Oxidative stress as a therapeutic target during muscle wasting: considering the complex interactions
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\textbf{Introduction}

Oxidative stress has been considered to be a therapeutic target to reduce skeletal muscle wasting in a range of clinical conditions, but an effective antioxidant therapy has yet to be established. This current opinion of the field (it is not a review) focuses on oxidative stress as a stimulator of protein catabolism to highlight the multifaceted ways in which oxidative stress might stimulate loss of muscle mass. Some interactions have the potential to be complex and this is discussed with respect to signalling pathways. Other interactions may amplify feedback cycles. These possibilities are examined with examples involving calcium and tumor necrosis factor (TNF), with an emphasis on defining the likely in-vivo scenarios.

\textbf{Muscle wasting}

About 40\% of human body mass consists of skeletal muscles, with over 600 individual skeletal muscles involved in all aspects of movement including breathing, eating, posture, walking and reflexes [1]. Muscle is also important for overall metabolic balance and serves as a major source of body heat with resting metabolic rate of skeletal muscle accounting for about 20–30\% of resting whole-body oxygen consumption [2]. Accordingly, when a loss of muscle mass occurs, the effects on the individual are debilitating.

Loss of muscle mass is also described as muscle wasting or atrophy with the term sarcopenia sometimes used for loss of muscle mass and function associated with ageing, and cachexia for situations associated with inflammation. A range of conditions and diseases cause loss of muscle mass, including starvation, disuse, ageing, as well as several pathological conditions such as injury, sepsis, diabetes mellitus, AIDS, and cancer [1,3,4]. Loss of muscle mass is also a consequence of genetically inherited myopathies and neuropathies, such as muscular dystrophy [1,5]. Both systemic and local factors can initiate muscle atrophy. Systemic factors include increased myostatin and glucocorticoids; or a lack of anabolic hormones such as insulin or insulin-like growth factor-1 (IGF-1) [1,3,4,6]. Local factors include muscle...
inactivity, resulting from bed rest or limb immobilization for example; muscle denervation; or elevated calcium and reactive oxygen species (ROS) as commonly observed in muscular dystrophies and ageing [4\textsuperscript{a},7,8,9\textsuperscript{a}].

Loss of muscle mass can result from death of individual myofibers or from a decline in myofiber size (cross-sectional area). Adverse combinations of decreased protein synthesis and increased protein catabolism cause a net loss of protein content and result in decreased myofiber size. Characteristically, levels of oxidative stress are increased in muscle wasting conditions, such as disuse muscle atrophy and ageing, and oxidative stress accelerates age-dependent skeletal muscle wasting [3\textsuperscript{a},4\textsuperscript{a},10]. In the context of loss of protein content during muscle wasting, oxidative stress has been proposed to be a key intermediary in promoting protein catabolism and depressing protein synthesis [4\textsuperscript{a},9\textsuperscript{a},11].

If oxidative stress is a key intermediary in muscle wasting, then an appropriately tailored therapy to minimize oxidative stress has the potential to ameliorate loss of muscle mass in a range of conditions. An effective antioxidant therapy has yet to be established, which may indicate that oxidative stress is not biologically significant, or may reflect a lack of understanding of the diverse nature of oxidative stress [8,12]. In this overview, we examine some of the issues by focussing on oxidative stress as a stimulator of protein catabolism and use selected examples to draw attention to the different ways in which oxidative stress can act to promote protein catabolism. Multifaceted interactions with other factors capable of stimulating the loss of muscle mass are also considered by examining the relationships between oxidative stress, calcium and the proinflammatory cytokine TNF.

**The nature of reactive oxygen species**

Oxidative stress results from the activities of a group of reactive compounds derived from oxygen, collectively called ROS. The term ROS is often used generically, but there are numerous (more than 10) ROS which have a diverse range of actions in cells because the different reactive compounds have differing chemical properties [13\textsuperscript{a}]. We focus on hydrogen peroxide and hydroxyl radicals as examples to illustrate the differing chemical properties of ROS. Both hydrogen peroxide and hydroxyl radicals can be derived from superoxide, which is formed by the one electron reduction of oxygen (Fig. 1).

