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EDITORIAL

Cardiovascular and skeletal muscle ageing: consequences for longevity

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The invited Topical Reviews, symposia articles and selected research papers in this Special Issue of *The Journal of Physiology* focus on the effects of ageing on cardiovascular and skeletal muscle function, including cardiac and muscle performance in exercise. The articles provide an up-to-date overview of the molecular mechanisms underlying cardiovascular and skeletal muscle ageing and further highlight the therapeutic potential of targeting function to enhance healthspan and longevity.

A recent *Lancet* series focused on ageing (reviewed by Suzman *et al.* 2015) highlighted that ageing populations constitute a global public health challenge, noting that adults above 65 years of age outnumber children under the age of 5. Although rates of mortality and morbidity have decreased due to medical and socioeconomic developments, further research is needed to enhance healthspan (maintenance of good health) of older adults by sustaining physiological function and quality of life (Suzman *et al.* 2015). As reviewed by Seals and colleagues in this Special Issue, the term healthspan is used to distinguish 'healthy ageing' from 'age-related diseases and disability' (Seals *et al.* 2016). Notably, increases in longevity have predominantly been attributed to individuals surviving longer with an underlying disease(s) rather than an increase in healthspan. Geriatric medicine is facing an ever increasing burden from ageing populations, and a key objective of geroscience (biological ageing research) is to identify strategies to enhance healthspan (Seals *et al.* 2016). Thus, health care systems need to focus on the wellbeing of older adults living in both low- and middle-income countries (Suzman *et al.* 2015).

As physiological function declines with ageing, the efficacy of different interventions to increase healthspan and/or longevity may in some cases be limited. Russell Hepple and Charles Rice review the evidence that ageing is associated with motor neuron loss, neuromuscular junction instability and cycles of denervation and reinnervation, resulting ultimately in physical frailty (Hepple & Rice, 2016). These authors further conclude that, although physical activity may promote motor unit survival, exercise may not necessarily benefit motor unit function in advanced ageing. It is well known that loss of skeletal muscle mass and function in ageing contributes to frailty, yet the underlying mechanisms remain to be fully elucidated. Malcolm Jackson and Anne McArdle provide novel molecular insights into the role that reactive oxygen species play in modulating skeletal muscle function and how deficits in redox signalling contribute to neuromuscular decline in ageing (Jackson & McArdle, 2016), suggesting that excessive mitochondrial hydrogen peroxide generation may lead to partial or full fibre denervation in older individuals. The effects of exercise (intensity, duration, frequency, type of exercise) on lifespan remain to be defined more clearly in both rodent models and humans, noting that significant species differences have been reported (Garcia-Valles *et al.* 2013). In their Topical Review, Viña and colleagues propose that exercise may serve as a 'physiological' stimulus not only for ameliorating disease but also for improving healthy ageing and thereby delaying the onset of frailty (Vina *et al.* 2016).

In the 1950s, Denham Harman proposed the 'free radical theory of ageing', which states that 'aging and the degenerative diseases associated with it are attributed basically to the deleterious side attacks of free radicals on cell constituents and on the connected tissues' (Harman, 1956). The 'free radical theory of ageing' has recently been challenged, since it cannot fully explain the ageing process (Vina *et al.* 2013). Notably, reactive oxygen species not only cause cellular damage but also serve as 'physiological' modulators of endogenous redox-sensitive transcription factors regulating gene expression (Kunsch & Medford, 1999; Siow & Mann, 2010; Ray *et al.* 2012; Vina *et al.* 2013).

Enrique Cadenas and colleagues highlight the importance of mitochondria in redox homeostasis, emphasizing that mitochondrial dysfunction may serve as an 'initiator' of ageing-related disorders in metabolically active tissues such as brain, heart and liver (Yin *et al.* 2016). The schematic diagram in Fig. 4 of their Topical Review provides an informed overview of the mechanisms by which mitochondrial hydrogen peroxide can modulate redox-sensitive transcription factors involved in the regulation of cellular antioxidant and inflammatory responses (Yin *et al.* 2016). Cells have evolved endogenous mechanisms to modulate basal redox signalling and to counteract oxidative stress, with the ubiquitous NF-E2-related factor 2 (Nrf2)/kelch-like ECH associated protein 1 (Keap1) defence pathway playing a key role in the induction of antioxidant enzymes (Ishii *et al.* 2004; Mann & Forman, 2015; Suzuki & Yamamoto, 2015; Tebay *et al.* 2015). In this context, activation of Nrf2 affects mitochondrial biogenesis by counteracting increased generation of mitochondrial reactive oxygen species (Dinkova-Kostova & Abramov, 2015). As highlighted by Guillero López-Lluch and Plácido Navas, calorie restriction appears to promote longevity in part by modulating mitochondrial activity and cellular antioxidant defences (Lopez-Lluch & Navas, 2016).

