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The physiopathologic role of oxidative stress in skeletal muscle

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ABSTRACT

Muscle senescence is a complex mechanism that is usually associated with a decrease in mass, strength and velocity of contraction. This state, known as sarcopenia, is a multifactorial process and it may be the consequence of several events, including accumulation of oxidative stress.

The role of oxidative stress in the physiopathology of skeletal muscle is quite complex. Transiently increased levels of oxidative stress might reflect a potentially health promoting process, while an uncontrolled accumulation might have pathological implication. The physiopathological role of oxidative stress on skeletal muscle, its involvement in aging-induced sarcopenia, and potential countermeasures will be discussed.

1. Introduction

Aging involves a progressive deterioration of physiological function that impairs the ability of an organism to maintain homeostasis, increasing the susceptibility to disease and death.

The skeletal musculature is particularly susceptible to the effects of aging, which is often associated with a decline in mass and functional performance. This state, known as sarcopenia, is due to an overall decrease in muscle integrity (Thompson, 2009), as fibrotic invasions replace functional contractile tissue, with marked changes in muscle fiber composition characterized by the shift from fast to slow fibers (Alnaqeeb and Goldspink, 1987). Despite numerous theories and intensive research, the principal molecular mechanisms underlying the process of sarcopenia are still unknown. Current data point out that the development of sarcopenia is a multifactorial process and believed to be the result of both intrinsic factors, involving changes in molecular and cellular levels, and extrinsic ones, such as nutrition and exercise (Fig. 1). Many factors, including reduction in neural function and motor-unit remodelling (Drey et al., 2013; Kwan, 2013; Mosole et al., 2014), decreased growth factors and hormone levels (Winn et al., 2002; Sakuma and Yamaguchi, 2012; Giovannini et al., 2008; Michalakis et al., 2013), chronic inflammation (inflamm-aging) (Ferrucci et al., 1999; Visser et al., 2002; Cesari et al., 2004; Penninx et al., 2004; Degens, 2010; Beyer et al., 2012; Mavros et al., 2014), imbalance between protein synthesis and degradation (Dickinson et al., 2013; Churchward-Venne et al., 2014), damage due to oxidative damage (Fulle et al., 2004; Hiona and Leeuwenburgh, 2008; Jackson et al., 2010; Armand et al., 2011; Marzetti et al., 2013; Sullivan-Gunn and Lewandowski, 2013), alteration in satellite cell activity (Conboy et al., 2005; Beccafico et al., 2007; Snijders et al., 2009; Barberi et al., 2013; Sousa-Victor et al., 2014; Di Filippo et al., 2016; García-Prat et al., 2016) may all contribute to sarcopenia. Among different factors, the accumulation of reactive oxygen species (ROS) and a significant decrease in endogenous anti-oxidant mechanisms in aged human skeletal muscle, could play a key role in the genesis and maintenance of sarcopenia.

2. Reactive oxygen species (ROS): an overview

The Reactive Oxygen species (ROS) or free radicals are naturally and constantly formed inside of the organism, as result of cell activity. ROS are important regulators of growth, proliferation, differentiation, and adaptation, at least within physiological concentration. The imbalance between the physiological production of free radicals and the cells ability to scavenger them promotes an oxidation status, named oxidative stress. The cells counteract ROS activity at different levels, such as prevention of ROS-generating electron leakage, scavenging ROS by enzymatic activities of superoxide dismutase, catalase, peroxidase, and peroxiredoxin; by low molecular weight antioxidant species, such as Vitamin E, Vitamin C, glutathione (Tables 1 and 2), and by removal of ROS damaged molecules (Birben et al., 2012). The superoxide released by processes such as oxidative phosphorylation is first converted to hydrogen peroxide and then further reduced to give water. This detoxification pathway is the result of multiple enzymes, with

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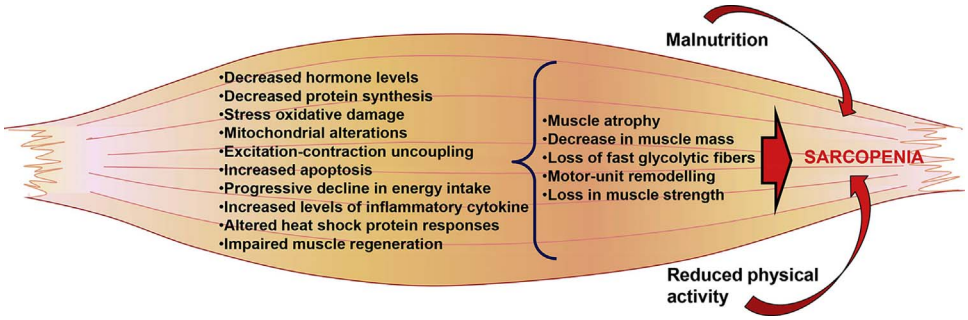

Fig. 1. Schematic model outlining the intrinsic and extrinsic (red arrows) factors triggering sarcopenia. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

superoxide dismutase (SOD) catalysing the first step and then catalases and various peroxidases removing hydrogen peroxide. Further the cellular antioxidant system also includes the glutathione system (glutathione reductase, glutathione peroxidases and glutathione S-transferases), which is a very efficient scavenger of hydrogen peroxide (glutathione peroxidase 1) and lipid hydroperoxides (glutathione peroxidase 4, glutathione S-transferases).

