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Review

Reactive oxygen species and calcium signals in skeletal muscle: A crosstalk involved in both normal signaling and disease

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ABSTRACT

Reactive Oxygen Species (ROS) have been profusely studied as agents of potential damage to living cells and they have been related to a number of pathological processes. Increasing evidence points to a more positive role of ROS in cell signaling and the detailed mechanism that regulates the precise amount of ROS needed for cell functioning without the deleterious effects of excess ROS still needs to be resolved in detail.

In skeletal muscle the main source of ROS during normal functioning appears to be NADPH oxidase 2 (NOX2), which is activated by electrical stimuli (or exercise) through a cascade of events that include ATP release through pannexin1 channels. NOX2 is a protein complex that assembles in the T-tubule membrane before activation and ROS production by NOX2 appears to be important for muscle adaptation through gene expression and mitochondrial biogenesis as well as for improving glucose transport after insulin action.

Excess ROS production (or diminished antioxidant defenses) plays a role in a number of pathological processes in skeletal muscle. Together with increased reactive nitrogen species, an increase in ROS appears to have a deleterious role in a model of Duchenne muscular dystrophy as well as muscle wasting in other diseases such as aging sarcopenia and cancer cachexia. In addition, ROS is involved in obesity and muscle insulin resistance, both of which are causally related to type 2 diabetes.

A detailed description of the fine-tuning of ROS (including all sources of ROS) in skeletal muscle in health and disease will significantly contribute to our knowledge of both muscle adaptation and muscle related pathologies.

Contents

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1. Introduction

Skeletal muscle is a primary tissue in the response to metabolic alteration induced by physiological or pathological stimulus. The *redox* homeostasis appears to be a key modulator of skeletal muscle plasticity/dysfunction in response to exercise or metabolic diseases. Several signaling pathways in striated muscle can be activated by an increase in reactive oxygen species (ROS) and reactive nitrogen species (RNS) production.

In skeletal muscle, ROS is produced by several sub-cellular compartments under stress or metabolic conditions [1]. The best-studied ROS sources in striated muscle include mitochondria, xanthine oxidase (XO), and nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOXs). The NOXs are oligomeric enzymes that generate O_2^- not only as a by-product of cellular metabolism but also as the main product. This process occurs in a regulated manner in response to cytokine, hormonal, and mechanical signals [2]. There is strong evidence that NOX2 and its homologues are a major source for ROS under resting and contracting conditions [3,4].

The dose-response relationship between ROS production and muscle adaptation/dysfunction has not been easy to determine. The hormesis concept, derived from the field of toxicology, describes the dose response relationship when a stressor is beneficial in moderate levels and detrimental in high levels [1]. It has been proposed that the ROS-dependent hormesis model could explain some of the responses to exercise, insulin resistance, and muscle wasting (Fig. 1). We will summarize the evidence that favors a tight regulation of ROS levels in skeletal muscle and its association to calcium signals. This relevant subject needs further studies to understand its important role in the physiology and pathophysiology of skeletal muscle.

2. ROS as second messengers in normal skeletal muscle

Skeletal muscle has a *redox* equilibrium between ROS/RNS generation and antioxidant-induced defense that are in constant rate even after contraction. Among ROS, H_2O_2 has signaling properties, because it is a molecule derived from dismutation of superoxide anion, produced by superoxide dismutase (SOD). H_2O_2 influences a range of cellular events through its kinetics properties, life span and intracellular specific generation, and plays a crucial role in signal transduction in skeletal muscle [5]. Second messenger characteristics of H_2O_2 are involved in gene expression and glucose uptake, among other cellular processes. Most of the H_2O_2 produced in skeletal muscle comes apparently from NOX2; it had been assumed for many years that mitochondria was the most important H_2O_2 source, but it was reported that superoxide production by mitochondria is about 0.15% of the total O_2 consumed [6].