There are multiple intracellular sources capable of generating superoxide. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase responds to external signals to generate superoxide which then forms hydrogen peroxide as a second messenger [13\textsuperscript{a}]. Other enzymes capable of generating ROS include phenylalanine hydroxylase, cyclooxygenase, cytochrome P450, myeloperoxidase, phospholipases, xanthine dehydrogenase and monomine oxidase. Mitochondria are considered to be a significant source of ROS, which has been linked to muscle atrophy [3\textsuperscript{a},9\textsuperscript{a},13\textsuperscript{a}]. Superoxide can also react with nitric oxide to form highly reactive peroxinitrite, which can damage proteins by modifying tyrosine, methionine and cysteine residues [14]. Superoxide is converted to hydrogen peroxide through the action of superoxide dismutases present in the cytosol and mitochondria. Extracellular sources of hydrogen peroxide can arise from several cell types, with activated neutrophils and macrophages in inflammatory conditions thought to be particularly significant [3\textsuperscript{a},15].

Hydrogen peroxide is considered to be a signalling molecule able to readily cross membranes [16,17]. Hydrogen peroxide modifies protein function by oxidizing the thiol (–SH) groups of redox sensitive cysteine residues to form disulfide bonds with adjacent cysteine residues, glutathione (glutathionylation), or small protein thiols such as thioredoxin. The disulfide can be returned to the thiol form (reduction) through the action of enzymes such as glutaredoxin or the peroxiredoxins [13\textsuperscript{a},17,18]. Enzymes

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**Figure 1** Formation and properties of selected ROS molecules

<table>
<thead>
<tr>
<th>ROS</th>
<th>Properties of interest</th>
<th>Reacts with nitric oxide to form peroxinitrite</th>
<th>Causes formation of disulfide bonds</th>
<th>Primary agent of protein, DNA and lipid damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>O\textsubscript{2} + e\textsuperscript{-} \rightarrow O\textsuperscript{2}\textsuperscript{+}</td>
<td>Negatively charged radical ion (superoxide)</td>
<td></td>
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</tr>
<tr>
<td>H\textsubscript{2}O\textsubscript{2}  + e\textsuperscript{-} \rightarrow \cdot OH + e\textsuperscript{-} \rightarrow H\textsubscript{2}O</td>
<td>Hydrogen peroxide (uncharged, nonradical, relatively stable)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>-OH + e\textsuperscript{-} \rightarrow H\textsubscript{2}O</td>
<td>Hydroxyl radical (highly reactive radical)</td>
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In this overview, the focus is on hydrogen peroxide and hydroxyl radicals as examples of ROS. As shown, these ROS are generated by the sequential addition of electrons. ROS, reactive oxygen species.
capable of degrading hydrogen peroxide are present in the cytosol and mitochondria, and include glutathione peroxidase, catalase and the peroxidoxins [13\textsuperscript{*}].

In contrast to hydrogen peroxide, hydroxyl radicals are highly reactive molecules capable of irreversibly damaging macromolecules including proteins and membrane phospholipids. Hydroxyl radical attack on proteins is generally irreversible and can cause proteins to aggregate, crosslink or fragment. The modification of some amino acid side groups serves as a guide to the extent of oxidative stress (e.g. carbonyl assay) [13\textsuperscript{*},19]. The highly reactive nature of hydroxyl radicals means that they are not amenable to enzymic removal. Consequently, cellular actions are directed towards preventing the generation of hydroxyl radicals (e.g. metal chelation), disrupting damaging chain reactions with small molecular weight antioxidants (e.g. vitamin E) or removing damaged macromolecules (e.g. proteins) [13\textsuperscript{*},20].

The nature of oxidative stress

During physiological homeostasis, an overall oxidative balance is maintained in tissue by matching the production of ROS, from a variety of sources, to removal via a variety of antioxidant systems [13\textsuperscript{*}]. In this environment, ROS serve as signalling molecules to stimulate, or act as second messengers in, a variety of signal transduction pathways.

