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Review

Reactive Oxygen and Nitrogen Species Regulate Key Metabolic, Anabolic, and Catabolic Pathways in Skeletal Muscle

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Received: 18 May 2018; Accepted: 29 June 2018; Published: 5 July 2018

Abstract: Reactive oxygen and nitrogen species (RONS) are important cellular regulators of key physiological processes in skeletal muscle. In this review, we explain how RONS regulate muscle contraction and signaling, and why they are important for membrane remodeling, protein turnover, gene expression, and epigenetic adaptation. We discuss how RONS regulate carbohydrate uptake and metabolism of skeletal muscle, and how they indirectly regulate fat metabolism through silent mating type information regulation 2 homolog 3 (SIRT3). RONS are causative/associative signaling molecules, which cause sarcopenia or muscle hypertrophy. Regular exercise influences redox biology, metabolism, and anabolic/catabolic pathways in skeletal muscle in an intensity dependent manner.

Keywords: training; skeletal muscle adaptation; oxidative stress

1. Introduction

Regular physical exercise results in systemic adaptation(s) of the whole body, alongside varied perturbations in blood flow and metabolism among different organs. The main adaptive effects, such as decreased levels of oxidative damage, increased activities of enzymatic antioxidants, enhanced mitochondrial efficiency, and more efficient physiological functions are, however, observed in the skeletal muscle, heart, brain, liver, kidneys, and testes, alongside other organs. Since skeletal muscle is the largest organ in the human body, and the main organ responsible for physical exercise, the present review focuses on exercise-associated adaptation of skeletal muscle, and reactive oxygen and nitrogen species (RONS).

2. Muscle Contraction and Reactive Oxygen and Nitrogen Species

Davies and co-workers [1] showed for the first time that after an exhaustive bout of exercise, a significant increase in reactive oxygen species (ROS) production occurs in the skeletal muscle, as measured by electron spin resonance. At that time, it was widely accepted that ROS were a so called "by-product" of aerobic metabolism that jeopardized the structure and function of muscle cells. However, an intriguing study was later published in which it was observed that whilst contracting skeletal muscle generates ROS, ex vivo exposure to the antioxidant enzymes, catalase and superoxide dismutase (SOD), decreased force generation [2]. This work was the first to show that

ROS could positively affect the function of skeletal muscle by facilitating muscle contraction at certain concentrations. In a previous study, the same research group showed that during muscle fatigue the concentration of ROS increased, which eventually led to a decreased force production, which could be delayed with the administration of exogenous antioxidants [2–4]. Therefore, this finding suggests that contracting skeletal muscle is producing ROS, which further facilitates the strength of the muscle contraction. However, if the ROS concentration exceeds a certain level, it reduces the force generation and causes fatigue. This phenomenon nicely demonstrates that ROS could have a positive or negative effect, depending on the concentration, and is a phenomenon that can be described by the hormesis curve [5–8]. Up-to a concentration, ROS and muscle force generation capacity increase together, but after reaching a point, greater levels of ROS decrease the force generation of skeletal muscle, and, therefore, the relationship between ROS and force generation of skeletal muscle has a bell-shaped dose-response curve.

It is known that mitochondrial electron transport chain is one main ROS generator found in skeletal muscle [9]. During high intensity exercise, ROS, mainly generated by Complex I and III with pyruvate/malate and succinate substrates, were increased by 187% and 138%, respectively [10]. Experimental data revealed that mitochondria isolated from skeletal muscle after contraction showed significantly increased levels of hydrogen peroxide (H_2O_2) generation [11] (Figure 1). H_2O_2 is the main signaling molecule because it can cross membranes and activate redox sensitive proteins, modulating cell signaling.

It has been shown that Complex I is the major ROS generator in skeletal muscle of ultra-endurance runners [12]. However, it must be noted that the earlier estimations of about 1–5% of the oxygen that entering the mitochondria being released as ROS [13] could be highly overestimated, with the real value being more than an order of magnitude lower [14]. However, the findings of Austin et al. [15] suggest that mitochondria might be important sources of ROS at Complex I and III, through peroxisome proliferator-activated receptor-γ coactivator alpha (PGC-1α).