2.1. Role of ROS during muscle contraction/exercise

Muscle contraction is an event characterized by activation of multiple intracellular pathways critical to skeletal muscle plasticity and adaptation [7]. Endocrine, mechanical, and metabolic signals control the muscle adaptation in response to contractile activity [8]. Excitation-contraction coupling (E–C coupling) is followed by an adaptive change in gene expression named excitation-transcription coupling [9,10]. Thus, changes in gene expression govern skeletal muscle adaptation in response to contractile activity.

The increase of ROS production during exercise was described for the first time in the eighties [11]. In skeletal muscle, ROS and RNS activate several *redox* sensitive pathways that participate in acute and chronic response to exercise [12]. For example, exercise training induces upregulation of antioxidants enzymes such as MnSOD, GPx, and catalase [12]. Interestingly, the supplementation of general ROS scavengers blunts these antioxidant upregulation induced by exercise (for review see Ref. [13]). Thus, ROS appear to be necessary to adaptive protein synthesis in response to training.

Mitochondrial biogenesis is a well-described training-induced muscle adaptation. Mitochondrial biosynthesis involves the regulated expression of mitochondrial and the nuclear genes [14]. The transcriptional coactivator, peroxisome proliferator-activated receptor γ coactivator-1 α (PGC-1α), is necessary for mitochondrial biogenesis, which improves the expression of nuclear genes encoding mitochondrial proteins [15]. Endogenous and exogenous ROS stimulation have been shown to induce upregulation of PGC-1α [16,17]. Moreover, high doses of dietary antioxidants block exercise-induced mitochondrial biogenesis [18,19], suggesting that ROS is needed for this adaptation in skeletal muscle.

A better understanding of the ROS pathways activated during exercise might be important to unveil the molecular mechanisms of muscle adaptation. Recent evidence suggests that specific circuits and localized ROS production explain the divergent response to oxidant molecules. During muscle contraction, there is a larger cytosolic ROS production with a discrete mitochondrial signal [3]. Thus, non-mitochondrial ROS sources such as xanthine oxidase (XO) and NOXs may play a major role in the contraction-induced intracellular signaling mediated by ROS. Our group has reported that NOX2 contributes to ROS production after depolarization in skeletal muscle [20,21]. Moreover, NOX2 inhibition reduces the adaptive gene expression induced by endurance exercise.

The hormesis model partially explains the role of ROS in the skeletal muscle physiology (Fig. 1); a physiological and transient ROS generation induces antioxidant genes expression and maintains *redox* balance. A decrease/increase in normal ROS levels alters *redox* homeostasis inducing muscle alterations [22–24].

2.2. Physiological role of ROS under insulin action

During the last decade, literature suggests that ROS generation in response to physiological stimuli such as insulin may also facilitate signaling by reversible protein modification and by inhibiting protein tyrosine phosphatases. For example, the glutathione peroxidase 1 KO mice ($Gpx1^{-/-}$) has higher insulin sensitivity and are resistant to high fat diet (HFD)-induced obesity, enhancing PI3 K/Akt signaling [25]. Apparently, H_2O_2 is part of the events triggered by insulin in skeletal muscle cells, acting as a second messenger; implying that both its production and its degradation occur via specific enzymes, which provide specificity and account for site-specific effects.

The first report that showed that insulin induces H_2O_2 was described in rat epididymal fat cells [26]. NOX2 appears to be the main ROS source under insulin stimulation in adipocytes. Moreover, we described that insulin induces ROS generation in skeletal myotubes [27] and adult fibers [28] in a NOX2-dependent manner. The physiological role of insulin-dependent ROS generation has been studied during the past years and ROS appears to be necessary for insulin-dependent glucose uptake [29,30] and GLUT4 translocation [31] in skeletal muscle cells.

We recently reported that insulin-dependent GLUT4 translocation to the cell surface requires intracellular Ca^{2+} release through both RyR1 and IP_3R Ca^{2+} channels [31]. For this reason, any impairment of intracellular calcium homeostasis could affect glucose uptake in skeletal muscle.

