INVITED REVIEW

ABSTRACT: Underlying the pathogenesis of chronic disease is the state of oxidative stress. Oxidative stress is an imbalance in oxidant and antioxidant levels. If an overproduction of oxidants overwhelms the antioxidant defenses, oxidative damage of cells, tissues, and organs ensues. In some cases, oxidative stress is assigned a causal role in disease pathogenesis, whereas in others the link is less certain. Along with underlying oxidative stress, chronic disease is often accompanied by muscle wasting. It has been hypothesized that catabolic programs leading to muscle wasting are mediated by oxidative stress. In cases where disease is localized to the muscle, this concept is easy to appreciate. Transmission of oxidative stress from diseased remote organs to skeletal muscle is thought to be mediated by humoral factors such as inflammatory cytokines. This review examines the relationship between oxidative stress, chronic disease, and muscle wasting, and the mechanisms by which oxidative stress acts as a catabolic signal.

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OXIDATIVE STRESS, CHRONIC DISEASE, AND MUSCLE WASTING

JENNIFER S. MOYLAN, PhD, and MICHAEL B. REID, PhD

Department of Physiology, University of Kentucky, 800 Rose Street, Room MS-509, Lexington, Kentucky 40536-0298, USA

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Oxidative stress is involved in the pathogenesis of a number of chronic diseases. In a great proportion of these, muscle wasting contributes to morbidity and mortality. This review examines the role of oxidative stress in the pathogenesis of disease, the systemic or muscle-specific mediators of oxidative stress, and the effects of oxidative stress on muscle tissue.

Oxidative stress is a state wherein the normally well-balanced control of oxidant production and antioxidant activity is disturbed. The sources of oxidants are numerous. Most are derived from enzymatic or chemical reactions that produce superoxide anion, hydrogen peroxide (H_2O_2), or nitric oxide (NO). Once produced, these species undergo conversion to secondary highly reactive oxygen species (ROS) and reactive nitrogen species (RNS), such as hydroxyl radical (OH·) and peroxynitrite ($ONOO^-$). At basal levels, ROS and RNS serve as important regulators of signal transduction and protein function. However, if left unchecked, elevated levels of ROS or RNS can damage critical cellular components such as membrane lipids, structural and regulatory proteins, and DNA. Antioxidants that neutralize excess oxidant production include enzymes that convert oxidants into less damaging or harmless species, and small molecules that serve as oxidant sinks or scavengers.

There is evidence of oxidative stress in the skeletal muscles of patients with chronic disease.[210,253] It is hypothesized that this oxidative stress directs muscle cells into a catabolic state and that chronic exposure leads to wasting.[30,129,148] Oxidative damage may contribute to skeletal muscle dysfunction and mark myofibrillar proteins for degradation.[3,160] Concurrently, oxidants may stimulate expression and activity of skeletal muscle protein degradation pathways.[150] These compounding factors of oxidative stress may ultimately lead to muscle wasting in chronic disease.

Abbreviations: AKT, protein kinase B; ASK1, apoptosis-stimulating kinase; COPD, chronic obstructive pulmonary disease; COX2, cyclooxygenase 2; ECSOD, extracellular SOD; eIF-4E, eukaryotic initiation factor; eNOS, endothelial NOS; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IFN-γ, interferon-γ; IL-1, interleukin-1; JNK, c-Jun N-terminal kinase; NOS, nitric oxide synthase; p38 MAPK, mitogen-activated kinase p38; NADH, reduced nicotinamide adenine dinucleotide; NADPH, reduced nicotinamide adenine dinucleotide phosphate; $p70^{S6k}$, ribosomal S6 kinase; PKC, protein kinase C; PLA_2, phospholipase A_2; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, superoxide dismutase; TNF, tumor necrosis factor; TRX, thioredoxin

Key words: disease; muscle wasting; oxidative stress; reactive nitrogen species; reactive oxygen species

Correspondence to: M. B. Reid; e-mail: michael.reid@uky.edu

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REDOX HOMEOSTASIS

Oxidant Sources. Figure 1 depicts both intra- and extracellular oxidant sources in muscle. Nitric oxide synthase (NOS) catalyzes oxidation of L-arginine to

