The International Journal of Biochemistry & Cell Biology xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

The International Journal of Biochemistry & Cell Biology

journal homepage: www.elsevier.com/locate/biocel

Review

# Mitochondrial dysfunction and sarcopenia of aging: From signaling pathways to clinical trials☆

Emanuele Marzetti[a,*,1], Riccardo Calvani[b,1], Matteo Cesari[c], Thomas W. Buford[d,e], Maria Lorenzi[a], Bradley J. Behnke[e], Christiaan Leeuwenburgh[d]

[a] Department of Geriatrics, Neurosciences and Orthopedics, Catholic University of the Sacred Heart School of Medicine, Rome 00168, Italy
[b] Institute of Crystallography, Italian National Research Council (CNR), Bari 70126, Italy
[c] Institut du Vieillissement, Gérontopôle and INSERM Unit 1027, University of Toulouse, Toulouse 31000, France
[d] Department of Aging and Geriatric Research, Institute on Aging, University of Florida, Gainesville, FL 32610, USA
[e] Department of Applied Physiology and Kinesiology, University of Florida, Gainesville, FL 32611, USA

ARTICLE INFO

*Article history:*
Available online xxx

*Keywords:*
Mitophagy
Vascular dysfunction
Fusion and fission
Apoptosis
Biomarkers

ABSTRACT

Sarcopenia, the age-related loss of muscle mass and function, imposes a dramatic burden on individuals and society. The development of preventive and therapeutic strategies against sarcopenia is therefore perceived as an urgent need by health professionals and has instigated intensive research on the pathophysiology of this syndrome. The pathogenesis of sarcopenia is multifaceted and encompasses lifestyle habits, systemic factors (e.g., chronic inflammation and hormonal alterations), local environment perturbations (e.g., vascular dysfunction), and intramuscular specific processes. In this scenario, derangements in skeletal myocyte mitochondrial function are recognized as major factors contributing to the age-dependent muscle degeneration. In this review, we summarize prominent findings and controversial issues on the contribution of specific mitochondrial processes – including oxidative stress, quality control mechanisms and apoptotic signaling – on the development of sarcopenia. Extramuscular alterations accompanying the aging process with a potential impact on myocyte mitochondrial function are also discussed. We conclude with presenting methodological and safety considerations for the design of clinical trials targeting mitochondrial dysfunction to treat sarcopenia. Special emphasis is placed on the importance of monitoring the effects of an intervention on muscle mitochondrial function and identifying the optimal target population for the trial.

This article is part of a Directed Issue entitled: Muscle wasting.



**Contents**



*Abbreviations:* $^{31}$P-NMR, $^{31}$P nuclear magnetic resonance; AIF, apoptosis-inducing factor; AngII, angiotensin II; Atg protein, autophagy-related protein; Bcl-2, B-cell leukemia-2; COPD, chronic obstructive pulmonary disease; COX, cytochrome *c* oxidase; CSA, cross-sectional area; Drp1, dynamin-related protein 1; EndoG, endonuclease G; eNOS, endothelial nitric oxide synthase; ETC, electron transport chain; Fis1, fission protein 1; FoxO3, Forkhead box O3; GH, growth hormone; IFM, interfibrillar mitochondria; IGF-1, insulin-like growth factor-1; iNOS, inducible nitric oxide synthase; LAMP-2, lysosomal-associated membrane protein 2; LC3, microtubule-associated protein 1 light chain 3; MFRTA, mitochondrial free radical theory of aging; Mfn, mitofusin; MQC, mitochondrial quality control; mtDNA, mitochondrial DNA; NF-κB, nuclear factor κB; nNOS, neuronal nitric oxide synthase; NOS, nitric oxide synthase; OMM, outer mitochondrial membrane; OXPHOS, oxidative phosphorylation; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; RCT, randomized controlled trial; ROS, reactive oxygen species; SDH, succinate dehydrogenase; SSM, subsarcolemmal mitochondria; TA, *tibialis anterior*; TFAM, mitochondrial transcription factor A; TNF-α, tumor-necrosis factor α; UPS, ubiquitin–proteasome system; VDR, vitamin D receptor; VL, *vastus lateralis*.

☆ This article is part of a Directed Issue entitled: Muscle wasting.

* Corresponding author at: Department of Geriatrics, Neurosciences and Orthopedics, Catholic University of the Sacred Heart School of Medicine, Teaching Hospital "Agostino Gemelli", L.go A. Gemelli 1, Rome 00168, Italy. Tel.: +39 06 3015 5669; fax: +39 06 3051 151.
*E-mail address:* emarzetti@live.com (E. Marzetti).

[1] These two authors contributed equally to this work.

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http://dx.doi.org/10.1016/j.biocel.2013.06.024

## 1. Introduction

Sarcopenia, the age-associated decline in skeletal muscle mass and function (Roseberg, 1989), represents a well-established risk factor for major negative health-related conditions and events, including frailty, disability, institutionalization and mortality (Visser and Schaap, 2011). The increasingly recognized clinical and public health relevance of this syndrome has been leading research activities at designing and developing novel preventive and therapeutic strategies (Cesari et al., 2008). The accomplishment of such task requires a thorough understanding of the cellular processes underlying the pathogenesis of sarcopenia, in order to identify selective targets for treatment.

