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Towards a better understanding of the role played by mitochondrial dynamics and morphology in skeletal muscle atrophy

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Energy supply, reactive oxygen species (ROS) production, regulation of calcium homeostasis and apoptosis are each components in the long (and non-exhaustive) list of crucial functions that mitochondria assume in skeletal muscle and make these fascinating organelles central in muscle physiology. Initially considered as bean-shaped organelles, mitochondria are now known to display a complex architecture in most cell types and particularly in skeletal muscle, with some mitochondria exhibiting elongated and branched tubular structures. One of the most recent and exciting discoveries in the field of mitochondrial biology was the demonstration that mitochondria are able to change their morphology through fusion and fission, processes collectively known as mitochondrial dynamics. Over the last decade, significant progress has been made in the identification of the molecular machinery involved in shaping mitochondria. Whereas mitochondrial fusion involves proteins such as mitofusin 1 and 2 (Mfn 1 and 2) and optic atrophy 1 (OPA 1), mitochondrial fission is governed by dynamin-related protein 1 (Drp1) and mitochondrial-fission 1 protein (FIS1). As the molecular machinery involved in the control of mitochondrial dynamics was progressively identified, numerous landmark cell culture experiments have provided evidence that changes in mitochondrial morphology can greatly impact mitochondrial function, and vice versa. However, the roles played by mitochondrial morphology and dynamics in skeletal muscle physiology still remain largely unclear.

Romanello *et al.* were amongst the first to provide evidence that mitochondrial dynamics can influence the regulation of muscle mass (Romanello *et al.* 2010). Indeed, they showed that increasing the expression of the mitochondrial fission machinery (Drp1 and FIS1 over-expression) triggers skeletal muscle atrophy, while inhibiting mitochondrial fission partly prevented the muscle atrophy triggered by FOXO3 over-expression (Romanello *et al.* 2010). By studying mice lacking mitofusin 1 and 2 function in skeletal muscle, Chen *et al.* showed that mitochondrial fusion is required to maintain the integrity of mitochondrial DNA, for normal mitochondrial function, and for normal muscle growth and development (Chen *et al.* 2010). Two recent articles published in *The Journal of Physiology* by Cannavino and colleagues (Cannavino *et al.* 2014, 2015) further increased our understanding of the role played by mitochondrial dynamics in muscle physiology and in the regulation of muscle mass. In their papers, Cannavino and colleagues provide experimental evidence indicating that impairment in mitochondrial dynamics might play an important role in disuse-induced skeletal muscle atrophy (Cannavino *et al.* 2014, 2015). Indeed, they show that skeletal muscle atrophy induced by hindlimb suspension, a classical model of disuse, is associated with an increase in Drp1 expression in the soleus muscle (Cannavino *et al.* 2014) and with a down-regulation of the mitochondrial fusion protein Mfn2 expression in the gastrocnemius muscle (Cannavino *et al.* 2015). In addition, they show that PGC-1α over-expression prevented muscle atrophy in both skeletal muscles and abolished the decrease in Mfn2 expression induced by hindlimb suspension in the gastrocnemius (Cannavino *et al.* 2014, 2015).

Overall, these experimental data indicate that proteins involved in mitochondrial dynamics play important roles in the regulation of muscle mass and muscle adaptation to stresses. Because mitochondrial dynamics and morphology are interconnected, it is tempting to speculate that mitochondrial dynamics might exert its effects on the regulation of muscle mass through its impact on mitochondrial morphology. With this hypothesis in mind, the data from Cannavino and colleagues, showing either an increase in the mitochondrial fission protein Drp1 in the soleus or a decrease in fusion protein Mfn2 in the gastrocnemius (Cannavino *et al.* 2014, 2015), would indicate mitochondrial fragmentation in response to hindlimb suspension. However, and although this hypothesis appears appealing, the link between changes in the expression and/or content of proteins involved in mitochondrial dynamics and mitochondrial morphology might not be as simple and straightforward. Indeed, evidence exists in the literature that Drp1 and Mfn2 both regulate processes independently of their role in mitochondrial fusion and fission. For instance, the over-expression of Mfn2 is known to up-regulate the expression of genes involved in the oxidative phosphorylation system independently of its role in mitochondrial fusion, and both Mfn2 and Drp1 regulate the interaction between mitochondria and the endoplasmic–sarcoplasmic reticulum. Similarly, PGC-1α also regulates numerous signalling pathways in skeletal muscle and might therefore exert its protective effects against disuse-induced muscle atrophy independently of its impact on the expression of proteins regulating mitochondrial dynamics and morphology. Therefore, whether mitochondrial morphology is altered during disuse-induced muscle atrophy and whether changes in mitochondrial morphology play a causal role in this process remain unknown. One of the reasons explaining why such questions are currently unanswered is that quantifying mitochondrial morphology in muscle cells is difficult and challenging due to the high complexity of muscle cell cytoskeletal

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architecture. However, the recent development of a two-dimensional transmission electron microscopy approach (Picard *et al.* 2013), based on the quantification of relevant mitochondrial shape descriptors in both longitudinal and transverse skeletal muscle sections, opens the route to a better understanding of the role of mitochondrial morphology and dynamics in skeletal muscle atrophy. The application of such an approach on various models of muscle atrophy (hindlimb suspension, denervation, cachexia, ageing, etc.) would help to define (i) the exact role played by changes in mitochondrial morphology in muscle atrophy, (ii) whether mitochondrial morphology behaves the same in all muscle atrophy models and (iii) whether mitochondrial subpopulations (i.e. the subsarcolemmal and intermyofibrillar mitochondria) are differently affected and/or play different roles in processes triggering muscle atrophy. Such knowledge would undoubtedly propel the fields of mitochondrial biology and muscle physiology forward and lead to a better understanding of the mechanisms involved in skeletal muscle atrophy.

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Additional information

Competing interests

There is no conflict of interest, financial or otherwise to declare.

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