Indeed, the iron-sulfur clusters, flavoprotein and oxidoreductase, at Complex I, and Q10 semiquinones at Complex III are thought to be the main sites of ROS generation [14,16]. In addition to mitochondria, 5-lipoxygenase, cyclooxygenase, sarcolemmal and leukocyte nicotinamide adenine dinucleotide phosphate-oxidase (NADPH), and xanthine oxidase (XO) have also been implicated in superoxide generation in skeletal muscle [9,17–19].

It has also been suggested that the basal level of intracellular H_2O_2 in skeletal muscle is between 10–100 nM, which increased to 100–200 nM with heavy muscle contraction [20]. Although the level of XO in skeletal muscle is very low, it is present to a significant degree in the endothelium, and, hence, it is a potential source of extracellular superoxide generation. High intensity exercise results in the generation of hypoxanthine [21,22], and a linear relationship has been observed between the levels of circulating lactic acid and XO. Interestingly, we could detect increased XO activity in the liver one day after exhaustive acute exercise [23], but administration of SOD derivatives identified endothelium associated with XO as one source of ROS generation during intense exercise [21]. However, the contribution of XO in ROS production during aerobic exercise is a real puzzle. A number of papers suggest that allopurinol administration can attenuate ROS production during aerobic exercise, and, moreover, allopurinol can even prevent the ROS associated adaptive responses to exercise [24].

Contraction of skeletal muscle results in ROS generation associated with phospholipase A (PLA_2). Indeed, ROS production decreased when various PLA_2 inhibitors were administered to a contracting diaphragm, suggesting that PLA_2 plays a critical role in modulating ROS formation during muscle contraction [25] (Figure 1). Furthermore, it has been suggested that, in the skeletal muscles of patients suffering from Duchenne muscular dystrophy, elevated intracellular calcium levels caused by altered regulation of calcium channels activate PLA_2, causing ROS production and increased membrane permeability [26]. In Duchenne muscular dystrophy, dystrophin is absent, and sarcolemmal neuronal nitric oxide synthase (nNOS) is lost because it is anchored to dystrophin. The absence of nNOS-generated NO could be one of the reasons for increased ROS generation by skeletal muscle of

patients with this atrophy. Indeed, when nNOS is knocked out, higher levels of intrinsic hydrogen peroxidase activity were demonstrated in the extensor digitorum longus (EDL) of nNOS-knockout mice, when compared to C57 control mice [27]. Therefore, nNOS-generated NO could have an important scavenging role in the detoxification of superoxide. Interestingly, Ca^{2+}-independent ($iPLA_2$) beta is involved in membrane repair; suggesting that the interaction between ROS and membrane lipids not only disrupts the cellular milieu and jeopardizes the fate of the cell, but could also be important for the continuous remodeling requirements of cell membranes [28].