Enhanced insulin sensitivity after exercise was first described in 1982 [32]. An insulin effect in skeletal muscle acutely increases between 2 and 48 h following exercise [33,34]. Recently, Trewin et al.[35] reported that ROS attenuation blunted the post-exercise insulin sensitivity using hyperinsulinemic–euglycemic clamp in

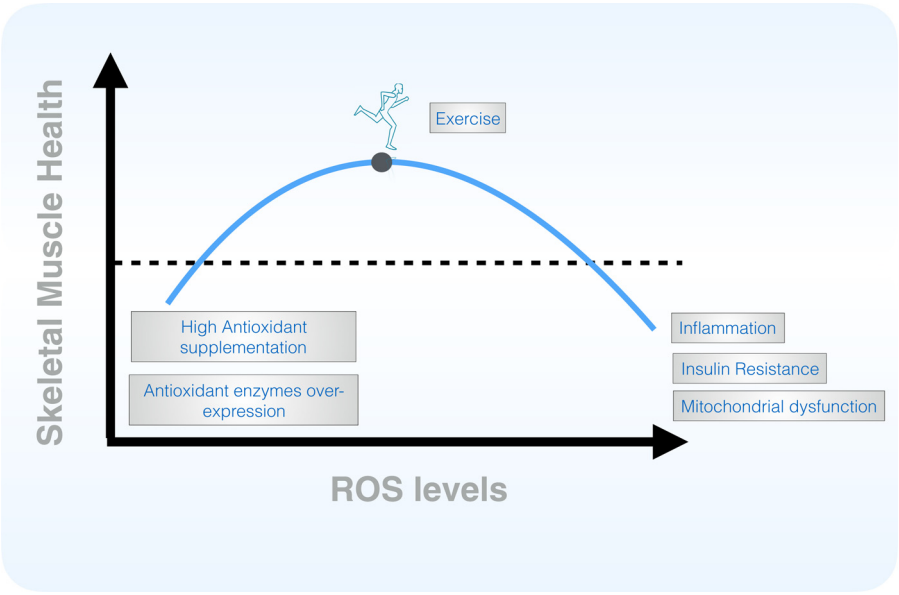

Fig. 1. Dose–response theoretical curve depicting ROS production. ROS participate as physiological agents that are necessary for normal function in skeletal muscle. An excess ROS levels is present in pathological processes, being probably the cause of damage in striated muscle.

humans. In a 4-week training study, dietary antioxidants were shown to impair the training-induced insulin sensitivity [36]. Collectively, these evidences suggest that ROS participates in insulin sensitivity induced by exercise/training. Thus, future studies should explore the underlying mechanism(s) that explain these observations.

3. ROS-mediated alterations in metabolic disease and muscle wasting

3.1. ROS as a consequence of obesity

Overweight and obesity are the main causes of insulin resistance and type 2 diabetes mellitus onsets. It is well accepted that a systemic oxidative stress present in obesity [37–39], including that in adipose tissue, is a source of oxidant molecules [40]. Murdolo et al. have proposed the term: "adipose oxidation" to characterize the effects of increased oxidative stress in fat, producing adipose tissue dysfunction and then, insulin resistance [41]. In adipose tissue it is possible to find higher protein carbonylation levels [42], decreased mitochondrial antioxidant enzymes activities [43], accumulation of oxidized and unfolded/misfolded proteins [44], and high level of glutathionylated products of oxidative stress. All of these effects lead to adipose tissue damage with release of pro-inflammatory mediators, contributing to systemic insulin resistance [45–47]. However, a local fat accumulation of intramyocellular triacylglycerol (IMTG) alter carbohydrate and lipid metabolism, impairing metabolic flexibility and energy production, which are essential for keeping normal contractile function of skeletal muscle [48,49]. In both mice and humans, lower bioenergetics efficiency and increased mitochondrial H_2O_2 emissions associated with obesity have been reported [50]. In obese women who were treated with exercise training, the activity of antioxidant systems increased and cellular oxidative damage in skeletal muscle decreased [51].

