Muscling in on mitochondrial sexual dimorphism; role of mitochondrial dimorphism in skeletal muscle health and disease

Gareth A. Nye1, Giorgos K. Sakellariou2, Hans Degens3,4 and Adam P. Lightfoot3

1Manchester Maternal and Fetal Health Research Centre, University of Manchester M13 9WL, U.K.; 2GeneFirst Ltd, Culham Science Centre, Abingdon, Oxfordshire OX14 3DB, U.K.; 3School of Healthcare Science, Manchester Metropolitan University, Manchester M1 5GD, U.K.; 4Institute of Sport Science and Innovation, Lithuanian Sports University, Kaunas, Lithuania

Correspondence: Adam P. Lightfoot (A.Lightfoot@mmu.ac.uk)

Mitochondria are no longer solely regarded as the cellular powerhouse; instead, they are now implicated in mediating a wide-range of cellular processes, in the context of health and disease. A recent article in Clinical Science, Ventura-Clapier et al. highlights the role of sexual dimorphism in mitochondrial function in health and disease. However, we feel the authors have overlooked arguably one of the most mitochondria-rich organs in skeletal muscle. Many studies have demonstrated that mitochondria have a central role in mediating the pathogenesis of myopathologies. However, the impact of sexual dimorphism in this context is less clear, with several studies reporting conflicting observations. For instance in ageing studies, a rodent model reported female muscles have higher antioxidant capacity compared with males; in contrast, human studies demonstrate no sex difference in mitochondrial bioenergetics and oxidative damage. These divergent observations highlight the importance of considering models and methods used to examine mitochondrial function, when interpreting these data. The use of either isolated or intact mitochondrial preparations in many studies appears likely to be a source of discord, when comparing many studies. Overall, it is now clear that more research is needed to determine if sexual dimorphism is a contributing factor in the development of myopathologies.

In a recent issue of Clinical Science, Ventura-Clapier et al. [1] highlight a potentially important aspect of mitochondrial biology: they may exhibit sexual dimorphism. This not-often-considered trait may well underlie the sex-related difference in risk to developing a wide range of pathologies. Our knowledge of mitochondria has increased vastly in recent times, and we now know that mitochondria are much more than simply the ‘powerhouse of the cell’; mitochondria are now widely recognized to be involved in a vast range of cellular processes, and their dysfunction is intrinsically associated with many pathologies.

Ventura-Clapier et al. [1] provide an excellent overview of mitochondrial function, and give evidence for sexual dimorphism of mitochondrial function in a range of cells and tissues. They elegantly cover a wide range of disease states, but we feel that the authors have overlooked the opportunity to discuss mitochondrial dysfunction and the impact of sex in one of the most mitochondria-rich/dense tissues in the body: the skeletal muscle. Skeletal muscle plays a crucial role in whole-body homeostasis, accounts for 40% of the total protein and 50% of body mass and is indispensable for maintenance of body posture, locomotion, respiration, thermoregulation and metabolism. Approximately
4–7% of the skeletal muscle volume consists of mitochondria [2]. The significance of skeletal muscle for whole-body homoeostasis becomes particularly apparent in ageing and in pathological conditions such as cachexia, chronic obstructive pulmonary disease (COPD) and a wide range of neuromuscular disorders, where the loss of skeletal muscle mass and function is a key predictor of mortality. Moreover, research has shed light on the potential impact of sexual dimorphism on a range of muscle pathologies, where dysfunctional mitochondria again, play a central role [3-5]. In this editorial, we endeavour to convey the importance of mitochondria in skeletal muscle pathologies further evaluating the postulate by Ventura-Clapier et al. [1], to consider mitochondrial sexual dimorphism in these conditions.

Mitochondria play an integral role in muscle homoeostasis, derived from their fundamental involvement in energy metabolism necessary for muscle contraction, mediation of adaptive responses via the generation of reactive oxygen and nitrogen species (RONS), regulation of apoptosis and as a calcium sink alongside many other processes [6,7]. Mitochondrial RONS generation has received considerable attention as the key cell signalling molecules [3,8]. Specifically, optimal levels of mitochondrial RONS play an important role in modulating multiple signalling pathways and adaptive responses [9,10], whereas elevated levels induce cell death and oxidative damage to cellular components [11]. An intriguing facet of mitochondria in skeletal muscle is that they are present in two subpopulations: the intermyofibrillar mitochondria located between the myofibrils and the subsarcolemmal mitochondria in the subsarcolemmal regions [12]. The intermyofibrillar mitochondria account for approximately 80% of total mitochondrial density and are primarily responsible for the generation of ATP required for muscle contraction [2], whereas the subsarcolemmal mitochondria provide ATP for restoring the membrane potential following depolarization and maintaining cytoplasmic homoeostasis [2].

Mitochondria and sexual dimorphism in myopathologies

We usually consider loss of muscle mass (atrophy), diminished capacity for aerobic ATP generation and impaired neuromuscular activation as the key tenets of myopathologies. Such changes in muscle structure and function can stem from genetic disorders (e.g. Duchenne muscular dystrophy), sepsis, cancer, disuse, ageing and/or have autoimmune (myositis) and/or neurodegenerative (e.g. amyotrophic lateral sclerosis) origins. Mitochondrial dysfunction contributes to muscle dysfunction in these instances, in analogous ways to those reported by Ventura-Clapier et al. [1] in the context of wider pathologies.