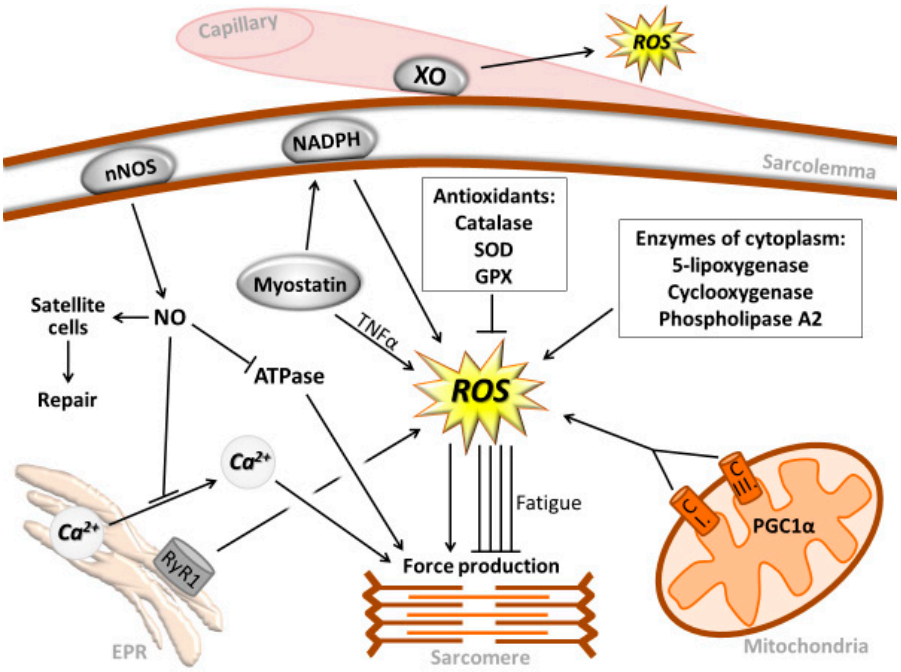

Figure 1. Sources of reactive oxygen species. Summarized potential sources of reactive oxygen species (ROS) in skeletal muscle. H_2O_2 up to a certain concentration enhance the force production of skeletal muscle, while in large concentrations, ROS causes fatigue and suppresses force generation.

Recently, myostatin emerged as a potential ROS-inducing factor, especially during sarcopenia [29]. It has been demonstrated that knocking out the myostatin gene resulted in attenuated loss of muscle mass with aging, and that myostatin can induce ROS production through tumor necrosis factor-α (TNF-α) and NADPH oxidase [29]. However, the role of exercise in myostatin-mediated redox signaling is still unclear and further research is warranted on this topic. Activation of ryanodine receptor 1 (RyR1) in the sarcoplasmic reticulum of skeletal muscle is necessary for Ca^{2+} release and the subsequent generation of cross-bridge-related force production. With the aging of skeletal muscle, a continuous Ca^{2+} leak is observed in RyR1 channels, which is associated with a decreased force production capacity and increased ROS production. Pharmacological intervention to normalize RyR1 function by stabilizing the binding of calstabin1 to RyR1 significantly reduced Ca^{2+} leakage and increased endurance capacity [30].

It has been shown that single and regular bouts of exercise differentially modulate ROS production in neutrophils. During acute exercise the adaptive response is limited, and, indeed, it has been shown that a single bout of exercise results in a loss of mitochondrial membrane potential, e [31]. Marathon running, which is a severe form of exercise, caused cytokines and neutrophil activation markers (myeloperoxidase (MPO) and lactoferrin (LTF), and priming neutrophils and monocytes were secreted and functional after exhaustive exercise [32]. These responses seemed to be overwhelming, inducing antioxidant and anti-inflammatory defenses systems, and preventing exercise-induced

oxidative stress [32]. Therefore, it is quite clear that a single bout of exhaustive exercise induces inflammation [33,34] which can readily lead to oxidative stress.

Muscle contraction generates heat, which has been shown to enhance ROS production [35]. However, ROS production is an essential physiological process for muscle contraction, where it is estimated that H_2O_2 concentrations can increase by 100 nM during contractions [20]. Indeed, whilst it is known that low levels of exogenous H_2O_2 treatment increase force production, e.g., in the diaphragm, the addition of catalase decreases diaphragm force production [2]. This response has been associated with H_2O_2 modulating muscle contraction via Ca^{++} channels [36].

Moreover, it appears that not only Ca^{2+} sensitivity, but also the release of Ca^{2+} is altered by oxidants [37]. On the other hand, it is also known that Ca^{2+}-ATP-ase activity of the sarcoplasmic reticulum is easily depressed by H_2O_2 [38]. Whilst not completely clear, current information suggests that the physiological regulatory role of H_2O_2 is more significant than that of superoxide or hydroxyl radical due to the very shot half-life of the latter two [39]. Furthermore, H_2O_2 can cross the cell membrane, while superoxide ($O\bullet^-_2$) and hydroxyl radicals (•OH) apparently cannot.

