

Mapping Mitochondrial-Neuromuscular Crosstalk

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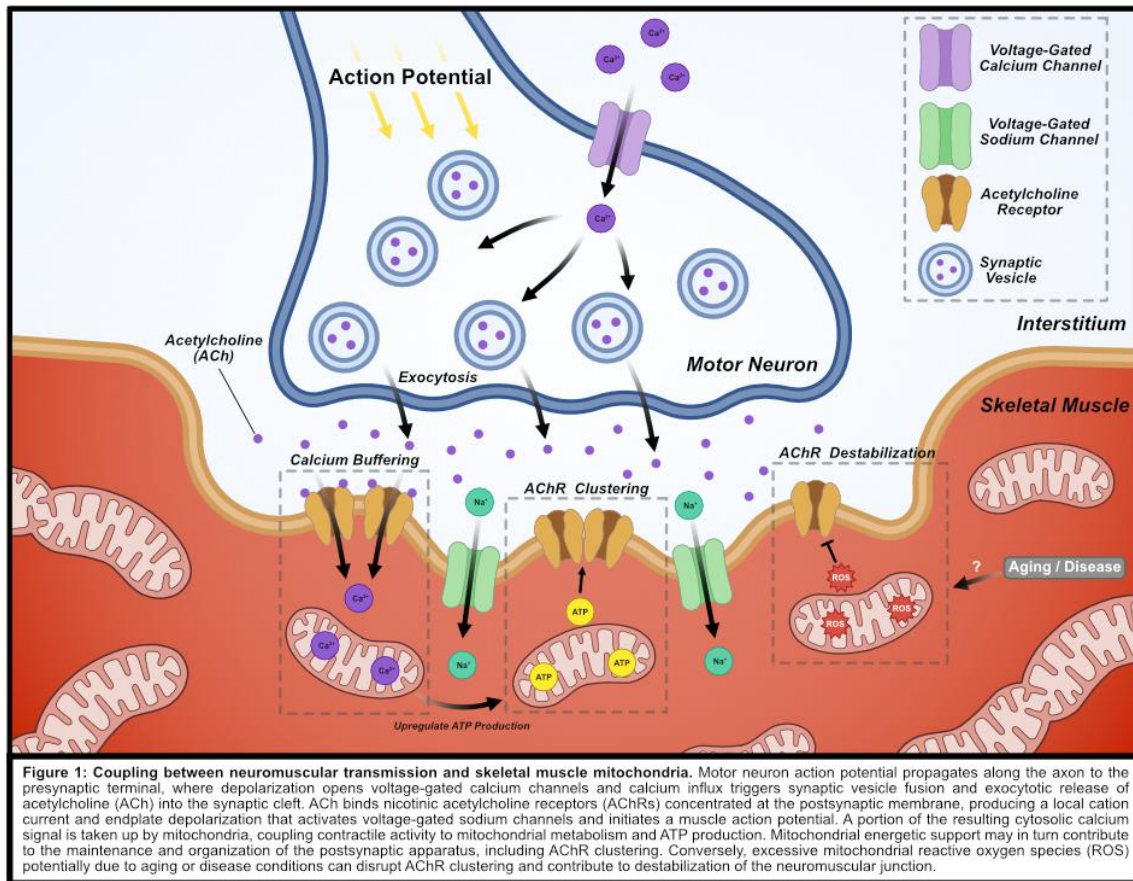
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Abstract

Skeletal muscle relies on mitochondria to support excitation-contraction coupling, ATP generation, calcium handling and redox regulation. While mitochondria have well-defined roles in these regulatory processes, in this perspective we examine emerging evidence supporting bidirectional communication between mitochondria and the neuromuscular junction, and consider whether neuromuscular junction-associated mitochondria represent a spatially localized population with distinct biological properties. We propose that defining the role of these mitochondria may reveal previously unrecognized mechanisms governing synaptic resilience and neuromuscular function, creating new opportunities to preserve muscle health during aging, cancer, and other disease states.