Ventura-Clapier et al. [1] offer insight into the role of Ca2+ in mediating mitochondrial dysfunction via opening of the mitochondrial permeability transition pore (mPTP) and swelling. The authors highlight several studies, which report that females are more resilient to Ca2+-mediated mitochondrial dysfunction. A higher resilience to mitochondrial dysfunction in females has significant implications for myopathologies, in particular, myositis. Myositis is an acquired autoimmune disease, which causes profound muscle weakness, myalgia and disability – a significant unmet clinical need. Patients display chronic endoplasmic reticulum (ER) stress in affected muscles, which has been associated with Ca2+ leakage from the ER to the mitochondria. The accumulation of Ca2+ induces mitochondrial dysfunction, associated with aberrant ROS generation and bioenergetic deficits – both reported to contribute to muscle weakness in myositis patients [13,14]. Current research into the mechanisms underpinning myositis pays little to no consideration to the impact of sexual dimorphism on muscle weakness, but the narrative presented by Ventura-Clapier et al. [1] highlights the importance of stratifying the population of myositis patients by sex.

By the time humans reach their 80s, they will have lost approximately 50% of their muscle mass [15], contributing significantly to reduction in strength, locomotion and co-ordination. The age-related loss of muscle mass and function is inevitable and occurs independent of any comorbidities or physical activity levels. Despite the large number of studies, there is no consensus on how mitochondrial function in skeletal muscle changes during ageing [6,16-22]. Given the evidence summarized by Ventura-Clapier et al. [1], it is reasonable to hypothesize that sexual dimorphism in mitochondria leads to a higher rate of loss of muscle mass in males and females during ageing. In support of this hypothesis, it has been observed in rat gastrocnemius muscles that even though they had smaller mass, female muscles exhibited higher levels of mtDNA, mitochondrial complex proteins and antioxidant enzymes [23]. Many other studies show a higher mitochondrial capacity in muscles from females compared with the males in a number of species. These findings may explain at least to some extent the higher muscle fatigue resistance and better ability to combat the impact of increased RONS generation in male than female muscles [24-27]. This is not unequivocal, however, as another study in adult mice (10 months) reported no sex differences in mitochondrial bioenergetics, oxidative damage and apoptosis [28] or mass-specific aerobic capacity in muscles from men and women [29]. Nevertheless, muscle mitochondria remain a popular target to counteract the age-related loss of muscle mass and function. Administration of SS-31 (a mitochondria-targeted antioxidant) to mice resulted in an overall decrease in markers of oxidative
damage, improved specific aspects of skeletal muscle mitochondrial function, mitophagic potential and organelle integrity. However, SS-31 drug treatment did not attenuate the age-related myofibre atrophy and reduction in muscle force generation [30]. Similarly, a mitochondria-targeted antioxidant mitoquione mesylate (MitoQ) intervention in old mice failed to rescue the loss of muscle mass and function associated with ageing [31]. However, it is important to recognize the use of a mixed population of both male and female mice in both the studies [30,31]. Overall, these observations challenge the role of mitochondria-derived RONS in mediating the age-related loss of muscle mass and function, suggesting that in contrast with pathologies as suggested by Ventura-Clapier et al. [1], mitochondrial dimorphism is unlikely to cause a differential rate of age-related changes in skeletal muscle in males and females.

The contrasting observations among many studies are likely to be attributable to several factors, such as species and strain of animal models, and the methodologies used to examine mitochondrial function. The latter point is particularly salient and needs to be considered while evaluating the narrative of Ventura-Clapier et al. [1]. Many studies used isolated mitochondria to assess bioenergetic function. However, mitochondria exist in a reticulum, and disruption of this reticulum during isolation alters and impairs mitochondrial morphology and function respectively, in contrast with intact or permeabilized preparations [17,32]. Thus, preparations that disrupt the mitochondrial reticulum may well exacerbate or mask changes in bioenergetics in a pathology. Therefore, characterizing models with different methods of preparation is a crucial aspect of gaining a robust understanding of mitochondrial function in a wide range of pathologies.

Collectively, the concept of sexual dimorphism in mitochondria is new and it is no surprise that this aspect has been given little, if any, attention to explain the differences in muscle function and muscle disease susceptibility between men and women. It is questionable whether such a sexual dimorphism does exist, particularly when one considers that both males and females derive their mitochondria from their mothers. Even if mitochondrial sexual dimorphism does exist, it requires more research to establish whether it indeed explains or contributes to the different risk and progression of myopathologies between men and women. In ageing, for instance the pattern of muscle loss is similar in males and females, and men and women also have similar mitochondrial metabolic activity [29]. This does not mean, however, that targeting mitochondria therapeutically should not be pursued. Rather, it invites us to carefully study whether in muscle also such a sexual dimorphism in mitochondria does contribute to different susceptibility to myopathologies in men and women.

**Competing interests**
The authors declare that there are no competing interests associated with the manuscript.

**Author contribution**
All authors contributed in the preparation of the manuscript.

**Funding**
The authors declare that there are no sources of funding to be acknowledged.

**Abbreviations**
ER, endoplasmic reticulum; RONS, reactive oxygen and nitrogen species; SS-31, Szeto-Schiller peptide 31.

**References**

© 2017 The Author(s). Published by Portland Press Limited on behalf of the Biochemical Society