NO could also affect the function of skeletal muscle. The synthesis of NO is catalyzed by the enzyme, NOS. NOS converts arginine and molecular oxygen to NO and citrulline in a reaction that requires NADPH, flavin adenine dinucleotide, flavin mononucleotide, and tetrahydrobiopterin as cofactors. The predominant NOS isoform in skeletal muscle is neuronal NOS (nNOS), although skeletal muscle also expresses endothelial NOS (eNOS) and inducible NOS (iNOS). The nNOS is present in the sarcolemma of both extra- and intra-fusal muscle fibers. In addition, nNOS is concentrated at the postsynaptic surface of the mammalian neuromuscular junction of all fibers. Also, whilst eNOS is abundant in skeletal muscle vasculature, iNOS is present at low levels in rodent and human skeletal muscles, and is localized to the sarcolemma through caveolin-3. NO could influence neuromuscular transmission and act as a retrograde signal to modify pre-synaptic function [40]. The effect of NO on contractile function is better known and studied than its role in neuromuscular transmission. However, observations have revealed that NO decreases isometric force, and, in general, decreases force production in skeletal muscle [41]. One of the reasons behind this phenomenon could be that actomyosin ATP-ase activity is reduced by nitrosylation, which is mediated by NO, and results in a decreased force production [42]. Moreover, NO can inhibit Ca^{2+} release from the sarcoplasmic reticulum [43], resulting in a decreased force production. Whilst muscle soreness is associated with marked decreases in maximal force generation, we have shown that NO could be one of the factors that is responsible for this. Significant increases have been shown in NO content with muscle soreness, which correlates with a decreased maximal force production [44]. We hypothesized that an increased NO level with muscle soreness could be a protective mechanism that does not allow high force production, which, due to high muscular tension, can lead to the development of micro-injuries. In addition, elevated levels of NO during muscle contraction could also be responsible for pain. This is a result of NO activating nociceptors that host the calcitonin gene-related peptide (CGRP) receptor, which is activated by NO, thus, causing pain. Moreover, it is well known that muscle soreness causes damage to sarcomeres due to the unaccustomed tension. The damage must be repaired and it appears that NO is involved in the repair process by activating satellite cells [44]. NO induces satellite cell proliferation, which is a crucial process in muscle repair; a process which is absent in patients with Duchenne muscular dystrophy due to a lack of nNOS.

NO is able to significantly interfere with cellular metabolism by decreasing oxygen consumption [45], altering glucose uptake, and controlling vasodilation. With muscle injury and inflammation, NO is generated to a greater extent by macrophages, mostly through the iNOS process. Nuclear factor kappa B (NF-kB), which is one of the master regulators of inflammation by the regulation of transcription of a number of inflammatory proteins, could also regulate the expression of iNOS. NF-kB is a redox sensitive transcription factor, which, besides its role in inflammation, could also alter the transcription of manganese-SOD (MnSOD) [46].

3. RONS-Associated Oxidative Damage and Repair

RONS are very potent inducers of the enzymatic antioxidant system. The extent of oxidative damage reveals the efficiency of antioxidant and oxidative damage repair systems, although it is intriguing that the level of oxidative damage is never zero. This could indicate that the damage might have some physiological roles, such as signaling [46]. It is known that during DNA replication generated errors initiate the repair process, and similar phenomena could happen with the oxidant-generated damage to DNA. The study of skeletal muscle is limited with regards to the effects of RONS. Nonetheless, adequate literature is available to suggest that more studies should be carried out, especially within exercise models. For example, the activity of 8-oxoguanine-DNA glycosylase 1 (OGG1) increased in human rectus femoris muscle after a marathon race [47]. We suggested that the level of 8-oxodeoxyguanosine (8-oxodG) increased in the muscle because of the exercise, which was followed by the induction of the enzyme necessary to repair the mutagenic damage. We have also reported that aging results in an increased level of nuclear 8-oxodG in the skeletal muscle of rats. This increase was prevented by exercise training and the induction of OGG1 [48]. This result led to an interest in measuring the activity of OGG1 and uracil DNA glycosylase (UDG) in white and red portions of the quadriceps muscle [49] because Type I and Type II fibers differ greatly in metabolic rate, as well as in their levels of antioxidant capacity. We found that OGG1 activity increased in the nuclei of red fibers as was expected; but, surprisingly, OGG1 activity decreased in the mitochondria of both red and white fibers. We were puzzled by this phenomenon and, in a related study, found that the export of OGG1 to the mitochondria could be accelerated by exercise training [50]. In other words, a sedentary life-style and/or detraining impairs the transfer of OGG1 into the mitochondrial matrix [50]. We suggest that exercise training results in biogenesis of mitochondria, and provides more accessible membranes for proteins to be transferred into mitochondria after their synthesis in the ribosomes.