Disrupting oxidative balance causes oxidative stress [13\textsuperscript{*}] (Fig. 2). However, oxidative stress is an overarching term, the biological response will vary depending on the specific nature of the ROS involved. Hydroxyl radicals cause oxidative damage resulting in muscle dysfunction with irreversibly damaged proteins a target for catabolic proteolysis [21]. Damage to membranes can increase membrane permeability, leading to increased intracellular calcium which, amongst other effects, activates proteases such as calpains. In addition to damage to macromolecules, pathological effects are caused by biological active products that are also formed, such as isoprostanes, malondialdehyde and 4-hydroxynonenal [4\textsuperscript{*},13\textsuperscript{*},22].

In contrast to the irreversible damage caused by hydroxyl radicals, oxidative stress caused by hydrogen peroxide reversibly affects the function of a range of redox sensitive proteins within the cell, including channel proteins, transcription factors and signal transduction proteins [23–25]. In this scenario, oxidative stress is thought to disrupt homeostatic signalling mechanisms and stimulate pathological signalling.

Oxidative stress in vivo has been assessed by a range of techniques including measuring isoprostanes or protein carbonyls in blood, by measuring the ratio of reduced to oxidized cysteine in plasma, or reduced to oxidized glutathione ratios within tissue [13\textsuperscript{*},15,22,26]. It is unclear how well differing measures of oxidative stress reflect the biological actions of the different ROS in vivo.

Involvement of oxidative stress in protein catabolism

Oxidative stress can increase protein catabolism by directly modifying proteins to increase their susceptibility as substrates in catabolic pathways, by increasing the synthesis of key proteins involved in catabolic pathways and by affecting the regulation of catabolic pathways.

Figure 2 A model depicting how different levels of oxidative stress might affect cell function

Increases in oxidative stress cause a hierarchal dysregulation of physiological processes leading to increased protein catabolism, with severe oxidative stress causing cell death. In this model, (a) there are effects on signal transduction proteins (shown as the formation of disulfide) occurring prior to (b) irreversible protein damage (shown as the formation of protein carbonyl). This model also indicates that complete removal of ROS (low oxidative stress) may not be desirable [67]. It is emphasized that this is a theoretical model and its relevance to in-vivo disease remains to be demonstrated. ROS, reactive oxygen species.
These aspects of protein catabolism are examined with the context of proteasomal pathways, proteases and autophagy pathways, which represent the major routes for protein catabolism.

**Proteasome pathway**
Where loss of muscle mass involves decreases in protein content, a major route for protein catabolism is the proteasome pathway (Fig. 3) [3*15]. The proteasome complex (26S), consisting of a core proteasome subunit (20S) and a regulatory subunit (19S), degrades ubiquitinated proteins [3*]. Ubiquitination is a three-step process involving target protein recognition by one of several E3 ligase isoforms, ubiquitin activation (E1 protein) and ubiquitin transfer to the target protein by one of the many E2 isoforms.

ROS can promote protein catabolism via several pathways involving proteasomes. One pathway involves activating a subset of redox-sensitive genes that code for ubiquitin and regulatory E2 and E3 proteins [3*]. In this context, the E3 ubiquitin ligase muscle ring finger-1 (MuRF-1) has been shown to promote the catabolism of myosin heavy chain protein [27**].

ROS can also promote protein catabolism by oxidatively modifying proteins, which enhances their susceptibility to ubiquitination and catabolism by the 26S-proteasome pathway [20]. The ubiquitin 26S-proteasome complex can also be bypassed, since the 20S core proteasome subunit is capable of degrading oxidized proteins without ubiquitination [4*,11,28]. Oxidative damage induces changes in protein structure, through amino acid modification and fragmentation, leading to an unfolding of the protein and a subsequent increase in surface hydrophobicity [29]. The 20S-proteasome has a preference for hydrophobic and aromatic amino acids. Consequently, oxidatively damaged proteins appear to be particularly susceptible to catabolism by the 20S-proteasome because of the increase in surface hydrophobicity [11].

**Proteases**
In addition to the proteasome pathways, proteases such as calpains and caspases can contribute to muscle protein catabolism. Calpains cleave a range of substrates, including proteins involved in signal transduction pathways, membrane proteins and cytosolic enzymes [4*,30]. Calpains do not appear to have a direct role in the catabolism of the contractile proteins, actin and myosin.
but they may be important in releasing proteins for further catabolism by cleaving cytoskeletal proteins that anchor contractile elements [4*,30,31].

