



Mechanisms of skeletal muscle ageing; avenues for therapeutic intervention

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Age-related loss of muscle mass and function, termed sarcopenia, is a catastrophic process, which impacts severely on quality of life of older people. The mechanisms underlying sarcopenia are unclear and the development of optimal therapeutic interventions remains elusive. Impaired regenerative capacity, attenuated ability to respond to stress, elevated reactive oxygen species production and low-grade systemic inflammation are all key contributors to sarcopenia. Pharmacological intervention using compounds such as 17AAG, SS-31 and Bimagrumab or naturally occurring polyphenols to target specific pathways show potential benefit to combat sarcopenia although further research is required, particularly to identify the mechanisms by which muscle fibres are completely lost with increasing age.

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Introduction

Skeletal muscle ageing is characterised by a catastrophic loss of muscle mass and function

Age-related loss of muscle mass and function is a major contributor to frailty in older people. The definition of frailty is varied, but includes an impaired mobility with an increased risk of falls [1]. The effects on quality of life in the increasing world ageing population and the concomitant increase in age-related diseases are a significant personal and financial burden on healthcare authorities worldwide.

Muscle mass declines at an approximate rate of 1–2% per year, from around the age of 50 years onwards [2]. During ageing a reduction in muscle fibre cross-sectional area and a preferential loss of the glycolytic fast twitch type II fibres is seen [2,3]. The reduction in total fibres and in the proportion of fast twitch fibres results in a phenotypically slow muscle, which also manifests as reduced maximal force output and decreased speed of activation. The mechanisms associated with the age-related loss of muscle mass and function is poorly understood. Elevated low-grade systemic inflammation [4], changes in the generation of reactive oxygen species [5], altered mitochondrial function [6], modified innervation of muscle [7], impaired regenerative processes [8] and compounding effects of inactivity [9] are proposed as key factors in skeletal muscle ageing (Figure 1).

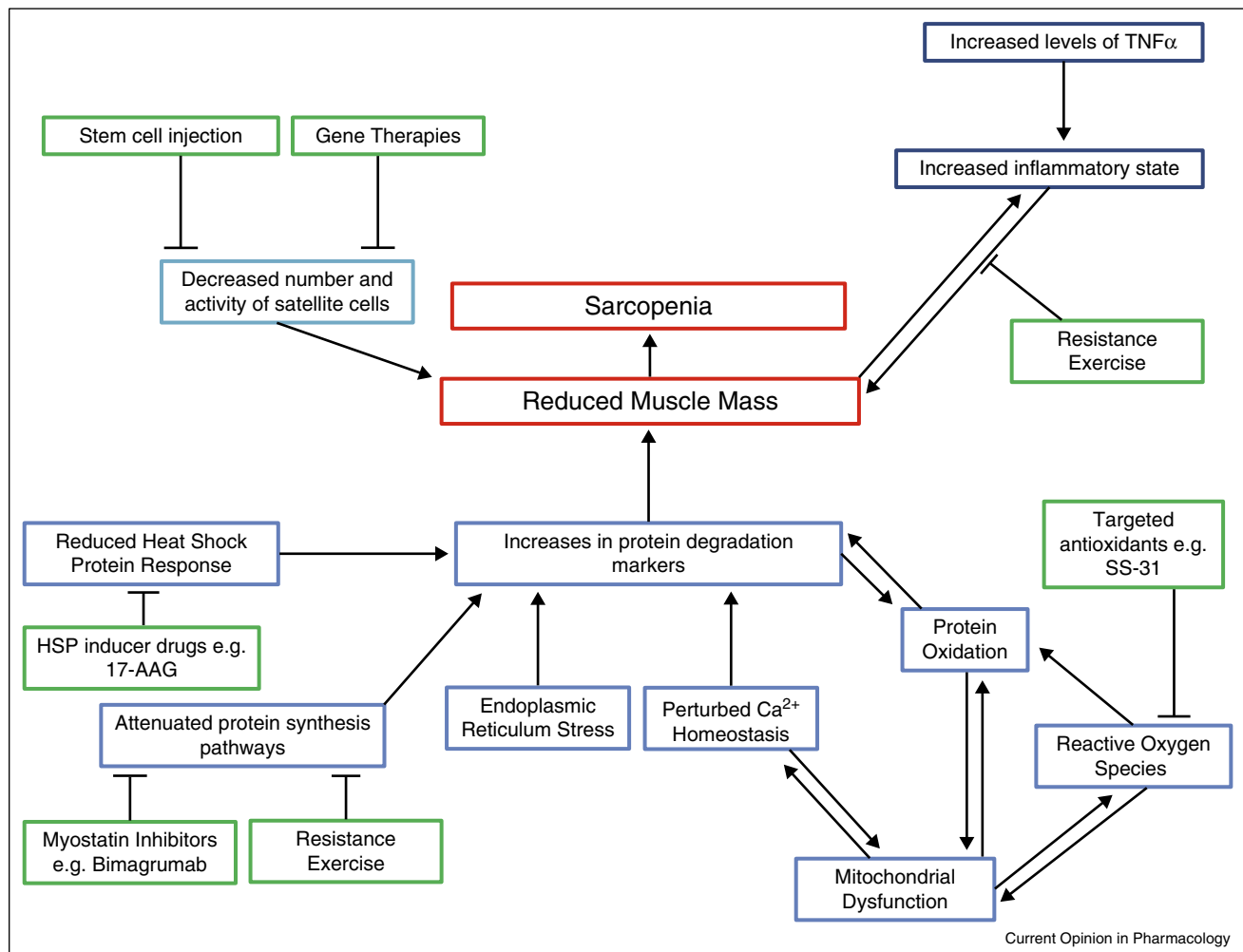
The aim of this review is to summarise the key mechanisms associated with skeletal muscle ageing, outline new advances in understanding and potential therapeutic avenues to alleviate sarcopenia.