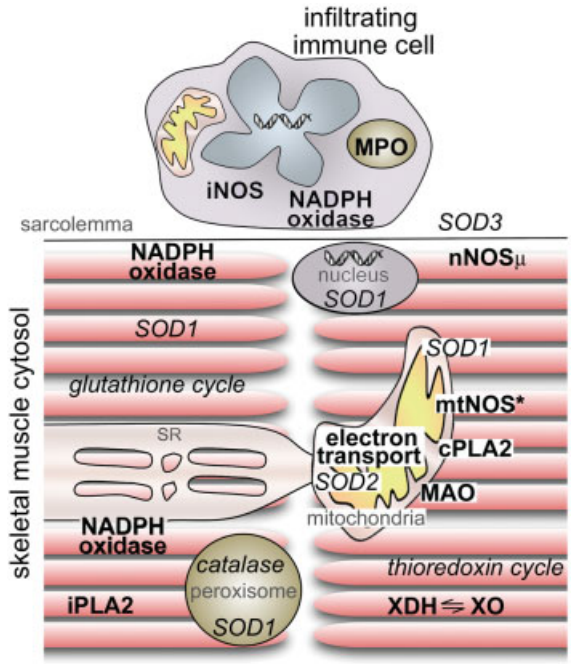

FIGURE 1. Oxidant and antioxidant sources in skeletal muscle. The diagram depicts a skeletal muscle cell (myofibrils shaded in gray) and infiltrating immune cell (irregular nucleus, mitochondria, and lysozome shown) with approximate intra- and extracellular locations of skeletal muscle oxidant and antioxidant sources. Oxidant sources: (1) Immune cell–derived oxidants from cytoplasmic inducible nitric oxide synthase (iNOS), lysosomal myeloperoxidase (MPO), and plasma membrane nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. (2) Skeletal muscle–derived oxidants from sarcolemmal NADPH oxidase; subsarcolemmal skeletal muscle–specific neuronal NOS (nNOSμ); cytoplasmic Ca^{2+}-independent phospholipase A_2 (iPLA2) and xanthine dehydrogenase/xanthine oxidase (XDH↔XO); sarcoplasmic reticulum–localized NADPH oxidase; mitochondria-localized NOS (mtNOS; asterisk indicates hypothetical nature of this NOS isoform), monomine oxidase (MOA), Ca^{2+}-dependent PLA2 (cPLA2), and mitochondrial electron transport. Antioxidant sources: (1) Extracellular-localized superoxide dismutase (EC SOD, SOD3); cytoplasmic glutathione cycle (glutathione, glutathione transferase, glutathione peroxidase, glutathione reductase, and NADPH), thioredoxin cycle (thioredoxin, thioredoxin peroxidase, thioredoxin reductase and NADPH), and CuZnSOD (SOD1); peroxisomal catalase and SOD1; mitochondrial intermembrane space–localized SOD1 and mitochondrial matrix–localized MnSOD (SOD2); and nuclear SOD1.

L-citrulline to release NO. There are at least three NOS isoforms: (1) neuronal NOS (nNOS, NOS1); (2) inducible NOS (iNOS, NOS2); and (3) endothelial NOS (eNOS, NOS3).[240] A fourth mitochondrial-specific isoform may also exist (mtNOS).[75] NOS enzymes function in the peripheral and central nervous systems, cardiovascular and immune systems, and skeletal muscle. The predominant isoform in skeletal muscle is an alternatively spliced form of nNOS, nNOSμ.[236] It is localized to the subsarcolemmal region and associated with the dystrophin complex. Skeletal muscle–derived NO affects excitation–contraction coupling, mitochondrial energy production, glucose metabolism, and regulation of blood flow.[240] In addition to regulatory functions, NO has the potential to negatively impact skeletal muscle. For example, iNOS-derived NO from activated immune cells has cytostatic or cytotoxic properties that are normally targeted to pathogens and tumor cells. However, under chronic exposure NO can also damage healthy tissue, including skeletal muscle.[161]

Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and myeloperoxidase are plasma membrane and lysozomal enzymes, respectively. In neutrophils, monocytes, and tissue macrophages, these enzymes function in host defense (reviewed by Decoursey and Ligeti[54]). NADPH oxidase is a 5-subunit protein complex that produces $O_2^-\cdot$ by catalyzing the transfer of one electron from reduced nicotinamide adenine dinucleotide (NADH) or NADPH to molecular oxygen. There are at least seven NADPH oxidase isoforms and they are expressed in a variety of cell types including epithelium, smooth and skeletal muscles, and endothelium. The non-immune isoforms produce low levels of ROS and may provide second messengers for signal transduction.[134] Skeletal muscle NADPH oxidase associates with several cellular compartments. Immunostaining localizes it near the sarcolemma,[118] but NADPH oxidase activity is also associated with the sarcoplasmic reticulum.[284] It has been proposed that the sarcoplasmic reticulum–associated NADPH oxidase regulates Ca^{2+} release and contraction, whereas the sarcolemma-associated NADPH oxidase may be involved in signal transduction.[284] Myeloperoxidase, found most abundantly in neutrophils, produces hypochlorous acid (HOCl) from H_2O_2 and chloride anion (Cl^-). This toxic oxidant functions as an antimicrobial agent but also has potential tissue-damaging effects when released from the cell.[126] Myeloperoxidase is implicated in exhaustive exercise–induced oxidative stress where skeletal muscle tissue shows increased neutrophil infiltration and elevated myeloperoxidase activity.[186]

Xanthine oxidase and xanthine dehydrogenase are interconvertible forms of the same gene product, known as xanthine oxidoreductase.[20] Xanthine dehydrogenase is the predominant form in mammalian cells, including skeletal muscle. Under pathologic conditions, it can be converted to xanthine oxidase irreversibly by proteolysis or reversibly by cysteine oxidation.[2,47,219] Both enzymes catalyze the formation of H_2O_2,$O_2^-\cdot$, and uric acid from purine substrates such as xanthine and hypoxanthine. Xan-

thine oxidoreductase is a cytosolic enzyme found in liver, intestine, kidney, lungs, heart, brain, plasma, erythrocytes, and skeletal muscle. Liver and intestine xanthine dehydrogenase act to detoxify metabolic byproducts.[20] With acute infections, heat stress, respiratory stress, hypercholesterolemia, and cancer, xanthine dehydrogenase is converted to xanthine oxidase and released into the blood stream. Here it has the potential to cause oxidative damage to tissues such as skeletal muscle.[20,231]

An important source of superoxide is mitochondrial electron transport. Superoxide is generated at both complex I and III of the electron transport chain,[119] but may also be produced by complex II, especially when damaged by oxidative stress or aging.[287] Superoxide generated by mitochondria represents approximately 1% of total oxygen consumption.[21] However, net release of superoxide by mitochondria is much lower due to conversion to H_2O_2 by manganese superoxide dismutase (Mn-SOD) in the mitochondrial matrix and by copper–zinc SOD (CuZnSOD) in the intermembrane space. The resulting H_2O_2 freely diffuses to the cytoplasm and constitutes 20%–30% of the steady-state level.[21,119] In tissues with a higher aerobic rate, such as skeletal muscle and heart, the contribution can be as much as 96%.[21,116] This level is estimated to be 10–100 nM in hepatocytes or as much as 1 μM in breast cancer and melanoma cells.[21] Hydrogen peroxide conversion to damaging radicals such as OH· is catalyzed by non-enzymatic transition-metal reactions, most notably by Fe^{2+} (Fenton reaction[96]). Consequently, oxidants produced in the mitochondria can be targeted to specific cellular locations by the availability and distribution of transition metals that together with H_2O_2 give rise to OH·.[119] This may be a mechanism for precise targeting of ROS to activate signaling pathways or specifically affect myofibrillar components of skeletal muscle cells. Mitochondrial membranes also contain monoamine oxidase. Monomine oxidase catalyzes oxidative deamination, releasing reactive aldehydes and H_2O_2. Monoamine oxidase expression is upregulated in the presence of glucocorticoids and has been implicated in the pathogenesis of glucocorticoid-induced muscle wasting.[166]