Caspases, well known for their role in apoptotic processes, may also contribute to protein catabolism [32,33]. For example, caspases have been implicated in the catabolism of actomyosin complexes [4*]. Most (50–70%) muscle proteins exist in actomyosin complexes and proteolytic release of myofilaments is thought to be required for the proteasome system to degrade contractile proteins such as actin and myosin [4*,25].

**Autophagy**

Autophagy is a general term referring to pathways, which deliver proteins and organelles to lysosomes where they are degraded and their components are recycled. In mammals, three major pathways have been recognized; macroautophagy, microautophagy and chaperone-mediated autophagy (Fig. 3). Autophagy is stimulated in muscle wasting and there is increasing evidence that it is a major route for protein catabolism [34**,35**]. ROS have a role as potential stimulators of autophagy. For example ROS have been identified as signalling molecules in starvation-induced autophagy with oxidative stress activating autophagy by blocking the activity of the protease Atg4 [36**].

**Degree of oxidative stress**

Additional complexity is introduced by the possibility that elevated levels of oxidative stress can decrease rates of protein catabolism. Both 20S and 26S proteasomal activity can be decreased by oxidative stress, possibly due to the formation of cross-linked protein aggregates inhibiting the proteasome [29]. The activities of E1 and E2 proteins can also be decreased by reversible oxidation of thiol groups [37]. Caspase 3 activity is also affected by the degree of oxidative stress, with mild oxidative stress causing activation indirectly and severe oxidative stress causing inactivation [38]. As a consequence, consideration needs to be given to the degree of oxidative stress when evaluating protein catabolism pathways in vivo.

**Involvement of oxidative stress in signal transduction pathways**

Multiple signalling pathways, operating in networks, are likely responsible for maintaining protein balance in muscles [6]. Disease-related changes in ROS have the potential to cause dysfunction by modifying the activities of these signalling pathways. However, there is considerable complexity in the interactions because an array of proteins in signalling pathways has been identified as redox sensitive, these include kinases, phosphatases, and transcription factors (Fig. 4). To draw attention to how potentially complex the interactions of ROS with signal transduction pathways could be, examples involving TNF, apoptosis signal-regulating kinase 1 (ASK1) and Akt [protein kinase B (PKB)] are considered. Note that not all of these interactions have been directly linked to protein catabolism.

For the TNF pathway, ROS is a second messenger, possibly generated from mitochondria, involved in the activation of nuclear factor-kappa B (NF-κB) [3*,24,39–41]. ROS may interact with the pathway by oxidizing inhibitor kappa B-alpha (IκBα), which then releases a NF-κB heterodimer of p65 (RelA) and p50 to promote protein catabolism [33,42,43]. Loss of IκBα is sufficient to promote protein catabolism [42]. Complexity is introduced by the observations that NF-κB, besides promoting protein catabolism also has the potential to reduce oxidative stress by stimulating the production of antioxidant enzymes such as mitochondrial superoxide dismutase [44,45].

Stress activated protein kinase pathways are also activated by ROS and a well described example is ASK1 (Fig. 4) [41,46**]. ASK1 activates Jun N-terminal kinase (JNK) and p38 pathways with the oxidative stress linked to the nuclear localization of forkhead box O (FoxO) family of transcriptional factors [47,48]. FoxO nuclear localization has been shown to promote muscle atrophy, possibly via atrogin-1 and MuRF-1 [25,48].

There is strong evidence that specific phosphatases, which catalyse phosphate removal from signal transduction proteins, can be inactivated by ROS [49,50**]. As a consequence, there is the potential for ROS to indirectly stimulate signal transduction pathways. Taking the Akt pathway as an example, there are several phosphatases in this pathway susceptible to inactivation by ROS, which might be expected to lead to Akt stimulation. One target of the Akt pathway is the FoxO family of transcriptional factors [25]. Inactivation of FoxO (by Akt phosphorylation) blocks the activation of muscle ubiquitin ligases and suppresses autophagy [25,34**,51].

The expectation that ROS would activate the Akt pathway in vivo is not met. Evidence indicates elevated oxidative stress is associated with decreased Akt activation in atrophy of diaphragm muscles and age-related skeletal muscle wasting [52,53]. This inconsistency may indicate that ROS do not significantly impact on the Akt pathway in particular in-vivo disease processes or it may indicate that there are substantially more complex interactions that need to be identified before the impact of ROS on particular signalling pathway such as Akt is understood.