It is well demonstrated that red fibers with high oxidative capacity host a substantial enzymatic antioxidant system, and express increased resistance to oxidative stress; whereas white fibers do not. The activity of OGG1 is also higher in red fibers, but significant differences in the activity of UDG in different fiber types are not evident. DNA repair enzymes work as house-keeping enzymes and are designed to decrease the level of oxidative damage for the protection of cells, and to avoid apoptosis and necrosis, as well as mutation. Although DNA suffers a significant attack from ROS, the extent of protein damage is one-fold higher [51]. Oxidized proteins are not repaired in the same fashion as DNA, but, to prevent the aggregation and cross-folding of oxidized defective proteins, the proteasome system is the first line of defense. Again, skeletal muscle is not a very well monitored tissue in the case of the proteasome system. It has been suggested that aging, which results in a very significant loss of muscle mass, does not alter the activity of the proteasome system [52,53] or decrease its activity [51,54]. However, there are reports that caloric restriction and exercise training increase the activity of the proteasome system [48,55]. This suggestion could be important for remodeling the tissues and removing damaged proteins. The response of the proteasome system to exercise is dependent on the exercise loading and the time of sampling [56]. Therefore, the findings must be evaluated accordingly. For example, Sultan and his co-workers [57] have shown that chronic low-frequency electrical stimulation, which induces fast-to-slow transitions of muscle fibers, alters the proteasome system, once again demonstrating the plasticity of skeletal muscle. Lipid peroxidation is not repaired as efficiently as DNA damage (that damage repaired first, which most directly affects the fate of the cell), but iPLA$_2$ beta can repair lipid damage to a certain degree. We have suggested that the limited extent of DNA damage is an important stimulator of gene expression, protein damage, protein turn-over, and lipid damage, and could be important for membrane remodeling [28].

4. The Role of ROS in Exercise-Induced Metabolism

During muscle contraction, there is a significant change in intracellular redox levels, and H_2O_2 concentration is elevated to 100–200 nM. However, an intriguing question is whether this could

help cover the energy cost of muscle contraction. An early study on L6 myotubes showed that H_2O_2 increased the mRNA levels of glucose transporter 1 (GLUT1) and the glucose uptake of these cells [58]. Further, a later study on mouse skeletal muscle showed that repeated contractions increased 2-deoxyglucose (2-DG) uptake roughly threefold in isolated EDL (fast-twitch) muscle. N-Acetylcysteine (NAC), a non-specific antioxidant, inhibited contraction-mediated 2-DG uptake by approximately 50% ($p < 0.05$) compared with control values), yet did not significantly affect basal 2-DG uptake [59]. This suggests that elevated levels of H_2O_2 stimulate glucose uptake of skeletal muscle during exercise [59]. A follow-up study on isolated rat EDL muscle revealed that H_2O_2 also resulted in a dose-dependent increase in 2-DG uptake in isolated EDL muscles, and the maximal increase was threefold over basal levels at a concentration of 600 µM/L H_2O_2. H_2O_2-stimulated 2-DG uptake was completely inhibited by the phosphatidylinositol 3-kinase (PI3K) inhibitor, wortmannin, indicating a crucial role of the PI3K pathway in H_2O_2-mediated glucose uptake during contractions [60]. In addition, it has been reported that H_2O_2 induces phosphorylation of nNOS at the same residue as insulin does, but also stimulates NO production and GLUT4 translocation. nNOS inhibition prevented H_2O_2-induced GLUT4 translocation [61] (Figure 2). Moreover, inhibition of AMP activated protein kinase (AMPK) prevented H_2O_2 activation and phosphorylation of nNOS, leading to a reduction in NO production and significantly attenuated GLUT4 translocation [61]. It is important to note that acute exposure to H_2O_2 or NO increases insulin sensitivity and glucose uptake, while chronic exposure suppresses it, and can easily lead to type 2 diabetes [62]. A significant feature of physical exercise is the cyclic change of adaptive resting periods and exercise periods, with enhanced metabolic processes and ROS production. This cyclic nature is an important part of preconditioning. With increasing exercise intensity, there is an increased dependence on carbohydrate metabolism, which parallels the increased generation of ROS. This is unlikely to be a coincidental phenomenon, based on the direct relationship between H_2O_2, NO levels and glucose uptake of skeletal muscle.