Finally, phospholipase A_2 (PLA_2) is a family of enzymes that deacetylate phospholipids releasing free fatty acids such as arachidonic acid.[238] Arachidonic acid is converted to inflammatory leukotrienes and prostaglandins by 5-lipoxygenase and cyclooxygenase, respectively.[39,272] Two PLA_2 isoforms contribute to skeletal muscle ROS. Ca^{2+}-insensitive PLA_2 is essential for basal production of extracellular ROS by 5-lipoxygenase[290] and is important for force production in unfatigued muscle.[84] Ca^{2+}-sensitive PLA_2 activity disrupts mitochondrial electron transport, thereby increasing ROS in response to repetitive contraction.[190]

Antioxidants. Cellular antioxidants consist of oxidant scavengers and antioxidant enzymes that convert free radicals to more benign molecules. Scavengers include vitamins C and E and carotenoids. These molecules are able to donate an electron and neutralize free radicals but are destroyed upon oxidation. Alternatively, thiol-containing compounds such as glutathione and thioredoxin are oxidized by free radicals and rapidly regenerated. Oxidation reactions are catalyzed by glutathione peroxidase, glutathione transferase, thioredoxin peroxidase, and peroxiredoxin. The end result is the formation of glutathione disulfide and oxidized thioredoxin, which are rapidly converted to their reduced forms by glutathione reductase or thioredoxin reductase using NADPH as a cofactor.[32,56] Glutathione disulfide is normally less than 1% of total glutathione but is elevated under severe oxidative stress. As an adaptive response, glutathione content increases upon exposure to heavy metals, high glucose, or heat shock.[131,257,281] Glutathione can also form disulfides with cellular proteins and this *S*-glutathiolation is postulated to have a regulatory function.[176] In addition to control of oxidant balance, thioredoxin also provides a regulatory function by forming disulfides with cellular proteins.[120,267,268]

NO has both oxidant and antioxidant properties. It is thought that NO increases the cytotoxicity of $O_2^{-}\cdot$ by generation of $ONOO^{-}$; however, reports have shown that NO-releasing compounds protect against the toxic effects of $O_2^{-}\cdot$ in fibroblasts and neuron primary cultures.[278] In addition, NO attenuates lipid peroxidation and the metal-catalyzed conversion of H_2O_2 to OH ·,[228,280] promotes the expression of antioxidant enzymes,[123,196] and, via *S*-nitrosylation, enhances the antioxidant activity of glutathione and thioredoxin.[42,93] NO also limits leukocyte adhesion, thereby reducing potential damage from activated leukocytes.[280]

In addition to the glutathione and thioredoxin oxidation/reduction enzymes just mentioned, antioxidant enzymes include SOD, which catalyzes the dismutation of $O_2^{-}\cdot$ to O_2 and H_2O_2. There are three SOD isoforms in humans. CuZnSOD (SOD1) and extracellular SOD (ECSOD, SOD3) use Cu^{2+} and Zn^{2+} as cofactors and are found in the cytoplasm and extracellular space, respectively.[50,169] CuZnSOD is also present in the nucleus, peroxisomes, and

Table 1. Redox, inflammatory state, and muscle wasting in chronic disease.

Disease	Oxidants	Antioxidants	Inflammation	Prevalence of wasting
Myotonic dystrophy	↑ Muscle[255]	↑ Muscle[255]	Unknown	100%[179]
Duchenne dystrophy	↑ Muscle[227]	↓ Muscle[227]	↑ [251]	100%[227]
Malignant hyperthermia/central core disease	↑ [60]	Unknown	Unknown	Equivocal[263]
COPD	↑ [218,264]	↓ [218,264]	↑ ↑ [218]	100%[282]
Kidney disease	↑ [206]	↓ [206]	↑ ↑ [206]	100%[108]
Chronic heart failure	↑ [193]	↓ [193]	↑ [15]	10%–16%[4,234]
Rheumatoid arthritis	↑ [94]	↓ [94,105]	↑ ↑ [23,199]	60%[199,265]
Chrohn's disease	↑ [146,213]	↓ [146,213]	↑ ↑ [146,213]	In young[33,34]
Severe sepsis	↑ [13,18,245]	↑ [13,245]	↑ ↑ ↑ [13,245]	100%[102]
HIV/AIDS	↑ [7,107]	↑ HIV,[246] host[7,107]	↑ [157]	47%[89,164]
Cancer	↑ Host[12,155]	↑ Tumor[176]	↑ [176]	50%–80%[29]
Type 2 diabetes	↑ [109]	↓ [109]	↑ [38]	In elderly[92,275]
Liver disease	↑ [205]	↓ [205]	↑ ↑ [174]	46%[65]
Aging	↑ [19,239,266]	↓ [19,239,266]	↑ [69]	100%[110]
Alzheimer's disease	↑ [180,195,207]	↑ NFT,* Aβ[†195]	↑ [271]	100%[122,177]

Up and down arrows indicate increases or decreases in oxidants, antioxidants, and inflammation in chronic diseases. These are systemic changes unless local sites are indicated. The right-most column indicates the percentage of individuals who experience muscle wasting with each disease. Where percentages are not listed, muscle wasting is present in the subpopulation indicated.
**NFT, neurofibrillary tangles; †Aβ, β-amyloid.*

mitochondrial intermembrane space. ECSOD is secreted from smooth muscle and airway vasculature and has potent anti-inflammatory and ROS-scavenging activity.[71,216,243] MnSOD (SOD2) is the mitochondrial isoform that utilizes Mn^{2+} as a cofactor.[270] Cellular MnSOD content generally parallels aerobic activity and is induced by chronic hypoxia, cytotoxic drugs, and inflammatory cytokines.[124] Under severe stress, such as lung hyperoxia and renal graft rejection, or upon exposure to $ONOO^-$, nitrotyrosine modification of MnSOD causes a loss of both MnSOD protein and activity.[45,162] A second antioxidant enzyme, catalase, decomposes H_2O_2 to H_2O and O_2.[176] Catalase is localized in peroxisomes and functions to remove H_2O_2 during fatty acid oxidation. It is believed to function in oxidant defense by limiting accumulation of cytosolic H_2O_2, which diffuses into peroxisomes and is degraded.