3.2. Insulin resistance and ROS

A rise in intracellular ROS appears to play important physiological roles in many organs, however, excess ROS overwhelms antioxidant defenses, leading to oxidative stress, and this apparently plays an important role in the pathogenesis of insulin resistance. A physiologically regulated H_2O_2 generation is necessary to warrant the insulin effects. It was shown that if H_2O_2 over quenching is induced by an overexpression of glutathione peroxidase 1, signaling events triggered by insulin, are impaired [52].

An excessive production of H_2O_2 probably affects the same signaling pathway because treatment of isolated skeletal muscle of lean Zucker rats with H_2O_2 is capable of decreasing both glucose transport and glycogen synthesis induced by insulin [53]. This double effect of ROS in regulating the insulin signal was extensively discussed by Tigani et al. [54]. However, until date there is no consensus on physiological and pathological concentrations of ROS and time course of ROS-induced by insulin.

First reports suggesting NOX participation in insulin resistance showed that in adipocytes stimulated with 100 nM insulin produced a rapid increase of ROS production, measured with 5,6-chloromethyl-2′,7′-dichlorodihydrofluorescein diacetate (CM-DCF). This effect was inhibited using diphenyleneiodonium (DPI) [55], a drug which is widely used as a ROS inhibitor but does not allow identification of the ROS source. The same authors overexpressed recombinant Nox4 deletion constructs, increasing insulin-stimulated production of H_2O_2 in adipocytes [56]. Insulin-resistant mice showed increased insulin-stimulated H_2O_2 release and decreased reduced-to-oxidized glutathione ratio (GSH/GSSG). We have shown that NOX2 levels are higher in these mice [57]. A pro-oxidative environment could affect lipid molecules producing cellular damage. ROS overproduction produces several molecular modifications in skeletal muscle: S-oxidation and disulfide modification oxygen-regulated RyR1 activity [58] and protein S-nitrosylation [59]. Lipid peroxidation is a process occurring naturally in small amounts in the body, mainly by the effect of ROS, which can readily attack the polyunsaturated fatty acids of the lipid membrane, initiating a self-propagating chain reaction that, in turn, disrupts the structure of biological membranes and produce toxic metabolites such as malondialdehyde (MDA) [60].

The ATPase of the sarcoplasmic reticulum (SERCA) is another skeletal muscle protein that has several cysteines susceptible to oxidation [61]. ROS can influence *redox*-sensitive processes within the cell in several cell systems while H_2O_2 modifies the function