There is compelling evidence that ROS are able to stimulate and modulate numerous signalling pathways involved
in protein catabolism \[3^{*},13^{*},15,54^{*},55\]. Nevertheless, further evidence is required to demonstrate that actions of ROS on signalling pathways are significant contributors to pathology in various diseases leading to muscle wasting. Where ROS is demonstrated to be contributing to pathology, there is potential for novel therapeutic interventions targeted at the proteins in signalling pathways identified as susceptible to oxidative stress.

Interactions of oxidative stress with calcium and tumour necrosis factor

Oxidative stress, calcium and the proinflammatory cytokine TNF are all proposed to promote protein catabolism. These factors also have the potential to interact with each other to enhance protein catabolism.

Interactions with intracellular calcium

Calcium has been identified as a factor stimulating protein catabolism directly by activating calpain and cytosolic calcium concentrations have been shown to lead to an increase in mitochondrial calcium, which drives an increase in ROS production by mitochondria \[57\]. ROS, in turn, can increase membrane leakiness by irreversibly damaging membrane components, such as phospholipids or transport proteins.

Calcium is also of interest because it can stimulate ROS production. Elevated cytosolic calcium concentrations have been shown to lead to an increase in mitochondrial calcium, which drives an increase in ROS production by mitochondria \[57\]. ROS, in turn, can increase membrane leakiness by irreversibly damaging membrane components, such as phospholipids or transport proteins.

Calcium may be the factor initiating the pathology associated with Duchenne muscular dystrophy. In this inherited

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myopathy, a lack of dystrophin has been hypothesized to destabilize the sarcolemma so that mechanical stresses cause an influx of calcium [3,60]. Enhanced ROS production can stimulate protein catabolism and an unchecked amplification cycle has the potential to lead to cell death, since both oxidative stress and elevated calcium are considered to be initiators of cell death by necrosis [61,62]. A further consequence is that necrosis stimulates inflammatory responses, which can further exacerbate oxidative stress and increase intracellular calcium in tissues.

Interactions with tumour necrosis factor
Proinflammatory cytokines such as interleukin 1 (IL-1), IL-6, TNF and interferon-γ are frequently elevated in pathological states characterized by muscle wasting [3,33]. Cytokines can also activate peripheral neutrophils that invade tissues and produce excess ROS [3]. As an example of cytokine interaction, we will focus on TNF because of its well studied role in muscle pathology.

TNF is mainly produced by inflammatory cells such as neutrophils and macrophages, but can also be produced by a broad variety of other cell types including lymphoid cells, mast cells, endothelial cells, skeletal muscle cells (myoblasts and myotubes), cardiac myocytes, adipose tissue, fibroblasts and neuronal tissue [63]. Large amounts of TNF are released in response to lipopolysaccharides, other bacterial products, and IL-1 with TNF-mediated cellular responses including apoptosis, as well as activation of NF-κB and JNK [4,41,64]. In muscle, TNF stimulates muscle catabolism and causes contractile dysfunction [3]. In addition TNF, via JNK, may directly interfere with IGF-1 signalling, which acts to stimulate anabolic pathways and inhibits protein catabolism in muscle [65].

TNF is interesting from an oxidative stress perspective because TNF stimulates the production of ROS, primarily from mitochondria [3,41]. ROS, along with reactive nitrogen species (such as nitric oxide), are thought to be secondary messengers in the signal transduction pathways stimulated by TNF [3,41]. There is also a potential interaction between ROS and TNF synthesis, where the activation of NF-κB by ROS stimulates the synthesis of TNF [41,65]. Since hydrogen peroxide can readily cross membranes, a potential amplification cycle exists where TNF synthesis is also stimulated in adjacent cells and invading neutrophils and macrophages.

Oxidative stress as a therapeutic target
There is considerable in-vitro evidence demonstrating that ROS can promote protein catabolism by direct oxidation of proteins or indirectly by modulating signal transduction pathways. Given the potential for multiple interactions, additional information is required to help understand the in-vivo significance of oxidative stress in protein catabolism and muscle wasting (Fig. 5). For example, does pathological signalling by ROS occur prior to, or is it concurrent with, significant damage of proteins during oxidative stress? The answer to this question would conceivably affect the type(s) of therapy chosen to minimize oxidative stress, particularly if pathological signalling by ROS is a critical step leading to ROS causing damage to macromolecules.