CHRONIC DISEASE

In addition to muscle-specific diseases such as muscular dystrophy, muscle wasting and cachexia are major complicating factors of certain cancers, chronic heart failure, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, liver disease, kidney disease, sepsis, and aging (Table 1). Individuals with these conditions exhibit varying degrees of muscle wasting, which often present as part of a cachectic syndrome that includes anorexia, loss of body weight, and decreased adipose tissue.[28,103]

Muscle-Specific Disease. Myotonic dystrophy is the most common adult form of muscular dystrophy. The disease causes muscle weakness but also affects the central nervous system, heart, gastrointestinal tract, eyes, and endocrine system. The pathogenesis of myotonic dystrophy is still unclear but it has been described as a premature aging disease due to increased oxidative stress.[81,113] The genetic basis of the disease has been identified as myotonin protein kinase. Cells lacking this kinase show increased susceptibility to oxidative stress.[258] Duchenne muscular dystrophy is a severe genetic disease that affects young boys, with onset between 2 and 6 years of age. There is an increase in oxidative stress in dystrophic muscle as indicated by increased DNA damage, protein carbonyls, and lipid peroxidation.[111,191,227] A gene encoding for the muscle protein dystrophin is the causative factor. The function of dystrophin is still debated, but most agree it stabilizes the sarcolemma during contractions.[127] An alternative hypothesis is that dystrophin prevents excessive generation of free radicals.[26] Dystrophin is thought to anchor nNOS to the sarcolemma. In Duchenne dystrophy, nNOS is either dramatically reduced or absent. Because NO regulates antioxidant levels, dysregulation of nNOS may contribute to the oxidative stress and pathological changes associated with the disease.[279]

Malignant hyperthermia and central core disease are related conditions caused, in most cases, by a mutation of the ryanodine receptor. This mutation causes unregulated Ca^{2+} release from the sarcoplasmic reticulum that results in muscular rigidity, increased oxygen consumption, and increased temperature, eventually leading to rhabdomyolysis.[263] Central core disease is an autosomal-dominant dis-

order with variable severity, ranging from lack of visible abnormality to loss of independent mobility. Most patients have muscle weakness during infancy that persists through adulthood, with reduced muscle bulk that may be due to atrophy.[215] Malignant hyperthermia is usually triggered by exposure to volatile anesthesia or stress.[263] There is some evidence that susceptible individuals are more likely to have muscle pathologies such as atrophy and necrosis, but this is controversial.[263] Susceptible individuals also have increased free radicals as measured by electron spin resonance spectroscopy, suggesting that oxidative stress may play a role in the pathology.[60]

Remote Organ Disease. Virtually all patients with COPD, severe sepsis, or chronic kidney disease exhibit some degree of muscle wasting that increases with the severity of disease.[59,100,282] Six hundred million people are afflicted with COPD, which is predicted to be the third largest cause of death and fifth most common cause of disability in the world by 2020.[159] The disease is defined as a progressive, irreversible airflow limitation and an abnormal inflammatory response of the lung.[204] The pathogenesis of COPD is closely linked to oxidative stress. The lungs are exposed to both environmental and cellular oxidants. Environmental oxidants are derived from air pollution, cigarette smoke, and ozone,[125] whereas cellular-derived oxidants are produced by inflammatory and epithelial cells within the lung in response to irritants.[226] The most important factor driving the pathogenesis of COPD is cigarette smoke, which contains high concentrations of oxidants (10^{14} molecules/puff).[44,125] COPD patients also exhibit significant systemic consequences of inflammation and oxidant imbalance with increased plasma lipid peroxidation, oxidized coenzyme Q10, activated peripheral neutrophils, and decreased plasma antioxidants.[218,264]

Patients with chronic kidney disease also have increased markers of oxidative stress and uremia. The wasting that accompanies kidney disease parallels the gradual and progressive loss of the ability to excrete waste, concentrate urine, and conserve electrolytes.[59,108] Both oxidative stress and wasting are exacerbated by dialysis, perhaps due to dialysis-induced inflammation.[206]

The prevalence of muscle wasting is also significant in cardiac patients, where approximately 10%–16% of patients are affected.[234] Inflammation and oxidative stress contribute to the pathogenesis of chronic heart failure.[15,193] Inflammation induces production of tumor necrosis factor (TNF) in both immune cells and myocardium. TNF subsequently suppresses myocardial contractions and induces production of excess oxidants, thus causing further damage to the myocardium.[52]

Inflammation is a major contributor to the pathogenesis of rheumatoid arthritis, a condition that attacks synovial tissue surrounding the joints, leading to cartilage and bone erosion.[199] Oxidants produced by T-lymphocytes cause direct tissue damage and amplify the inflammatory response by inducing production of TNF and interleukin-1 (IL-1).[23] Reduced serum antioxidants predispose patients to rheumatoid arthritis.[94,105] Two thirds of patients with rheumatoid arthritis exhibit muscle wasting that compromises muscle strength and functional capacity.[265]