Introduction

Skeletal muscle is a highly adaptive tissue that must continuously match energy production to meet contractile demand. Mitochondria play a central role in this process through ATP production, while also contributing to calcium handling, redox regulation, and cellular stress signaling. Importantly, mitochondria within skeletal muscle are spatially organized into distinct populations, including peripherally localized subsarcolemmal (SS) and intermyofibrillar (IMF) mitochondria. This organization supports efficient energy distribution and ion buffering throughout the muscle fiber. A less studied but important aspect of this spatial organization is the proximity of SS mitochondria to the neuromuscular junction (NMJ). Despite this close association, mitochondria and the NMJ are typically examined independently. Emerging evidence instead supports a reciprocal relationship whereby neuromuscular activity regulates mitochondrial state, while changes in mitochondrial function can influence NMJ stability and function (Figure 1). This relationship is particularly important since mitochondria positioned near the NMJ are exposed to a signaling environment that differs from mitochondria located near the contractile machinery. In the present paper, we discuss evidence supporting the reciprocal communication between mitochondria and the NMJ, and speculate the spatial localization of mitochondria contributes to this relationship.



Neuromuscular activity and spatial regulation of mitochondria

Neuromuscular activity represents an important physiological regulator of mitochondrial biology within skeletal muscle. Motor neuron stimulation generates rapid fluctuations in ionic gradients that require ATP-dependent restoration through diverse mechanisms, including ATP1A2 activity. Simultaneously, contraction associated calcium transients stimulate mitochondrial calcium uptake, linking neuromuscular activity to energetic demands and mitochondrial metabolism [1]. Conversely, the significance of neuromuscular regulation of mitochondrial function is highlighted in denervation models whereby the lack of neural input abolishes normal calcium transients, mitochondrial calcium uptake and rapidly induces mitochondrial stress [1]. Restoration of electrical activity suppresses much of this response, suggesting that continued muscle excitation is required to maintain normal mitochondrial homeostasis [1]. Thus, neural input is translated through muscle excitation into ionic, energetic, and redox signals that continually regulate the mitochondrial network.

Sustained loss of neural activity produces broader remodeling of mitochondrial content, function, and quality control. Denervation reduces mitochondrial biogenesis signaling and respiratory capacity while increasing oxidative stress and disrupting mitochondrial turnover [2]. Importantly, these adaptations are spatially heterogeneous. Although both SS and IMF mitochondria are affected, SS mitochondria appear particularly sensitive to denervation, with respiration declining by approximately 45% compared with approximately 16% in IMF mitochondria after three days [2].

Mitochondrial protein import is also reduced, limiting the delivery of nuclear encoded proteins required to maintain and replace mitochondrial components [2]. In parallel, markers associated with mitophagy, including LC3-II, SQSTM1, and PRKN increase following denervation [2]. Collectively, denervation disrupts both mitochondrial function and quality control with the SS compartment exhibiting greater sensitivity.

This spatial response is particularly relevant to mitochondrial-NMJ communication. Mitochondria positioned beneath the postsynaptic apparatus reside within this peripheral compartment. Conventional SS mitochondrial preparations cannot distinguish these NMJ associated mitochondria from mitochondria positioned elsewhere beneath the sarcolemma, but recent work has begun to examine this population directly. Following nerve injury, subsynaptic myonuclei in young muscle show increased expression of mitochondrial oxidative phosphorylation, biogenesis, protein import, and remodeling programs together with increased CHCHD10 enrichment at the NMJ during reinnervation [3]. These responses are attenuated with aging, where postsynaptic mitochondrial abundance is also reduced and reinnervation is delayed [3]. Nonetheless, it is unknown whether NMJ associated mitochondria are locally specialized relative to the broader SS mitochondrial pool or whether these responses extend to other disease conditions.

