynaptic mitochondria contribute to actin assembly, synaptic vesicle transportation, and release. Postsynaptic mitochondria, on the other hand, regulate the clustering of muscle acetylcholine nicotinic receptor (AChR) and overall NMJ function, including transportation and release [3-5].

Diseases impacting NMJ function arise from the dysfunction, disruption, or absence of specific proteins responsible for transmitting signals between nerves and skeletal muscles. Myasthenia gravis stands out as the most prevalent disorder affecting neuromuscular transmission, characterized by muscle weakness exacerbated with activity [6,7]. This autoimmune disorder is attributed to autoantibodies targeting AChR. Notably, myasthenia gravis shares distinct similarities with certain forms of MD. Both disorders commonly manifest symptoms like muscle weakness, ophthalmoplegia, and ptosis. Multiple studies emphasize the challenges in distinguishing between these two conditions based solely on clinical criteria [8,9].

The prevalence of NMJ abnormalities in MD remains uncertain, and it is unclear whether these abnormalities result directly from mitochondrial dysfunction at the endplate or merely reflect NMJ damage arising from the neuropathy and myopathy frequently observed in affected individuals. To address these uncertainties, Braz and colleagues conducted a study on NMJ function in a cohort of patients with genetically confirmed MD [10]. The authors observed abnormal NMJ transmission in 25.6% of participants within the study population. Jitter values, serving as a direct and sensitive measure of neuromuscular transmission, were comparable to those observed in patients with myasthenia gravis. Furthermore, the authors substantiate that NMJ dysfunction is not contingent upon concurrent neuropathy and myopathy, implying an autonomous involvement of NMJs in MD [10].

The CHCHD10 (Coiled-coil-Helix-Coiled-coil-Helix Domain containing 10) gene, coding for a mitochondrial protein, could be an interesting model for studying NMJ in MD. Previously, we identified a heterozygous variant (p.Ser59Leu) in CHCHD10 in two families [11]. In the first family, patients exhibited a mitochondrial myopathy, along with additional symptoms such as MN damage resembling amyotrophic lateral sclerosis (ALS), and cognitive decline resembling frontotemporal dementia (FTD). In the second family, the p. Ser59Leu variant was associated with a classic form of ALS/FTD. Subsequently, CHCHD10 variants were identified across a broader clinical spectrum, encompassing ALS, FTD, early-onset mitochondrial myopathies, late-onset spinal motor neuropathy (SMAJ), and Charcot-Marie-Tooth disease type 2 (CMT2). CHCHD10 is implicated in a diverse range of diseases primarily affecting peripheral muscle and MNs, all sharing an initial mitochondrial defect.

Knockdown of Chchd10 expression in zebrafish displayed shortened axons, suggesting that CHCHD10 may play a role at both the pre- and post-synapses [12]. In the Chchd10S59L/+ mouse model, morphological changes in the postsynaptic part of NMJ were observed, characterized by NMJ fragmentation [13]. Additionally, CHCHD10 expression is concentrated in the postsynaptic environment of the NMJ. In Chchd10S59L/+ mice, motor endplate fragmentation is correlated with the presence of CHCHD10 aggregates, which were also identified in morphologically normal NMJ. Importantly, the onset of the disorder manifests in muscle before MNs are affected [13]. These observations collectively suggest a pivotal role for NMJ in the pathogenesis of this mouse model. Additionally, a murine model involving the targeted knockout of Chchd10 in skeletal muscle exhibited defects in neuromuscular transmission and morphological alterations at the NMJ, including reduced clusters of AChRs [14]. Collectively, these findings strongly emphasize the involvement of NMJs in MD. A more profound comprehension of the molecular mechanisms implicated in these processes could pave the way for the development of innovative therapeutic strategies not only for diseases directly associated with CHCHD10 variants but also for MD associated with abnormalities in NMJs.

Conclusion

Given the extensive heterogeneity inherent of MD, characterized by multi-organ involvement and onset across all age groups, the development of interventions to treat MD remains a major challenge. A predominant feature of MD is muscle weakness, which depends on damage to the skeletal muscles and peripheral nerves. Understanding the role of NMJs in MD may provide insights into the various clinical manifestations observed in these disorders, which include muscle weakness and neurological symptoms. Investigating NMJ function may facilitate the development of more precise and effective therapeutic strategies for patients suffering from MD with NMJ dysfunction.

In summary, targeting NMJ represents a promising avenue for research and therapeutic development in the context of MD. A deeper understanding of the molecular mechanisms involved in NMJ dysfunction associated with MD could potentially lead to innovative treatment strategies aimed at preserving NMJ function and improving symptoms of these complex and heterogeneous diseases. Given the involvement of CHCHD10 in both mitochondrial processes and neuromuscular junction integrity [15] decipher the CHCHD10 roles would be relevant to research aimed at understanding, preserving, and potentially treating NMJs in MD.

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