Numerous pathways are proposed to be implicated in the age-dependent muscle degeneration (reviewed by Marzetti et al., 2009 and Buford et al., 2010). The vital functions carried out by mitochondria in the context of energy provision, redox homeostasis, and regulation of several catabolic pathways confer these organelles a central position in the maintenance of myocyte viability. The involvement of mitochondria in the regulation of skeletal myofiber plasticity further highlights the centrality of these organelles in muscle physiology. Adult skeletal myocytes are post-mitotic cells organized in syncitia of hundreds or thousands of nuclei, where each nucleus has jurisdiction over a surrounding volume of sarcoplasm (myonuclear domain or DNA unit) (Cheek, 1985). The dynamic behavior of DNA units is believed to govern muscle fiber remodeling in response to load conditions, aging and diseases (Allen et al., 1999).

Although recently called into question (Bruusgaard and Gundersen, 2008; Bruusgaard et al., 2012), this concept is supported by numerous studies reporting that modifications in fiber cross-sectional area (CSA) are associated with changes in the number of myonuclei (reviewed by Teixeira and Duarte, 2011). Moreover, during muscle accretion, DNA units increase their size, while smaller myonuclear domains are observed during disuse- and aging-associated muscle atrophy (Van der Meer et al., 2011). A wealth of experimental evidence indicates that mitochondria are central in the regulation of myonuclear domain both in physiological and pathological conditions (reviewed by Calvani et al., 2013a). As such, mitochondrial decay is advocated as one of the major factors driving muscle aging (Johnson et al., 2013).

The interpretation of the consequences of mitochondrial dysfunction on muscle physiology is complicated by the existence of two populations of mitochondria in skeletal myocytes: subsarcolemmal mitochondria (SSM), located beneath the plasma membrane and accounting for approximately 20% of total mitochondrial mass, and interfibrillar mitochondria (IFM), arranged between the myofibrils and representing the remaining 80% of myofiber mitochondrial volume (Hoppeler, 1986). These two subpopulations possess specific biochemical and functional properties and exhibit a distinct behavior during aging (Koves et al., 2005; Ferreira et al., 2010). For instance, SSM isolated from old muscles produce greater amounts of reactive oxygen species (ROS) and show higher rates of fragmentation and degradation relative to the IFM subfraction (Riley et al., 1990; Chabi et al., 2008; Seo et al., 2008; Wagatsuma et al., 2011). On the other hand, IFM are more prone than SSM to releasing apoptotic mediators under cell death stimuli (Adhihetty et al., 2005). These divergent properties raise the possibility that the two mitochondrial populations could be differentially involved in the pathogenesis of sarcopenia.

A further level of complexity is added by the fact that both mitochondrial function and muscle trophism are influenced by physical activity and anabolic hormones, which both decline with aging (Dela and Helge, 2013). Other age-related processes, such as chronic, low-grade inflammation and vascular alterations, can also affect both muscle health and mitochondrial function (Terjung et al., 2002; Jensen, 2008). Hence, segregating the impact of age *per se* from that of lifestyle habits and age-associated conditions on muscle pathophysiology poses a relevant challenge (Fig. 1).

In this review, we illustrate relevant mechanisms that are proposed to underlie the relationship among aging, muscle mitochondrial dysfunction and sarcopenia. First, we present a brief overview on the evidence linking mitochondrial dysfunction to human muscle aging. We then discuss prominent mitochondrial pathways that have been implicated in the pathogenesis of sarcopenia. Subsequently, we summarize extramuscular factors than can have an impact on myocyte mitochondrial function, thus potentially serving as targets for anti-sarcopenic interventions. Finally, methodological considerations for the design of clinical trials on mitochondrial dysfunction and sarcopenia are presented.

## 2. Involvement of mitochondrial dysfunction in muscle aging: evidence from human studies

One major consequence of the age-associated mitochondrial dysfunction is a decline in bioenergetics. Both resting and maximal oxygen ($O_2$) consumption decreases with advancing age (Short et al., 2004). This decline is independent of changes in fat-free mass, indicating that either muscle mitochondrial function or content (or both) is reduced as a function of age.

Studies on muscle specimens from healthy individuals have revealed age-related declines in mitochondrial mass (Welle et al., 2003), activities of tricarboxylic acid cycle enzymes (Crane et al., 2010), $O_2$ consumption (Joseph et al., 2012; Coen et al., 2013), and ATP synthesis (Short et al., 2005). Moreover, a 40–50% decrease in oxidative phosphorylation (OXPHOS) activity has been detected in vivo via $^{31}P$ nuclear magnetic resonance ($^{31}P$-NMR) spectroscopy in older persons compared with younger controls (Conley et al., 2000; Petersen et al., 2003).

The impact of mitochondrial bioenergetic decline on muscle aging is witnessed by the existence of a correlation between ATP

Please cite this article in press as: Marzetti E, et al. Mitochondrial dysfunction and sarcopenia of aging: From signaling pathways to clinical trials. Int J Biochem Cell Biol (2013), http://dx.doi.org/10.1016/j.biocel.2013.06.024