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# Mitochondrial cristae density: a dynamic entity that is critical for energy production and metabolic power in skeletal muscle

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The mitochondrion is a double membrane organelle, consisting of an inner and an outer membrane. This topological organization contributes to its function of energy production, via the electron transport chain (ETC). Briefly, the ETC is a series of enzymes found within the inner mitochondrial membrane that transfers electrons from donor to acceptor proteins through several redox reactions. This process is ultimately driven by oxygen, the final electron acceptor. The transfer of electrons is coupled with the active transport of protons across the membrane through complexes I, III and IV of the ETC, thereby establishing a proton gradient across the inner mitochondrial membrane (Mailloux *et al.* 2014). The stored energy harnessed by pumping hydrogen against its concentration gradient and into the intermembrane space provides the necessary energy for ATP synthase (complex V) to generate ATP.

Skeletal muscle is a highly plastic and metabolically active organ, making up a large percentage (40–50%) of total body mass. It is well known that exercise can influence the adaptations seen in skeletal muscle, such as increases in oxidative capacity. Until recently, it was believed that the sole way to enhance skeletal muscle oxidative capacity was through a volumetric increase in the total number of mitochondria in a given tissue. However, this increase in mitochondrial size comes at the expense of contractile filaments and sarcoplasmic reticulum, as there is a finite amount of space available within a given cell. This sets a physiological limit for the maximal rate of respiration in muscle. Contrary to what was previously believed, there is evidence that mitochondrial respiration may be increased without changes in mitochondrial size or number, although the mechanism for this phenomenon remains unknown (Pesta *et al.* 2011).

Mitochondrial cristae are the folds within the inner mitochondrial membrane. These folds allow for increased surface area in which chemical reactions, such as the redox reactions, can take place. As the enzymes involved in the ETC are embedded in the inner mitochondrial membrane, an increase in surface area through extensive cristae formation could lead to increased rates of respiration. However, prior to the study done by Nielsen *et al.*, published in this issue of *The Journal of Physiology* (Nielsen *et al.* 2017), it was believed that cristae are static components of the mitochondria and are incapable of adaptations in their density. Specifically, Nielsen and colleagues analysed muscle biopsies from human vastus lateralis muscles obtained from athletes and non-athletes using transmission electron microscopy. In their study, they found that mitochondrial cristae density in endurance-trained athletes was significantly higher (+23%) compared to non-athletes, which supports the idea that total mitochondrial content is not the sole predictor of oxidative respiration, and that differences in mitochondrial structure can also enhance its function (Nielsen *et al.* 2017). Furthermore, the authors also determined that mitochondrial cristae density is a better predictor of maximal oxygen uptake when compared to mitochondrial volume.

It is important to note that there are metabolic differences in different types of skeletal muscle fibres (Stefanyk *et al.* 2010). Slow-twitch oxidative muscles contain mostly type I fibres that rely on aerobic respiration for the generation of ATP, while fast-twitch glycolytic muscles contain mostly type II fibres that generally rely on anaerobic metabolism in which ATP is generated through glycolysis and other metabolic pathways independent of oxygen. This means that while type II fibres may not require much mitochondria for ATP production, type I fibres do. Interestingly, while examining cristae density in type I and II fibres, it was discovered that although the non-athletic group had no differences in cristae density, the endurance-trained athletes had an increase in cristae density in type I fibres when compared to type II (Nielsen *et al.* 2017).

To test the dynamic nature of mitochondrial cristae density, Nielsen *et al.* (2017) investigated the effects of a 10 week endurance training programme. Although, they found no difference in cristae surface area before and after the endurance training programme, the authors concluded that short-term exercise may not affect mitochondrial cristae density. Nevertheless, by examining mitochondrial cristae from triceps brachii in cross country skiers and sedentary individuals, Nielsen and colleagues found high variation among the individuals, suggesting that mitochondrial cristae density may have plastic properties.

The findings from this current study demonstrate the importance of mitochondrial cristae density in mitochondrial function and are of interest within our own laboratory. Currently, the research conducted in Dr Paul J. LeBlanc's lab at Brock University in Ontario, Canada, is focused on the effect of phospholipid composition on mitochondrial function. One phospholipid of particular interest is cardiolipin (CL) (Stefanyk *et al.* 2010; Fajardo *et al.* 2015). CL is an anionic phospholipid that contains four fatty acyl chains and a small glycerol headgroup, thus affording this phospholipid with its unique cone-like structure. Cone-shaped phospholipids are important in inducing membrane curvature by augmenting the lateral pressure on neighbouring phospholipids. As CL is found predominantly within the inner mitochondrial membrane, it is thought that CL is an integral aspect of the characteristic folds pertaining to the mitochondrial cristae. Thus, CL is an important phospholipid within the mitochondrial membrane that allows for proper mitochondrial function. As an example, CL deficiency in patients with Barth syndrome, an X-linked recessive disorder characterized by cardiac and skeletal myopathy, leads to a reduced rate of mitochondrial respiration and increased reactive oxygen species production. Along with CL content, its fatty acid composition, particularly its linoleic acid composition is also important for mitochondrial

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function (Fajardo *et al.* 2015). Currently, we have some work (Fajardo VA, Mikhaeil J, Leveille CF, Saint C & LeBlanc PJ, unpublished observations) that demonstrates the dynamic nature of CL content and fatty acid composition in response to muscle overloading and unloading stimuli. After reading the report by Nielsen and colleagues, we think that it is possible that perhaps both CL content and fatty acid composition may have a role in mitochondrial cristae plasticity and warrants further investigation.

## References

Fajardo VA, McMeekin L, Saint C & LeBlanc PJ (2015). Cardiolipin linoleic acid content and mitochondrial cytochrome c oxidase activity are associated in rat skeletal muscle. *Chem Phys Lipids* **187**, 50–55.

Mailloux RJ, Jin X & Willmore WG (2014). Redox regulation of mitochondrial function with emphasis on cysteine oxidation reactions. *Redox Biol* **2**, 123–139.

Nielsen J, Gejl KD, Hey-Mogensen M, Holmberg H-C, Suetta C, Krustrup P, Elemans CPH & Ørtenblad N (2017). Plasticity in mitochondrial cristae density allows metabolic capacity modulation in human skeletal muscle. *J Physiol* **595**, 2839–2847.

Pesta D, Hoppel F, Macek C, Messner H, Faulhaber M, Kobel C, Parson W, Burtscher M, Schocke M & Gnaiger E (2011). Similar qualitative and quantitative changes of mitochondrial respiration following strength and endurance training in normoxia and hypoxia in sedentary humans. *Am J Physiol Regul Integr Comp Physiol* **301**, R1078–R1087.

Stefanyk LE, Coverdale N, Roy BD, Peters SJ & LeBlanc PJ (2010). Skeletal muscle type comparison of subsarcolemmal mitochondrial membrane phospholipid fatty acid composition in rat. *J Membr Biol* **234**, 207–215.

## Additional information

### Competing interests

None declared.

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