3. The physiological role of oxidative stress

There is growing evidence demonstrating that low concentrations of reactive oxygen species induce the expression of antioxidant enzymes and other defense mechanisms.

Physical exercise is associated with the production of ROS, which might play a key role on the beneficial effects exerted by physical activity. Endurance exercise promotes oxidative, metabolic, and heat stress on skeletal muscle which activates a variety of cellular signaling pathways leading to beneficial muscle adaptations (Saltin, 1977; Holloszy and Coyle, 1984; Mason et al., 2016). Critical components of this mechanisms are mitochondria and ROS production. Increase in mitochondrial content (mitochondrial biogenesis) improves the control of energy metabolism, and results in the oxidation of more fatty acids and less glycogen for ATP production. Moreover, endurance training may also improve mitochondrial quality through two mutually exclusive pathways: alterations in mitochondrial dynamics (Kirkwood et al., 1987; Ding et al., 2010; Perry et al., 2010; Picard et al., 2013; Iqbal and Hood, 2014) and selective autophagic degradation of mitochondria (mitophagy) (Grumati et al., 2011; Lira et al., 2013). Increased mitophagy following exercise is beneficial by improving overall mitochondrial quality through the selective removal of damaged or dysfunctional mitochondria (Safdar et al., 2011; Zampieri et al., 2015). Indeed, long-life regular exercise in humans has been shown to preserve functional autophagy, guaranteeing better muscle mass and strength in senior sportsmen than elderly sedentary subjects (Carnio et al., 2014).

The evidence that exercise induces ROS in skeletal muscle was first reported by Davies et al. (1982) and since that many studies have confirmed that muscle contraction markedly increases the amount of ROS production compared to resting skeletal muscle (Powers and Jackson, 2008; Wiggs, 2015). Noteworthy, the beneficial effects of exercise are abolished by administration of antioxidant compounds, such as vitamin C and E (Gomez-Cabrera et al., 2008; Ristow et al., 2009; Paulsen et al., 2014; Morrison et al., 2015). The adverse effects of antioxidant treatment suggests that ROS act as critical signals in exercise because decreasing their formation prevents activation of important signaling pathways that cause useful adaptations in muscle (Hashimoto and Brooks, 2008).

It is plausible that under physiological conditions, skeletal muscle activates an endogenous program of antioxidant defense to maintain the ROS product at a "functional" level (Musarò et al., 2010). Indeed, regular/moderate exercise has been shown to induce an antioxidant defense by enhancing the activity of endogenous antioxidant enzymes such as SOD, glutathione peroxidase, and catalase (Mastaloudis et al., 2001; Knez et al., 2014) (Fig. 2, left panel).

Typical cellular components also sensitive to redox changes are nuclear factor-kappaB (NF-kB), activator protein-1 (AP-1), mitogene activated proteine kinases (MAPKs), heat shock transcriptional factor-1 (HSF-1), and insulin receptor kinase (Lawler et al., 2003a,b, 2006), all factors involved in muscle homeostasis. Of note, moderate exercise promotes an activation of MAP kinases, which activates NF-κB that in turn induces the expression of antioxidizing enzymes such as

Table 2
Non-enzymatic Scavenger.

Non-enzymatic Antioxidants
Vitamin A
Vitamin C
Vitamin E
β-Carotene
Glutathione
α-Lipoic acid
Uric acid
Bilirubin
Conenzyme Q10

Table 1
Main role of antioxidant enzymes.

Antioxidant Enzymes	Forms	Main Role
Superoxide dismutase (SOD)	SOD1, SOD2, SOD3	forms the first line of defense against superoxide radicals as SOD dismutates superoxide radicals to form hydrogen peroxide (H_2O_2) and oxygen (O_2).
Catalase (CAT)	CAT	catalyzes the break-down of H_2O_2 into H_2O and O_2
Glutathione peroxidase (GTPx)	GPX1-GPX5	catalyzes the reduction of H_2O_2or organic hydroperoxide (ROOH) to water (H_2O) and alcohol (ROH), respectively
Thioredoxin (TRX)	TRX1, TRX2	prevention of protein oxidation, control of apoptosis. Protection against oxidative stress by reducing hydroperoxides and functioning as a NADPH-dependent dehydroascorbate reductase to recycle vitamin C
Peroxiredoxin (PRX)	PRX I–VI	peroxidase capable of reducing both hydroperoxides and peroxynitrate
Glutaredoxin (GRX)	GRX1, GRX2, GRX5	protection and repair of protein and non-protein thiols
Glutathione transferase (GST)	GST class: Alpha, Delta, Kappa, Mu, Omega, Pi, Theta, Zeta	inactivates secondary metabolites, such as unsaturated aldehydes, epoxides, and hydroperoxides.