Finally, redox imbalance and inflammation underlie the pathogenesis of ulcerative colitis or inflammatory bowel disease. The radical induction theory of ulcerative colitis[146,213] states that H_2O_2 produced within colonic epithelial cells is converted to $OH^{\cdot}$, which causes extensive damage to colonic epithelial cells. This damage allows fecal bacteria to invade the submucosal tissue and provoke an immune response. The cause of excess H_2O_2 is thought to be stress related.[87] The first animal model of inflammatory bowel disease was generated by rectal injection of rats with 3% H_2O_2.[235] A more recent model was generated from glutathione peroxidase knockout mice that spontaneously develop a destructive colitis similar to human inflammatory bowel disease.[66] The combination of both disturbances in redox balance and the increased inflammatory state suggests that patients with this condition may also be susceptible to muscle wasting. In support of this idea, a recent study by Burnham et al. demonstrated that children and young adults with Crohn's disease show body composition changes consistent with cachexia, with deficits in both lean and fat mass.[33,34]

Infectious Disease. Dysregulated inflammation and the accompanying oxidative stress are involved in several infectious conditions including sepsis and infection with human immunodeficiency virus (HIV). In sepsis, the blood-borne infection evokes a massive immune response and excessive oxidant and cytokine production by inflammatory cells. Subsequent oxidant and cytokine exposure of muscle and other affected tissue leads to further oxidant production in these tissues.[13,18,245] All patients with severe protracted sepsis exhibit muscle wasting.[102] Compounding the sepsis-related wasting, patients often require mechanical ventilation and bed rest. Even in

the absence of sepsis, these conditions, characterized by decreased muscle use, contribute to redox imbalance, muscle dysfunction, and wasting.[64,259]

Before the use of highly active antiretroviral therapy (HAART), HIV-associated weight loss and muscle atrophy was a major contributor to mortality in the western world and it is still a contributing factor to mortality in regions where HAART is unavailable.[89] In effectively treated patients with undetectable plasma HIV RNA, weight is gained. Unfortunately, the weight gain is primarily adipose tissue, and muscle mass is not restored.[164,175] HIV-1–infected individuals exhibit a disturbed redox balance and a depletion of antioxidants such as glutathione.[7,107] This oxidant imbalance as well as the loss of muscle mass has been attributed to chronic low-grade inflammation.[157] However, an alternative hypothesis has developed since the discovery that HIV-1 encodes a homolog of the human antioxidant enzyme glutathione peroxidase.[246] Human glutathione peroxidase detoxifies peroxide radicals while oxidizing glutathione. HIV–glutathione peroxidase bears structural similarities with the mammalian homolog and both require a selenium cofactor.[288] It is thought that the HIV-1 glutathione peroxidase competes with the host for cofactors and, consequently, compromises host enzyme function while protecting HIV-infected cells against an immune response.[76,158] The depletion of glutathione and selenium cofactor could have a systemic effect that also contributes to redox imbalance in skeletal muscle, thus promoting a catabolic program, as discussed later.

Cancer. Many cancer patients (50%–80%) become cachectic and, in 20%, cachexia is the main cause of death.[252] Cachexia is a syndrome that includes wasting of body energy reserves. The major affected tissues are adipose and skeletal muscle. The loss of skeletal muscle mass is particularly detrimental and contributes to fatigue, loss of strength, mobility, and quality of life. Cancer patients also have a disturbed oxidant balance that appears to be important for carcinogenesis and tumor progression. Antioxidant activity is increased in a broad range of cancer cells including cervical cancer, non–small-cell lung cancer, pancreatic cancer, and hepatoma. Elevated antioxidants correlate with tumor aggression, and may contribute to tumor resistance to host defense mechanisms.[176] Although the cancer cells seem to be effectively protected from oxidative stress, the host is more susceptible and, in animal models, signs of oxidative stress are seen in plasma and other tissues including skeletal muscle.[12]

Metabolic Disease. Other chronic diseases exhibit oxidant imbalances that are critical for pathogenesis but have a more tenuous connection with muscle wasting. In diabetes, wasting may go unnoticed due to reduced severity or may be attributed to complicating factors such as age. In the United States alone, 20.8 million people are affected with diabetes. Of these, 5%–10% have type 1 diabetes. Models of type 1 diabetes show that insulin-deficient animals have accelerated muscle atrophy and increased protein degradation.[182] The remainder and majority of diagnosed individuals have type 2 diabetes. In this case, insulin resistance or inadequate insulin production leads to impaired glucose uptake. Both insulin resistance and type 2 diabetes are associated with muscle wasting in the elderly.[92,275] Oxidative stress may promote development of type 2 diabetes.[109,237] The most important tissues involved in the pathogenesis of diabetes are muscle and adipose tissue. When caloric intake exceeds energy expenditure, a substrate-induced increase in state 3 respiration or an ADP and oxygen limitation–induced shift to state 4 respiration generates an excess of mitochondrial ROS.[22,79] To protect against the harmful effects of ROS, cells may eliminate excess substrate by inhibiting insulin-stimulated glucose uptake.[37,109,198] The ability to maintain redox balance may dictate whether muscle wasting manifests in a diabetic state. Consequently, insulin resistance and diabetes have been associated with muscle wasting in the elderly, a population of individuals with reduced oxidant defenses.[92,275]

Chronic alcohol consumption is also associated with muscle wasting that is evident prior to the onset of liver disease. In a study of 250 alcoholics, 46% exhibited muscle pathology and only 8% had cirrhosis.[65] Free radicals generated during ethanol metabolism can damage many tissues including liver and skeletal muscle. Patients with liver disease due to chronic alcohol abuse have a marked inflammation and oxidant imbalance with elevated uric acid and malondialdehyde, and decreased levels of the antioxidant enzymes CuZnSOD (−86%) and glutathione peroxidase (−37%).[1,65,91,174,194,205]