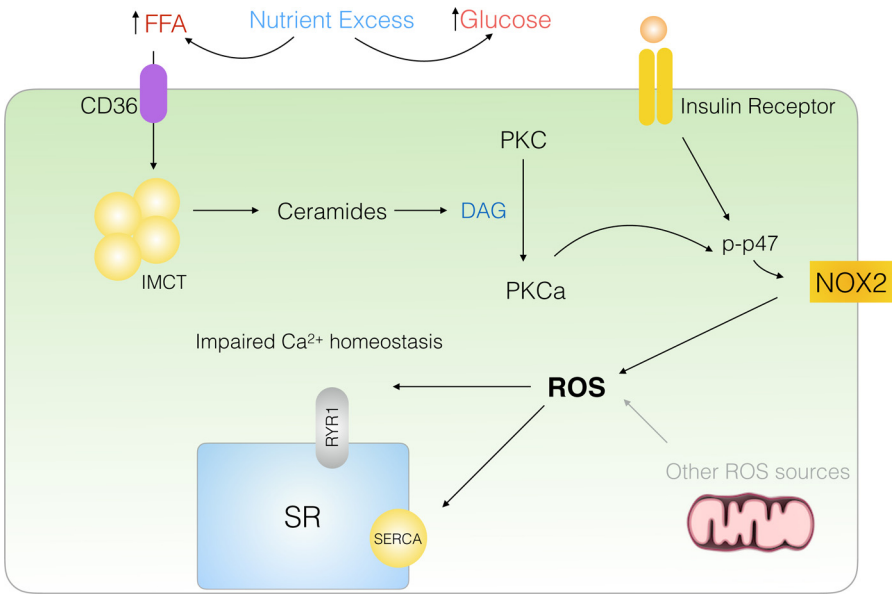

Fig. 2. ROS and Ca^{2+} alterationsin obesity-related phenotypes in skeletal muscle. Increased free fatty acids observed in obesity increase IMCT and ceramide formation, activating PKC which in turn increases NOX2-dependent ROS production. Insulin can induce excess oxydant molecules due to NOX2 overexpression; ROS induce post-tranlational changes in RYR1,increasing Ca^{2+} leak.

of various proteins including transcription factors, kinases, and phosphatases. SERCA exhibits marked dysfunction when suffers extensive oxidative modification [62]. Fatty acid synthase (FAS) is overexpressed in HFD-fed mice and increase of FAS triggers intracellular calcium increase by decreasing SERCA activity. This indicates that changes in SERCA activity can affect skeletal calcium homeostasis in obesity [63]. Moreover, it is accepted that SERCA is downregulated in cardiac and beta cells of diabetes models due, in part, to oxidative stress [64]. Ryanodine receptor 1 (RyR1), involved in muscle contraction, can also be oxidized by insulin to stimulate RyR1-mediated Ca^{2+} release by promoting RyR1 S-glutathionylation [31], suggesting that ROS may be playing a physiological role in skeletal muscle E-C coupling. High-fat feeding in male rats increases H_2O_2 emission from mitochondria in obese Zucker rats with enhancement of 4HNE, suggesting that induction of oxidative stress, which increases nitrosylated tyrosine residues on the RyR, produces a chronic Ca^{2+} leak [64]. Most likely, the intracellular oxidant environment present in skeletal muscle in type2 diabetes (T2D), has an effect on the intracellular calcium homeostasis, a "leak" of calcium from sarcoplasmic reticulum will be a cause of basal intracellular calcium increase, a likely cause of sarcopenia. H_2O_2 induced SR calcium leak from the RyR1 has recently been proposed by others [65].

3.3. *Diabetic skeletal muscle wasting*

Skeletal muscle oxidative stress is considered an important mechanism for the development of muscle damage due to T2D. When skeletal muscle is insulin resistant, the activation of insulin pathway is impaired, producing a systemic hyperglycemic condition that triggers insulin release from the pancreas to compensate for the high glycemia. The pancreatic compensation continues while a sufficient number of beta cells are kept healthy, but if chronic hyperglicemia is maintained, beta cells undergo apoptosis, which is mediated by oxidative damage in different models [66,67]. Pancreatic damage triggers impaired glucose-stimulated insulin secretion in beta cells though H_2O_2, producing the onset of T2D [68].

Diabetic myopathy (DM) is a condition characterized by a decreased skeletal muscle size and strength [69]. Mechanisms involved in DM are associated with advanced glycation end products (AGEs) accumulation and lipo-toxicity. AGEs accumulation in skeletal human muscle induces atrophy, through an AMPK-down-regulated Akt signaling [70]. AGEs can produce fiber changes increasing lipogenesis by sterol regulatory element-binding protein-1c (SREBP-1c) activation, mitochondrial biogenesis and ROS generation, increasing oxidative stress in muscle [71].