A second issue is how should oxidative stress be assessed in vivo? Assessment of oxidative stress may require multiple measures to reflect the different actions of oxidants. Knowledge of the degree of oxidative stress in vivo would be useful for at least two reasons. Given the different redox sensitivities of cysteine residues there is

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414 Nutrition in wasting disease

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Figure 5 Is oxidative stress a worthwhile therapeutic target?

The diagrams summarize different scenarios involving ROS and the factors described in this review. The biological reality is more complex with the significance of ROS in protein catabolism depending on the disease state. Scenario (a): There is an absolute requirement for ROS to drive protein catabolism, with the actions of TNF and calcium driven by the amplifying effects of ROS. In this scenario targeting oxidative stress is a particularly attractive option. Scenario (b): Oxidative stress is one of a number of factors which are stimulating protein catabolism. There are amplifying effects of ROS but the removal of ROS will not completely prevent protein catabolism. In this scenario, it would be worth pursuing therapeutic strategies to minimize oxidative stress but within context of a combinatorial approach. Scenario (c): Oxidative stress can enhance protein catabolism, but there are more worthwhile therapeutic targets. ROS, reactive oxygen species; TNF, tumour necrosis factor.
likely a hierarchical response to oxidative stress [66]. Models have been proposed where increasing levels of oxidative stress can cause different biological responses as additional proteins become oxidized [54,65,67]. This issue is particularly germane to the proteolytic systems, which can be inhibited at apparently higher levels of oxidative stress. An accurate assessment of oxidative stress would be expected to provide insight into the biological significance of oxidative stress in vivo. Second, understanding the relationship between the nature of oxidative stress and protein oxidation in vivo would be very useful when evaluating the effectiveness of antioxidant therapies.

A third important issue is that the identity and the precise degree to which proteins are being oxidized in vivo is generally unknown because of a lack of specific techniques [68]. Systematic analysis of oxidized proteins could provide valuable insight into the impact of oxidative stress on the overall balance between different signalling pathways in different disease types. Knowledge of the particular proteins causing pathology would also be useful when evaluating therapeutic strategies to reduce the rate of protein catabolism.

Conclusion

Protein catabolism involves multiple proteolytic systems controlled by multiple internal and external signals interacting with signal transduction networks. There is substantial in-vitro evidence demonstrating that ROS can increase protein catabolism. In this context, we have highlighted a number of routes by which ROS could potentially increase the rate of protein catabolism, including enhanced protein catabolism through damage to proteins, modifying the activity of signal transduction pathways and by amplifying feedback cycles. The in-vivo challenge is to generate sufficient information to understand the significance, and nature, of oxidative stress in the complex interplay that leads to muscle wasting.

Acknowledgements

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest
•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 541–542).


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A comprehensive textbook: excellent background on free radicals and the biological consequences of oxidative stress.


Oxidative stress during muscle wasting Arthur et al. 415
416 Nutrition in wasting disease


47 This study examined the mitochondrial ROS-dependent regulation of the phosphoinositols 3-kinase pathway. Pharmacologically inhibiting electron transport chain complex III production of ROS prevented activation of phosphoinositols 3-kinase during macronutrient perturbation, whereas pharmacologically promoting electron transport chain complex III ROS production activated phosphoinositols 3-kinase. Experimental data indicate that H2(O2)2 amplifies the phosphoinositols 3-kinase signal by maintaining phosphatase and tensin homolog in its inactive phosphorylated state.


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63 This study examined the mitochondrial ROS-dependent regulation of the phosphoinositols 3-kinase pathway. Pharmacologically inhibiting electron transport chain complex III production of ROS prevented activation of phosphoinositols 3-kinase during macronutrient perturbation, whereas pharmacologically promoting electron transport chain complex III ROS production activated phosphoinositols 3-kinase. Experimental data indicate that H2(O2)2 amplifies the phosphoinositols 3-kinase signal by maintaining phosphatase and tensin homolog in its inactive phosphorylated state.