Aging and Alzheimer's Disease. Aging can be associated with a loss of muscle.[110] A recent study demonstrated that cross-sectional area and specific force are reduced by 16% and 30%, respectively, in the gastrocnemius of elderly men, average age 74 years, compared to young men with an average age of 25 years.[187] Low-grade inflammation is associated with this loss, and individuals with elevated interleukin-6 (IL-6) are more likely to have reduced mass and

strength.[232] Age-related increases in oxidative damage are found in organisms ranging from invertebrates to humans.[19,239,266] In 1956, Harman[97] proposed that ROS formed during normal oxygen metabolism induce macromolecular damage. He proposed that the accumulation of products of oxidative damage accounts for the progressive deleterious changes of aging, a concept reviewed by Terman and Brunk.[247] This hypothesis was named the free radical theory of aging and has been supported by studies showing that age-related changes accelerate with elevated oxidative stress.[11,14,35] For example, mice lacking CuZnSOD display increased oxidative stress and a dramatic acceleration of age-related loss of skeletal muscle mass.[188] These mice have significantly lower muscle mass than wild-type mice as early as 3–4 months of age, and hindlimb muscle mass is nearly 50% lower by 20 months. Alternatively, there is evidence that increasing antioxidant levels can reduce oxidative stress and increase lifespan in nematodes, *Drosophila*, and mice.[133] SOD mimetics, or Mn- and CuZnSOD overexpression, were found to increase the lifespan of nematodes and *Drosophila*, respectively.[178,200,244] Although increasing SOD in mice has no effect, overexpression of thioredoxin significantly increases lifespan.[183] Mitochondria have been implicated as the primary oxidant source during aging.[69] Correspondingly, overexpression of catalase fused to the leader sequence of ornithine transcarbamylase targets catalase to the mitochondria, reduces markers of oxidative stress, and increases the lifespan of transgenic animals by 17%–21%.[233]

Age-related muscle loss is accelerated with pathological conditions such as Alzheimer's disease, which affects 5% of Americans over age 65 and 20% over age 80.[177] One of the earliest events in disease pathogenesis is a systemic oxidative stress, indicated by an increase in isoprostanes, lipid peroxides, and oxidized glutathione in cerebrospinal fluid, plasma, and urine.[195,212,261] These stress indicators often arise prior to the onset of symptoms.[195] Early intervention with antioxidants reduces the risk of developing the disease.[286] The National Institute of Neurological and Communicative Disorders and Strokes Task Force on Alzheimer's disease includes weight loss as a "clinical feature consistent with the diagnosis of Alzheimer's disease." Loss of body weight is typically associated with reduced muscle mass[177] that compromises mobility.[122] Although this weight loss is not a major focus of disease intervention strategies, it is a problem that contributes to reduced quality of life and may be an additional target of oxidant imbalance.

SYSTEMIC MEDIATORS OF OXIDATIVE STRESS

As already discussed, chronic diseases of remote organ systems may exert pathological effects on skeletal muscle. It has been proposed that these effects are mediated by the systemic transmission of oxidative stress from remote organs via radical-inducing substances such as cytokines and metabolic byproducts.

Humoral Factors. There are multiple humoral factors that induce oxidative stress. These include inflammatory cytokines such as IL-1, IL-6, TNF, and interferon-γ (IFN-γ).[172] Cytokines have been implicated in cancer cachexia[73] and they promote oxidative stress and wasting in muscle via several mechanisms (discussed later). Cytokines induce sickness behaviors, such as listlessness, depression, and anxiety, which promote malnutrition and subsequent oxidant imbalance.[167] They also activate peripheral leukocytes that invade tissues and produce excess oxidants. Correspondingly, neutrophils of COPD patients have enhanced ROS production[10] and HIV-1 transgenic mice that develop muscle wasting have increased leukocyte infiltration of muscle.[104] Oxidants produced by infiltrating immune cells may cause direct injury to muscle tissue or activate catabolic signaling. Alternatively, inflammatory cytokines can interact with muscle receptors to initiate catabolic signaling. In the latter case, there is evidence that ROS act as second messengers.[148,149] Accordingly, overexpression of TNF promotes muscle wasting in transgenic mice[41] that can be attenuated by antioxidants including D-α-tocopherol and the NOS inhibitor nitro-L-arginine.[30]

Other humoral factors that may mediate redox imbalances in muscle include glucocorticoids.[249] Glucocorticoids are thought to be important mediators of starvation-induced atrophy[182] and are elevated with atrophy due to reduced activity and cachexia.[115,117,142] Glucocorticoid treatment of cultured human muscle cells results in oxidative stress and mitochondrial dysfunction,[197] while muscles from patients undergoing cortisol treatments have increased oxidative stress, mitochondrial dysfunction, and muscle protein loss.[51,184] Glucocorticoid levels are also elevated during sepsis[95] and treatment of septic rats with the glucocorticoid receptor antagonist RU 38486 reduces muscle atrophy.[283]

Metabolic Byproducts. Byproducts of abnormal metabolic states such as obesity or renal failure may promote oxidative stress in skeletal muscle. For example, overeating leads to glucose and fatty acid overload that

results in excess muscle-derived ROS. Glucose overload in muscle induces excess ROS from glycolysis and mitochondrial oxidative phosphorylation pathways.[27] In addition, skeletal muscle glucose overload could activate NADPH oxidase. This mechanism exists in smooth muscle where high concentrations of glucose lead to an increase in diacylglycerol, which subsequently induces protein kinase C (PKC) to activate NADPH oxidase.[114] Elevated glucose also contributes to oxidant imbalance in plasma through non-enzymatic interactions with plasma constituents.[274] These oxidation reactions result in the formation of isoprostanes and reactive aldehydes.[201,256] In addition to increased plasma oxidants, increased plasma acidity is associated with chronic renal failure, diabetic ketosis, sepsis, and COPD.[36] It has been postulated that acidosis mediates muscle wasting. Chronic acidosis is linked to loss of muscle mass.[62,173] In addition, acute acidosis (blood pH of less than 6.9) in rats and humans fed ammonium chloride is associated with loss of muscle mass.[223] In vitro studies have shown that direct acidification of cultured muscle cells induces protein degradation.[62] However, in vivo measurements in rat models of chronic acidosis have shown that pH is unaltered in skeletal muscle.[9] Therefore, the effects of systemic acidosis on skeletal muscle may be due not to a direct acidification of the muscle, but rather to indirect effects on systemic inflammation or oxidative stress.