Skeletal muscle suffers fiber-type specific changes, in STZ-induced atrophy model; gastrocnemius muscle is more affected than others and atrophy appears to be mediated by NF-κB activation [72]. Inflammatory genes are induced in T2D subjects as MCP1 and TLR4 [73] and TLR4 activation can impair sarcoplasmic reticulum (SR) Ca^{2+} handling and muscle function that has been associated to myositis [74]. T2D is characterized by increased plasma levels of free fatty acids; palmitate in particular has lipotoxic effects that affect skeletal muscle. In HFD treatment, palmitate appears as the main lipid responsible of lipotoxicity in both skeletal muscle and beta cells [75]. HFD produces an accumulation of intramyocellular triacylglycerol (IMTG), responsible of impaired glucose uptake. The mechanism involved is dependent on DAG and ceramide accumulation and both impair insulin signals. Moreover, DAG and ceramides are involved in the activation of both conventional and novel protein kinases C (PKC) isoforms and c-Jun N-terminal kinases (JNK) [76,77]. DAG increases protein kinase C activity, which inhibits IRS-1 through serine phosphorylation and activates NOX2 to generate ROS [78]. PKC-NOX2 activation requirement for palmitate induced-ROS has been described recently in cardiomiocytes [79].

Skeletal muscle develops several phenotypic changes in Type 1 diabetes (T1D), such as a decrease in mitochondria number, an increase in type IIx fibers, increase of SERCA 1 and 2 and decrease of RyR1 in EDL. These changes apparently relate to a decrease in force profile and elevated intracellular Ca^{2+} [80]. These effects could be mediated through PKC activity, which is capable of influencing L-type calcium channels [81], increasing its conductance and calcium transients associated with E-C coupling [82]. A permanent PKC activation could be responsible for chronic elevated intracellular calcium in T2D (Fig. 2). More recent evidence coming from studies in adipocytes, point to a deregulation in Ca^{2+} homeostasis present

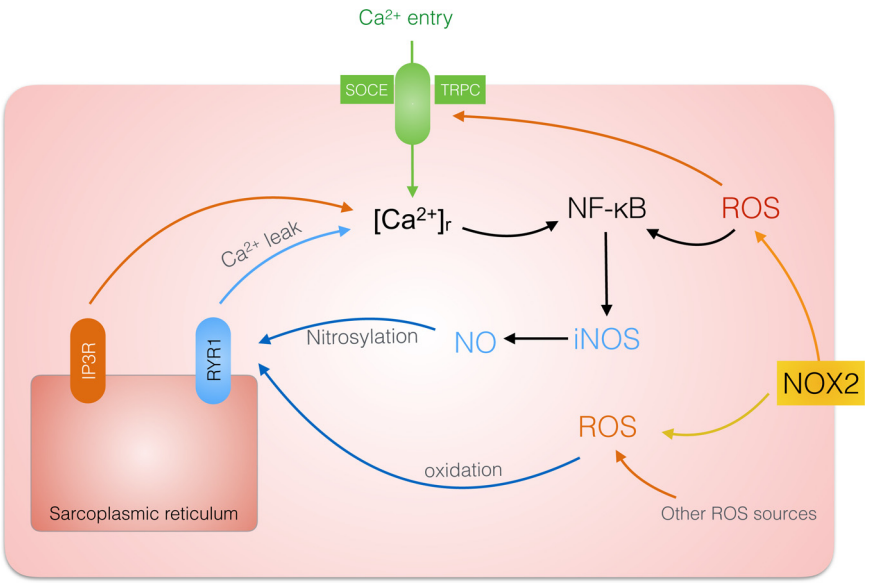

Fig. 3. Interaction between ROS and Ca^{2+} signaling in dystrophic muscle. Ca^{2+} dysregulation is related to an elevated NF-κB activity and iNOS overexpression. Both NO and ROS contribute to an increase in both Ca^{2+} leak from the SR and Ca^{2+} entry.

in T2D and possibly caused by mitochondrial dysfunction. This area of research suggests that mitochondrial ROS affect calcium buffer properties of mitochondria and impair calcium dependent signals needed for GLUT4 translocation [83].