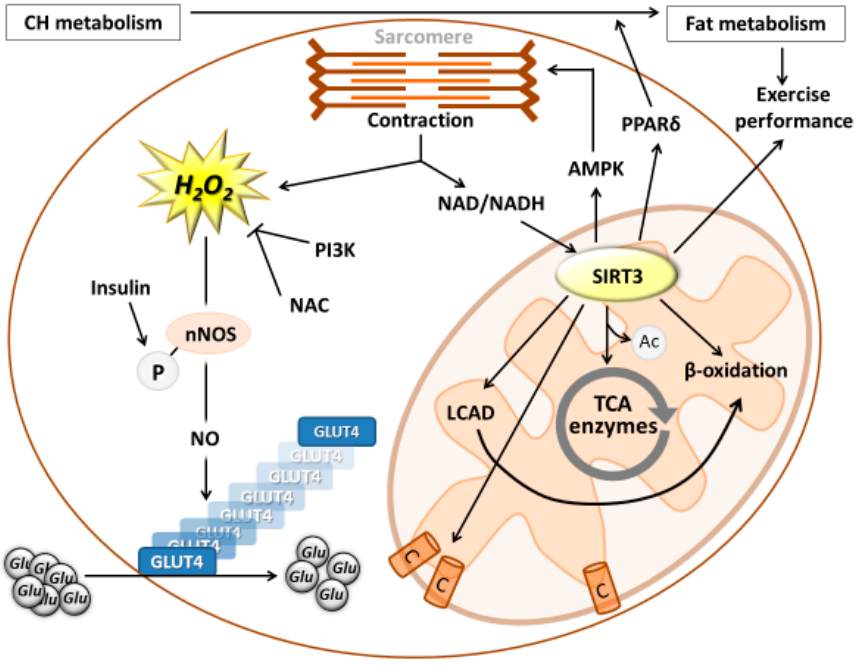

Figure 2. The role of reactive oxygen species on metabolism. H_2O_2 can stimulate cellular signaling pathways to dislocate GLUT4 to cellular membranes, which is crucial for glucose uptake. ROS levels influence the activity of SIRT3, which is an important regulator of fat metabolism.

On the other hand, a pertinent question regarding fat metabolism is whether ROS also regulate the availability of free fatty acids (FFA), and the metabolism of FFA in the TCA cycle. Data suggest

that ROS can indirectly regulate the efficiency of fat metabolism through the enzyme silent mating type information regulation 2 homolog 3 (SIRT3), which is localized in the mitochondria, and NAD-dependent lysine deacetylase. In resting human muscle, total NAD^+ and NADH concentrations are estimated to be ~1.5–1.9 and ~0.08–0.20 mmol/kg dry weight of muscle, respectively [63]. Low intensity muscle contraction increases NAD/NADH concentration. However, the increase in the mitochondrial NAD^+/NADH ratio during the same absolute exercise seems lower in trained rats [64]. The NAD/NADH ratio reflects the redox state of cell or cellular compartments, which directly affects redox sensitive cellular processes, including metabolism, and particularly those enzymes that are dependent on the availability of NAD. SIRT3 is a NAD-dependent mitochondrial enzyme important for ATP production, since it deacetylates and activates a number of key enzymes in the TCA cycle. Indeed, when nicotinamide riboside, a precursor of NAD^+ biosynthesis, was supplemented, high fat, diet induced, nonalcoholic fatty liver disease was reverted, partly by the induction of hepatic β-oxidation and mitochondrial complex content and activity [65]. Moreover, when SIRT3 is knocked-out, there is a marked reduction of fatty acid metabolism due to the hyperacetylation of long-chain acyl coenzyme A dehydrogenase (LCAD) at lysine 42 [66]. These results suggest that SIRT3 is a potential regulator of fat metabolism. We, and others, have shown that exercise increases the level of SIRT3 in humans [67,68] and animals [69].