Francesco Cosentino and colleagues highlight that only recent molecular studies have identified common signalling pathways linking the ageing process with cardiovascular and metabolic diseases (Costantino *et al.* 2016). Accumulation of reactive oxygen species and mitochondrial damage contribute to the development of cardio-metabolic disorders such as obesity and type 2 diabetes. These authors further suggest that premature dysregulation of genes involved in antioxidant defences, insulin signalling, autophagy and inflammation underlies pathologies in the heart and vasculature. Leah Cannon and Rolf Bodmer provide valuable insights into the mechanisms regulating genes associated with cardiac ageing in *Drosophila melanogaster* (Cannon & Bodmer, 2016), highlighting similarities in genes linked with oxidative stress, cardiac hypertrophy and neurodegenerative

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diseases in mammals and fruit flies. The Topical Review by Timon Seeger and Reinier Boon provides novel insights into the mechanisms by which microRNAs influence cardiovascular ageing, and in particular that inhibition of miR-34a in the myocardium may ameliorate cardiac dysfunction and cardiomyocyte apoptosis induced by ageing (Seeger & Boon, 2016).

In the context of age-related atherosclerosis, Giuseppe Poli and colleagues review the molecular mechanisms by which oxysterols and cholesterol oxidation products accumulate in the vascular wall (see Fig. 1 in their Topical Review), promoting inflammation, oxidative stress and apoptosis (Gargiulo *et al.* 2016). Evidence for 'accelerated biological ageing' in atherosclerosis, reviewed by Anna Uryga and Martin Bennett, indicates that markers of ageing in atherosclerotic plaques exceed those expected due to chronological ageing (Uryga & Bennett, 2016). Leocadio Rodríguez-Mañas and colleagues further review the importance of long-term inflammation as a major cause of vascular dysfunction and the development of diabetes (El Assar *et al.* 2016). Notably, the majority of published data have been obtained in animal models, with only limited information available for older patients with diabetes. In addition to highlighting the importance of NFκB in altered redox signalling in diabetes and ageing-induced vascular inflammation, these authors discuss the evidence that diabetes significantly impairs Nrf2-regulated gene transcription, rendering cells and tissues more susceptible to oxidative damage (Cheng *et al.* 2011, 2013; Uruno *et al.* 2013).

A *Journal of Physiology* research symposium entitled 'Vascular plasticity and developmental conditioning: impact on human health and ageing' was coordinated by Geraldine Clough (University of Southampton) and Giovanni Mann (King's College London) at the 10th World Conference for Microcirculation held in Kyoto, Japan in September 2015. The focus of this symposium was the wider implications of a 'developmental' perspective on human ageing. Mark Hanson and colleagues review the evidence that epigenetic influences during development may affect musculoskeletal and cardiovascular function in later life (Hanson *et al.* 2016). Thus, adaptive responses and susceptibility to disease in offspring may be initiated *in utero* and/or early life (Barker, 2002; Barker *et al.* 2006; Rodford *et al.* 2008; Gluckman *et al.* 2009; Pinney & Simmons, 2010; Bonacasa *et al.* 2011; Torrens *et al.* 2012; Ozanne, 2014; Chapple *et al.* 2015; Penfold & Ozanne, 2015; Morton *et al.* 2016). Phoebe Stapleton discusses the evidence that exposure of the fetus to air pollution particulate matter or nanomaterials not only affects the mother and developing fetus but also may predispose to disease susceptibility in later life (Stapleton, 2016). Wong and colleagues review the use of retinal vascular imaging as a useful clinical application to examine early life risk factors, e.g. in children from pregnancies affected by intra-uterine growth restriction (Li *et al.* 2016).

This Special Issue also contains review articles from two research symposia sponsored by The Physiological Society. A symposium entitled 'Impact of physical activity, ageing, obesity and metabolic syndrome on muscle microvascular perfusion and endothelial metabolism' was held in London in 2014 and co-sponsored by the European College of Sport Science. The symposium editorial (Wagenmakers, 2016) provides a valuable overview of the four review articles (Cocks & Wagenmakers, 2016; Frisbee *et al.* 2016; Keske *et al.* 2016; Wagenmakers *et al.* 2016). The other research symposium, entitled 'Limitations of skeletal muscle oxygen supply in ageing', was held in Edinburgh in 2015 and focused on vascular adaptations during ageing and skeletal muscle activity (Hearon & Dinenno, 2016; Nyberg & Hellsten, 2016; Thijssen *et al.* 2016).

The key objective of this Special Issue is to provide researchers with an up-to-date insight into the molecular mechanisms underlying ageing-related changes in cardiovascular and skeletal function. The Topical and Symposium review articles and associated primary papers (Boerman & Segal, 2016) will be of interest to established researchers as well as postdoctoral and graduate students working in the fields of ageing and cardiovascular and skeletal muscle physiology.

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Additional information

Competing interests

None declared.

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