Both ROS and RNS participate significantly in cellular signaling pathways involved in muscle adaptation, but when free radicals are overproduced, as occurs in T2D, proteins related to contraction could be affected, producing impaired calcium homeostasis. The fat overload, which induces this defect, is fiber-type-specific, increasing muscle relaxation time in fast-twitch fibers and decreasing force production in slow-twitch fibers [84].

3.4. Role of ROS/RNS in muscle wasting and aging

Duchenne muscular dystrophy (DMD) is a lethal X-linked human genetic muscular disorder caused by mutations in the dystrophin gene that lead to absence of dystrophin protein [85]. DMD is characterized by severe and progressive muscle wasting leading to wheelchair dependence and premature death. Dystrophic muscle degeneration was initially explained by the role of dystrophin in the sarcolemma stabilization, mechanical coupling, and the lateral force transmission in skeletal muscle [86]. However, although membrane fragility is an important factor, it does not fully explain the onset and progression of DMD. Ca^{2+} dysregulation and oxidative/nitrosative damage appear to have a central role in the pathology progression (Fig. 3). The molecular mechanisms by which Ca^{2+}-oxidative stress interaction contributes to DMD pathology are not fully understood. This section summarizes scientific evidence related to calcium/ROS interaction in dystrophic muscle.

Oxidative stress markers and antioxidants enzymes are increased in skeletal muscle of patients [87,88] and the *mdx* mice (a mouse model that, as the human DMD, does not express functional dystrophin protein) [89,90]. Primary myotubes from *mdx* mice present susceptibility to death by oxidative stress but not by other cell insults [91,92]. Moreover, myoblasts from *wt* and *mdx* mice are equally sensitive to oxidative stress [91], suggesting that the absence of dystrophin in *mdx* differentiated myotubes was the primary cause of the increased susceptibility to oxidative stress. In adult *mdx* mice, the treatment with NAC improves muscle pathology and partially restores the muscle function [93]. Together, these data strongly suggest the participation of oxidative stress in DMD etiology and progression.

Intracellular resting calcium concentration ($[Ca^{2+}]_r$) is elevated in both skeletal myotubes [94] and adult fibers [95] of *mdx* mice. Initially, the altered $[Ca^{2+}]_r$ was explained mainly by the alterations in Ca^{2+} entry, consistent with the sarcolemma fragility hypothesis [96]. However, there is evidence that ROS production leads to an increase $[Ca^{2+}]_r$ in *mdx* fibers under no-contracting conditions through Src phosphorylation and TRPC-dependent Ca^{2+} influx [97]. Moreover, NOX2 inhibition reduces the intracellular Ca^{2+} rise after stretched contractions in *mdx* fibers [98].

The contribution of sarcoplasmic reticulum to the elevated $[Ca^{2+}]_r$ in DMD has been reported [94,95]. In dystrophic muscles, RyR1 has a variety of posttranslational modifications that contribute to Ca^{2+} dysregulation. We have shown that pharmacological blockers of both RyR1 and IP_3R resulted in a reduction in the $[Ca^{2+}]_r$ in *mdx* myotubes [94]. The dysregulation of $[Ca^{2+}]_r$ is linked with an aberrant NF-kB transcriptional activity that leads to upregulation of iNOS and nitric oxide (NO) generation [94]. Interestingly, Mark's group showed that RyR1 S-nitrosylation contributes to muscle wasting in dystrophic muscles [99]. Moreover, we showed that reduced *in vivo* $[Ca^{2+}]_r$ leads to an iNOS and NOX2 downregulation, leading to improvement of muscle function [95]. These evidence strongly suggest a reciprocal role of an excessive ROS/RSN generation and $[Ca^{2+}]_r$ homoeostasis in DMD.