It has been demonstrated that transgenic mice with enhanced levels of SIRT3 in skeletal muscle exhibit 45% better running-based exercise performance than control animals [70]. In addition, these transgenic animals display a higher proportion of slow oxidative muscle fibers, increased muscle AMPK activation, and peroxisome proliferator-activated receptor delta (PPARδ) expression; both of which are known regulators promoting type I muscle fiber specification [70]. Up-regulation of PPARδ might be important because it can lead to a shift from glucose metabolism to fat metabolism, since PPARδ activation potently suppresses glucose catabolism, without affecting either muscle fiber type or mitochondrial content [71]. Higher levels of aerobic endurance capacity are associated with greater utilization of fatty acids. Indeed, it has been shown that mice with an overexpression of PPARδ had better endurance performance than control mice [71]. Overall, it is well demonstrated that redox sensitive SIRT3 activates the metabolism of fat, and, therefore, can influence exercise performance.

5. Role of ROS in Muscle Hypertrophy and Atrophy

The role of ROS in sarcopenia has seemingly been known for quite some time [72]. However, that role has recently been questioned. Transgenic mice expressing a proof-reading-deficient version of PolgA, the nucleus-encoded catalytic subunit of mitochondrial DNA polymerase, were generated [73]. These mice carried a three- to five-fold increase in the levels of point mutations, as well as increased amounts of deleted mitochondrial DNA [73]. As the consequence of genetic manipulation, PolG mice showed a premature onset of ageing-related phenotypes, such as weight loss, reduced subcutaneous fat, alopecia, kyphosis, osteoporosis, anaemia, reduced fertility, and heart enlargement [73]. However, PolG mice do not exhibit increased levels of mitochondrial ROS production [74], suggesting that in this transgenic model the premature aging is not a result of enhanced ROS production. On the other hand, when the gastrocnemius muscles of six month and 21 month-old rats were studied, it was shown that mitochondria obtained from aged muscle fibers show several functional abnormalities, explaining the enhancedproteolysis, ROS overproduction, and vulnerability to apoptosis exhibited by sarcopenic muscle [75]. In another transgenic mouse model where the Cu-ZnSOD was ablated, the aging process was accelerated in skeletal muscle, leading to a proposal that superoxide-induced neuromuscular junction degeneration and mitochondrial dysfunction are potential mechanisms of sarcopenia [76].

Systemic age-associated inflammation in the skeletal muscle has also been suggested to be one of the causative factors of loss of muscle strength and mass [77–79]. Massive involvement of ROS is suggested in sarcopenia-associated inflammation [78,80], with supporting data coming from a number of studies on aging [81–83]. One observed that inflammatory mediator angiopoietin-like protein 2 (ANGPTL2) increases in the skeletal muscle of aging mice, while exercise attenuates this

elevation [84]. When we compared markers of anabolic and catabolic processes in the skeletal muscle of five month and twenty-eight month-old rats, we observed that aging resulted in decreased levels of follistatin/mTOR/Akt/Erk activation and increased myostatin/Murf1/2, proteasome subunits, and protein ubiquitination levels. In addition, the TNF-α, ROS, p53, and Bax levels were increased, while Bcl-2 levels were decreased in the skeletal muscle of aged rats [85]. We trained rats at an intensity of 60% of VO2max on a treadmill, and this running training attenuated age-associated increases in apoptotic and catabolic processes [85]. From a muscle hypertrophy perspective, it is difficult to cause muscle hypertrophy in laboratory animals. However, one of the most successful models is wing loading on birds. When young and aged Japanese quails were loaded for seven or 21 days to induce hypertrophy, data showed that H_2O_2 content was higher in muscles from aged birds following seven days of loading [86]. Moreover, it appears that loading suppresses pro-apoptotic signaling in quail muscle, but aging delays or attenuates these anti-apoptotic changes [86].