Impact of inflammation in muscle ageing

During ageing, mammals develop an elevated level of low-grade chronic systemic inflammation [10]. This is characterised by increased circulating levels of several pro-inflammatory cytokines such as interleukin-6 (IL-6), Tumour necrosis factor alpha (TNF- α) and c-reactive protein (CRP) [11] in association with a reduction in anti-inflammatory factors such as interleukin-10 (IL-10) [12]. More recently skeletal muscle has been demonstrated to be a potential source of a diverse range of cytokines, termed myokines [13]. The role and impact of myokines in skeletal muscle ageing has not been extensively explored, however, it raises the possibility that myokines may influence the local muscle environment considerably and that muscle could be a significant source of cytokines during ageing.

Inflammation has been proposed as a key driver of skeletal muscle ageing, and the impact of inflammatory cytokines on skeletal muscle has been widely studied. Data shows that exposure of skeletal muscle to TNF- α results in a loss of total muscle protein, evidenced by increased ubiquitin conjugating activity, associated with increased nuclear factor kappa B (NF κ B) activation and mediated, at least in-part, by reactive oxygen species (ROS) [14,15]. In contrast, IL-6 is proposed to have

Figure 1



Schematic summarising the major mechanisms associated with the age-related loss of muscle mass and function.

The mechanisms underlying sarcopenia are multi-factorial; reduced stem cell presence, external mediating factors (inflammation), modified redox signalling pathways and alterations in molecular chaperone (HSP) function are all contributors to sarcopenia. These pathways, often interlinked are likely a cumulative stress upon skeletal muscle which results in sarcopenia. Potential therapeutic avenues are highlighted in green, from pharmacological interventions, to stem cell therapy and resistance training.

divergent effects on skeletal muscle, with evidence of a catabolic impact, resulting in atrophy [16] and playing a pivotal role in satellite cell-mediated hypertrophy [17]. Thus, the development of therapeutic interventions to target inflammatory pathways may provide a potential treatment for at least some aspects of age-related muscle dysfunction.

Elevated oxidative damage: mitochondria as a key source of ROS

There is significant evidence to indicate that fundamental changes in redox signalling and homeostasis occur during ageing [18]. Skeletal muscle demonstrates a significant age-related elevation in oxidative damage (e.g. [19]). Skeletal muscle of old mice displays profound oxidative damage to DNA, lipids and proteins [20]. The focus of

ROS-related research in skeletal muscle ageing has tended to be focussed on mitochondria. Historically, mitochondria have been proposed as key determinants of whole body ageing and that ageing manifests from an age-related decline in mitochondrial activity [21]. Data from rats have shown that sarcopenia is associated with loss of functional proteins associated with mitochondrial energy metabolism [22]. Accumulation of mutations in mitochondrial DNA (mtDNA) during ageing is well characterised [23], and suggested that ROS derived from the electron transport chain (ETC) are the source of this damage. Mitochondrial DNA is particularly susceptible to damage from ROS due to less robust repair mechanisms [24]. Skeletal muscle of old mice displays increased protein carbonylation localised to the mitochondria [19]. However, role of accumulation of such damage in ageing *per se* remains controversial.

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