Generation of ROS is increased in normal skeletal muscle as part of physiological responses to exercise. Recently, we showed that ROS production after electrical stimuli was higher in *mdx* muscle cells and could be blocked by NOX2 inhibitors [100]. Moreover, gene expression of key subunits of NADPH such as $p47^{phox}$ and $gp91^{phox}$ were upregulated in *mdx* myotubes [100]. The excessive ROS production by NOX2 in dystrophic muscle has been linked to an altered gene expression [100], impaired autophagy flux [101] and microtubules dysfunction [102].

In most mammalian species, including humans, aging is associated with a reduction in skeletal muscle mass and function termed sarcopenia. Sarcopenia leads to a reduced ability to perform activities of daily living and thus causes a loss of independence. Indeed, low skeletal muscle mass or strength is reported to be the most frequent cause of disability in the elderly [103]. Importantly, low skeletal muscle mass or strength has been reported to be a predictor

of morbidity, loss of independence, frailty and mortality, in addition to other risk factors or diseases [104]. At the cellular level, in limb and trunk muscles, sarcopenia is characterized by atrophy of the constituent fibers in the muscle (with a tendency for greater atrophy of fast-twitch type 2 compared to slow-twitch type 1 fibers), an increase in fiber size heterogeneity, and an increase in the composition of non-contractile (adipose and connective) tissues within the muscles [105]. Sarcopenia has been also described in masticator muscles, increasing dysphagia problems related to elderly [106]. However, in masticator muscles, aging causes prevalence in type 2 compared to type 1 fibers [107]. Molecular mechanisms involved in differential plasticity of these muscles have never been addressed. Nevertheless, at the molecular level, ROS production by muscle fibers has been identified as a primary signaling agent. Hence, balance between useful and excessive ROS production is a key feature during aging. Noteworthy, skeletal muscle from aged rats shows a 2–3-fold increase in non heme iron [108–110] and, through the Fenton reaction, redox-active iron generates the highly damaging hydroxyl free radical [111].

A role of ROS in the pathophysiology of cancer cachexia has also been proposed based on ample evidence in the literature (reviewed in Ref. [112]). Cachexia is a complex metabolic syndrome characterized by a severe and involuntary loss of muscle mass (defined by a >5% involuntary loss of edema-free body weight over 1 year [113]). Cachexia is associated with chronic diseases, especially cancer, and with other inflammatory conditions (chronic obstructive pulmonary disease, heart failure, chronic kidney disease, AIDS, and sepsis) [114,115]. Almost 80% of cancer patients suffering cachexia will die within one year after diagnosis.

ROS can stimulate apoptotic cell death after damaging cellular lipids, proteins and DNA [116]. Increased ROS can act via pro-inflammatory transcription factors, namely NFκB, which upregulates components of the unfolded protein response (UPS). Indeed, cell culture experiments in C2C12 cells documented that ROS have the capacity to induce the expression of E3-ubiquitin ligases [117] that correlates with increased ubiquitin-conjugating and proteasome activity and decreased myosin protein content [117,118]. In a rat cancer cachexia model induced in Yoshida AH-130 tumor cells, ubiquitin-proteasome activity, muscle wasting, and mortality were attenuated by the XO inhibitor allopurinol or oxypurinol [119].

4. Conclusions

We can conclude that ROS have an important signaling role in skeletal muscle, closely associated with calcium signals that are not involved in muscle contraction. Both the large magnitude of calcium signals involved in the contractile process and the deleterious processes induced by excess ROS/RNS production has made the study of the physiological role of ROS difficult and has prevented our detailed knowledge of these events for a long time.

Abnormal ROS/RNS production appear to be involved in a number of skeletal muscle related diseases, including muscle wasting as in muscular dystrophies, aging related sarcopenia and cancer cachexia. Metabolic diseases such as obesity have also been related to abnormal ROS/RNS handling by the muscle cell, leading to insulin resistance and T2D. Further knowledge of ROS/RNS homeostasis in skeletal muscle will provide important insight to the fine-tuning of meaningful signaling within the muscle cell.

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