We have also studied muscle hypertrophy. Soleus and gastrocnemius muscles were ablated to cause compensatory hypertrophy on plantaris muscle [87]. Two weeks after the removal of soleus and gastrocnemius muscles we observed about a 40% increase in the muscle mass of plantaris muscle. This hypertrophy was associated with a significant increase in silent mating type information regulation 2 homologue 1 (SIRT1) content and activity ($p < 0.001$). SIRT1-regulated Akt, endothelial nitric oxide synthase, and GLUT4 levels. SIRT1 levels were correlated with muscle mass, paired box protein 7 (Pax7), proliferating cell nuclear antigen (PCNA), and nicotinamide phosphoribosyltransferase (Nampt) levels [87] (Figure 3). These data suggest that the redox state of the cells influences muscle growth, at least in this model. We also found that increased levels of K63 and muscle RING finger 2 (MuRF2) protein could also be important enhancers of muscle mass, and reported that the levels of microRNA (miR)1 and miR133a decrease in hypertrophy, and negatively correlate with muscle mass, SIRT1, and Nampt levels. These data suggest a strong correlation between SIRT1 and overload-induced hypertrophy [87].

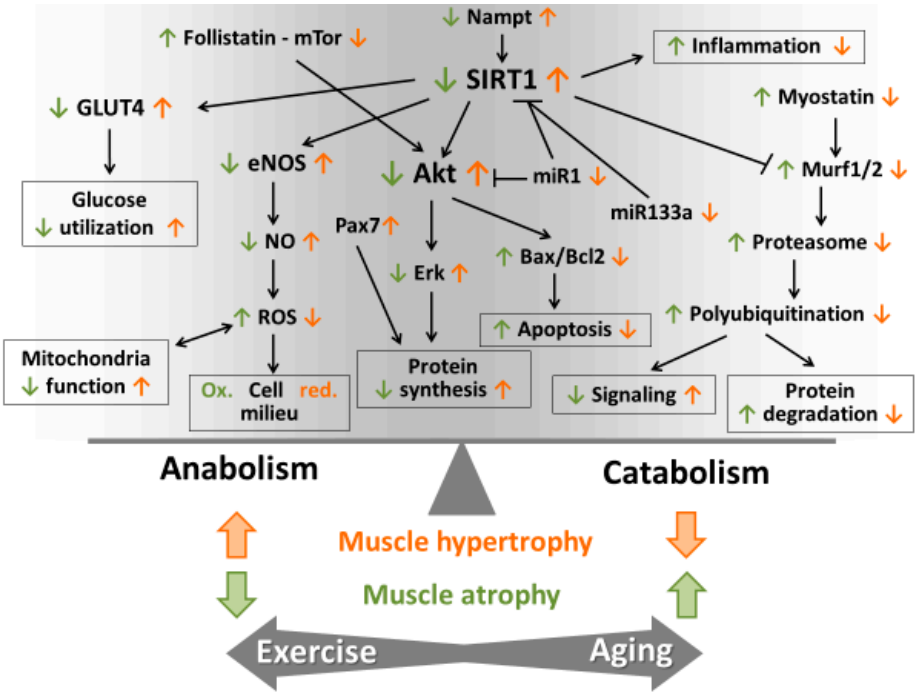

Figure 3. Schematic model of muscle hypertrophy and atrophy. The figure shows the schematic model, the molecular mechanisms of muscle hypertrophy, and age-associated muscle atrophy. SIRT1 is one of the key regulators of anabolic and catabolic processes in skeletal muscle.

6. Conclusions

Reactive oxygen species are continuously generated in contracting skeletal muscle, and their presence is obligatory for normal physiological function. Besides mitochondrial ROS production, XO and NADPH are the main sources of ROS. Moderate levels of ROS regulate metabolic processes in skeletal muscle, especially carbohydrate metabolism, and are also indirectly involved in fat metabolism through SIRT3. ROS-mediated structural changes of lipids, proteins, and DNA, to a degree, could be important for membrane remodeling, protein turnover, gene expression, or epigenetic regulation. Therefore, ROS are important causative or associative factors for sarcopenia and muscle hypertrophy.

Author Contributions: All author participated in reviewing the related literature and R.N., E.K., A.W.T., K.S., F.G., Z.R. wrote the paper.

Funding: This study was supported by OTKA (112810) and National Excellence Program (126823) grants awarded to Z.R.

Conflicts of Interest: Authors declare no conflict of interest.

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