Muscle mitochondrial ultrastructure: new insights into morphological divergences

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The study of mitochondrial morphology in skeletal muscle has a fairly long history. In 1966, Gauthier and Padykula (4) used electron microscopy to note the heterogeneity that exists in mitochondria within the diaphragm. They described “a conspicuous feature ... of large mitochondria beneath the sarcolemma ... they are large and more or less spherical.” Whereas, “the interior of the fiber, large mitochondria form chains running longitudinally among myofibrils” (4). Bakeeva et al. (1) and Kirkwood et al. (6) expanded upon this knowledge of muscle mitochondrial morphologies by demonstrating the presence of a mitochondrial reticulum, akin to the sarcoplasmic reticulum and representing a network of interconnected organelles. Ogata and Yamasaki (10, 11) and Kayar et al. (5) provided further detailed characterizations of mitochondrial morphologies within muscle fibers possessing different oxidative capacities in the rat (10), horse (5), and human (11). They noted the distinction between mitochondria localized in proximity to myonuclei and adjacent to the sarcolemma [subsarcolemmal (SS) mitochondria], as well as those situated between the myofibrils [intermyofibrillar (IMF) mitochondria]. Historically, these morphological measurements using electron microscopy techniques allowed for the first evidence of structural and “geographical” heterogeneity within mitochondrial subfractions of muscle. However, these studies also observed that the distinction between SS and IMF mitochondria was not absolute; continuity in the network could exist between the two subfractions, suggesting that one subfraction might arise from the synthesis of mitochondria in another region and that processes of organelle fission, fusion, and movement were likely to be important in determining mitochondrial location and morphology. Subsequent studies focused on whether these mitochondrial populations had different functional properties and evaluated their responses to exercise. Adopting subcellular fractionation techniques first developed for heart muscle (12), Krieger et al. (8) and Cogswell et al. (3) separated the two mitochondrial subfractions and noted differences in mitochondrial respiration, enzyme activities, lipid composition, protein synthesis, and adaptation to muscle use and disuse. Thus, when isolated from muscle, these mitochondrial subfractions exhibit somewhat subtle, but distinct, biochemical properties that may parallel their divergent morphological characteristics. Of course, mitochondrial morphological features viewed in electron micrograph images are not retained when the organelle is isolated. Mitochondria, like other lipid-containing cellular subfractions such as the sarcoclemma or the sarcoplasmic reticulum (SR) form spherical shapes similar to liposomes in vitro. However, these structures largely retain their functional integrity, and although this issue remains controversial, numerous studies have shown the distinctive biochemical properties of SS and IMF mitochondria. But what if one subfraction is truly a precursor of the other, or if SS and IMF mitochondria are actually physically interconnected? Is it possible for continuous membrane networks within cells to possess divergent functional characteristics given the fluidity of membrane bilayers? Certainly this appears to be true at the neuromuscular junction, where specialized synaptic proteins are localized in distinction from the rest of the sarcolemma. The interface between the lateral sac of the SR and the t-tubule is another example, where voltage-sensitive proteins promote the release of calcium, in contrast to the longitudinal portion of the SR where calcium uptake is favored. These situations provide evidence of protein heterogeneity within a continuous lipid bilayer. It seems reasonable to assume that divergences could also exist within the mitochondrial network, particularly in view of the more “labile” nature of the SS subfraction in response to chronic muscle use or disuse, as well as their proximity to myonuclei in comparison to more continuous IMF mitochondria.

The study by Picard et al. (13) adds further insight into the distinctive nature of SS and IMF mitochondria within skeletal muscle. The authors revisit the morphological characteristics of SS and IMF mitochondria and quantify the differences in great detail through the use of both transmission and scanning electron microscopy. The paper is timely, given that we now know much more about the proteins governing mitochondrial morphology and movement within cells. The authors observed significant differences in morphological descriptors between the two subfractions and provide evidence of occasional interconnections between SS and IMF organelles (13), as observed earlier (6). They also noted the presence of contacts sites between adjacent mitochondria, indicative of outer membrane tethering, and also that the frequency distributions of mitochondrial size and shape were highly skewed, suggesting the presence of mechanisms that regulate these parameters (13). Although rapid alterations in organelle shape and size have been demonstrated in cell culture studies, definitive proof of mitochondrial dynamics in vivo are limited. Geographic constraints imposed by abundant myofibrils, as well as cytoskeletal elements, likely contribute to this. And although the measurements made by Picard et al. are static snapshots of mitochondrial behavior, the results nonetheless support the role of mitochondrial interactions in mature skeletal muscle in vivo.

Changes in mitochondrial dynamics are regulated by opposing fusion and fission processes. Fusion of smaller organelles promotes the intermixing of mitochondrial material and an expansion of the mitochondrial reticulum, an observation made by Kirkwood et al. some years ago (7) as a result of endurance training. Fission, on the other hand, divides mitochondria into smaller pieces, possibly triggered by decreases in organelle membrane potential, in readiness for mitophagic engulfment and destruction. Essential mammalian skeletal muscle fusion proteins involved in these processes include mitofusin 2...
disclosures

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Author Contributions

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References