In addition, isoprostanes are ROS-catalyzed isomers of arachidonic acid, which circulate in plasma and are excreted in the urine.[211,221] Isoprostanes are used as markers of oxidative stress and are proinflammatory, affecting both monocyte and neutrophil cytokine release, and may play an important role in various chronic inflammatory diseases.[144,145,285] Isoprostanes could activate catabolic pathways in skeletal muscle either directly or through amplification of inflammatory responses.

External Factors. There are a number of other complicating factors that contribute to oxidative stress and may amplify a catabolic response. For example, the treatment of cancer with chemotherapy or radiation produces an increase in oxidative stress both directly and through nausea-induced poor nutrition.[17,154,167,269] In conditions such as chronic heart failure, reduced blood flow leads to oxidative stress.[55] In addition, inactivity as a consequence of illness, leads to the adaptive response of muscle atrophy. Atrophy due to inactivity or immobilization is strongly linked to oxidative stress. Both oxidative damage and elevated ROS have been detected in immobilized muscles of animal models.[129,130]

EFFECTS OF OXIDATIVE STRESS ON MUSCLE

Increased Protein Degradation. Under normal conditions there is a balanced and continuous degradation and resynthesis of skeletal muscle proteins.[181] With oxidative stress, this balance is disrupted. Most studies have focused on increases in protein degradation. It is widely accepted that the ubiquitin–proteasome pathway is the main route by which proteins are degraded during muscle atrophy. This involves the targeted degradation of proteins via modification by ubiquitin and subsequent proteolysis by the 26S proteasome (reviewed by Robinson and Ardley[225]). In addition, the 20S core proteasome can selectively degrade oxidatively modified proteins in a ubiquitin-independent manner.[90] Proteins targeted by ubiquitin are modified through the actions of three types of ubiquitin-conjugating enzymes—E1, E2, and E3. E1 is a ubiquitin-activating enzyme that maintains ubiquitin in a reactive state. To date, only one E1 isoform has been found. E2 is a ubiquitin-conjugating enzyme that catalyzes attachment of ubiquitin to target proteins. There are dozens of isoforms, including skeletal muscle–specific isoforms such as $E2_{14k}$ and UbcH2. The specificity of the system is dictated mostly by E3-ligases. There are over 100 E3 isoforms that function in concert with E2 enzymes to add multiple ubiquitins to target proteins. Three E3 proteins appear to mediate in skeletal muscle catabolism—atrogin1/MAFbx, MuRF1, and E3α. Atrogin1 and MuRF1 are upregulated in a number of catabolic conditions including cancer, diabetes, kidney failure, and sepsis.[143,283]

To dissect the role of oxidative stress and inflammatory mediators on the ubiquitin–proteasome pathway, studies have been performed both in vivo and in isolated cell culture systems, such as mouse-derived C2C12 myotubes. Direct application of H_2O_2 to C2C12 myotubes increases expression of $E2_{14k}$, atrogin1, and MuRF1.[150] These increases correlate with increased ubiquitin-conjugating activity, increased proteasome activity, and decreased myosin protein.[83,150] This response is mirrored by TNF in mouse diaphragm, where the TNF is injected into the intraperitoneal space, or with direct application to C2C12 myotubes.[150] Consequently, it has been hypothesized that ROS may act as a second messenger in TNF-induced muscle catabolism.[148,220] Supporting studies have shown that TNF exposure produces a burst of oxidant activity in C2C12 myotubes, and oxidant levels are elevated in the diaphragm of transgenic mice with cardiac-specific TNF overexpression.[147–149] The source of TNF-stimulated oxidants has not been confirmed, but inhibitors of mi-

tochondrial electron transport can diminish this response.[149] Alternatively, TNF stimulates phospholipase A_2 activity in skeletal muscle[84] and may also stimulate NAPDH oxidase as it does in other cell types.[40] Finally, TNF stimulates iNOS expression in C2C12 myocytes, but this requires costimulation with INF-γ.[276]

Many catabolic regulatory elements are activated by both TNF and ROS. Figure 2 depicts potential pathways activated by ROS in skeletal muscle. These include transcription factor, nuclear factor-kappaB (NFκB), and mitogen-activated kinase, p38 MAPK. NFκB is a ubiquitous factor activated by ultraviolet light, radiation, heat, inflammatory cytokines, and oxidative stress.[120] NFκB is retained in the cytoplasm by the inhibitor protein, IκB. Upon stimulation, it is released from IκB, translocates to the nucleus, and drives transcription of stress response genes including UbcH2.[151] The evidence that ROS is involved in NFκB activation in skeletal muscle includes the observations that treatment of C2C12 myotubes with H_2O_2 stimulates NFκB activity[150] and pretreatment with catalase inhibits TNF-induced NFκB activation,[148] and dietary *N*-acetylcysteine reduces NFκB activity in soleus muscles of mice.[68] The mechanism by which ROS activates NFκB is unknown. Studies have shown that NFκB activation by hypoxia or H_2O_2 is concurrent with tyrosine phosphorylation of IκB, which may trigger NFκB release.[132] More recent evidence has demonstrated that the upstream IκB kinase (IKK) is activated by H_2O_2 to phosphorylate IκB on serines 32 and 36, thus targeting it for ubiquitin conjugation and degradation, allowing for release of NFκB.[78] In addition, direct oxidation of NFκB subunits may enhance activity; oxidation of the p50 subunit of NFκB promotes association with thioredoxin and enhances DNA binding[170,214] (Fig. 2). Circumstantial evidence supporting this model has shown that thioredoxin localization parallels that of NFκB. It is found in the cytoplasm under basal conditions and translocates to the nucleus when cells are exposed to stimuli that promote oxidative stress. Thioredoxin lacks a nuclear localization signal, and it is therefore postulated that thioredoxin is carried into the nucleus via its association with NFκB.[120]