Mitochondria as a regulator of the NMJ

Given the regulation of mitochondrial biology by neural input, the reciprocal question arises of whether mitochondria can regulate the NMJ. Several experimental models indicate that mitochondrial dysfunction within skeletal muscle can directly contribute to disruption of the NMJ. A previous report found that the mitochondrial protein CHCHD10 is enriched within the postsynaptic region and skeletal muscle specific knockout of *Chchd10* reduced mitochondrial ATP production while also impairing acetylcholine receptor (AChR) clustering [4]. Importantly, ATP supplementation restores AChR clustering in vitro, thus providing mechanistic evidence supporting the contribution of energetic availability to postsynaptic organization [4]. This relationship appears to extend beyond CHCHD10, as direct disruption of CHCHD2 and CHCHD10 within skeletal muscle causes mitochondrial disorganization and reduced ATP production together with increased NMJ fragmentation and delayed reinnervation [3]. Similarly, skeletal muscle specific expression of mitochondrial uncoupling protein UCP1 is sufficient to produce progressive NMJ deterioration and denervation and markedly delays recovery following sciatic crush injury [5]. These findings further demonstrate that disruption of muscle mitochondrial function can be sufficient to impair NMJ maintenance even in the absence of a primary neuronal mitochondrial defect.

Mitochondrial redox status provides an additional mechanism through which mitochondrial dysfunction can influence the NMJ. Whole body *Sod1* knockout results in impaired mitochondrial respiration and elevated ROS emission together with NMJ fragmentation, denervation, muscle atrophy, and weakness [6]. Importantly, expression of mitochondrial catalase within skeletal muscle normalizes mitochondrial ROS emission, NMJ fragmentation, and denervation observed in *Sod1* knockout mice,

thus ultimately preserving muscle mass and force [6]. This provides direct evidence that mitochondrial ROS serves as a regulator of NMJ morphology and function. Overall, these studies demonstrate that both mitochondrial energetic and redox status can influence NMJ stability and the capacity for reinnervation. However, the mechanisms linking these changes to the postsynaptic apparatus remain unknown. In particular, it is unknown whether these effects arise specifically from mitochondria positioned within the postsynaptic region or instead reflect broader changes in mitochondrial function throughout the muscle fiber. Determining whether postsynaptic mitochondria generate a distinct energetic or redox environment capable of regulating AChR organization and other NMJ signaling pathways therefore represents an important next step.

Translational Implication

The emerging relationship between mitochondrial health and NMJ integrity raises therapeutic implications for conditions characterized by weakness and fatigue. In aging models, targeting mitochondrial oxidative stress can preserve neuromuscular innervation and muscle force, suggesting that improving mitochondrial homeostasis may protect the NMJ during progressive age-related decline [6]. In more severe atrophic conditions such as cancer, where mitochondrial dysfunction accompanies pronounced muscle weakness and fatigability, preserving mitochondrial function may similarly help maintain neuromuscular integrity. For instance, pharmacological treatment with a mitochondrial-targeted antioxidant can partially preserve nerve-evoked muscle force during early-stage ovarian cancer [7], raising the possibility that mitochondrial targeting may support NMJ function. Therefore, investigating whether mitochondrial-targeted interventions may provide a strategy to preserve muscle function across both gradual and severe forms of muscle deterioration.

Conclusion

In conclusion, current evidence supports a bidirectional relationship in which neural activity regulates mitochondrial biology and vice versa. A major unresolved question is whether mitochondria positioned in close proximity to the NMJ constitute a functionally distinct subset of the SS mitochondrial pool. This relationship may become particularly important during aging, where postsynaptic mitochondrial abundance declines alongside impaired reinnervation [3]. Similarly, cancer and chemotherapy associated muscle weakness has been accompanied by reduced motor unit connectivity, altered NMJ associated proteins, and changes in NMJ morphology [8]. Defining whether NMJ associated mitochondria actively determine synaptic resilience could therefore identify a previously underappreciated mechanism of muscle dysfunction and provide new opportunities to preserve neuromuscular function during aging and disease.

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Author Contribution: All authors wrote the manuscript.

Conflicts of Interest: All authors declare no conflicts of interest.

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