p38 MAPK is activated in skeletal muscle under catabolic conditions such as type 2 diabetes,[128] aging,[277] or exposure to TNF.[152] Studies with p38 MAPK inhibitors have shown that activation is required for subsequent atrogin1 expression and increased ubiquitin-conjugating activity.[152] The mechanism by which ROS activates p38 MAPK in skeletal muscle is also unknown but, as with NFκB, thioredoxin may be involved. Under normal metabolic conditions, thioredoxin binds and inhibits apoptosis-stimulating kinase 1 (ASK1).[230] ASK1 is required for TNF- and oxidative-stress–induced p38 activation during apoptosis of embryonic fibroblasts.[254] Oxidation of thioredoxin causes disassociation from ASK1, ASK1 activation, and phosphorylation and activation of p38 (Fig. 2). It is possible that this pathway functions similarly in skeletal muscle. Because thioredoxin is implicated in both TNF- and ROS-responsive pathways, it may be a critical second messenger in oxidative stress–induced muscle wasting.

Finally, Foxo, a member of the forkhead family of transcription factors, is important for expression of atrogin1 and MuRF1 in a variety of muscle-wasting conditions.[77,242] The extent to which oxidative stress regulates Foxo in skeletal muscle is unknown. However, Foxo activity is modulated by H_2O_2 and by menadione- or heat-shock–induced oxidative stress in mammalian fibroblasts and mouse C2C12 myoblasts.[72] Upon treatment with H_2O_2 or TNF, c-Jun N-terminal kinase (JNK) is activated and phosphorylates Foxo4 on amino acids T447 and T551. This phosphorylation leads to Foxo4 translocation to the nucleus and activation of transcription.[63] In addition, Foxo is negatively regulated by PI-3 kinase/AKT signaling. Stimulation with growth factors activates AKT and results in Foxo phosphorylation and translocation from the nucleus to the cytoplasm.[242] This negative regulation is disrupted by oxidative stress, perhaps via JNK activation, which triggers relocalization of Foxo to the nucleus and subsequent transcription of stress response genes[72] (Fig. 2).

Other protease systems may act in concert with the ubiquitin–proteasome pathway to promote muscle protein loss. For example, lysozomal, calpain, and caspase-3 proteases are activated during muscle atrophy.[101] Both calpain and caspase-3 may play an important role in ubiquitin–proteasome-mediated wasting by promoting release of myofibrillar proteins from the contractile apparatus.[58,82,250] The catabolic function of calpain has been demonstrated using exogenous inhibitors, calpeptin and BN82270, or overexpression of calpastatin to inhibit protein breakdown in septic rats and dexamethasone-treated myoblasts.[67] In addition, caspase-3 activation promotes degradation of actomyosin complexes, whereas inhibition of caspase-3 activity suppresses the overall rate of proteolysis in diabetes- and endotoxin-mediated cachexia.[58]

Reduced Protein Synthesis. In concert with increased degradation, ROS-regulated catabolic signaling may reduce protein synthesis. ROS have been shown to reduce translational activity in Chinese

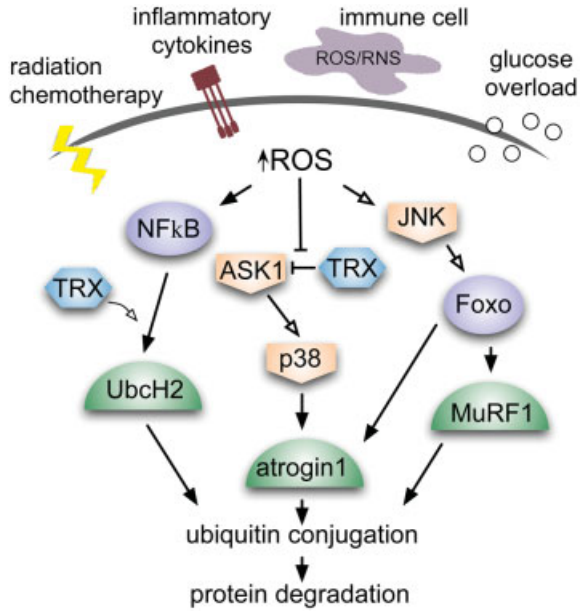

FIGURE 2. Hypothesized pathways for ROS-mediated catabolic signaling in skeletal muscle. Diagram depicts extracellular catabolic stimuli that induce ROS production and hypothesized downstream catabolic signaling pathways in skeletal muscle. Filled arrowheads: known interactions in skeletal muscle; open arrowheads: hypothetical interactions. ROS, reactive oxygen species; RNS, reactive nitrogen species; NFκB, nuclear factor-kappaB; TRX, thioredoxin; UbcH2, ubiquitin-conjugating enzyme E2; ASK1, apoptosis-stimulating kinase; p38, mitogen-activated protein kinase p38; atrogin1, MAFbx, muscle atrophy F-box, muscle-specific F-box protein; JNK, c-Jun N-terminal kinase; Foxo, forkhead box O transcription factor; MuRF1, muscle-specific RING finger 1.

hamster ovary cells; H_2O_2 treatment decreased the activity of translational regulators including ribosomal S6 kinase ($p70^{S6k}$) and eukaryotic initiation factor eIF-4E.[203] In animal models of hindlimb unloading and denervation, increased oxidative stress correlates with a significant decrease in both phosphorylated $p70^{S6k}$ levels and protein synthesis.[80,248] The muscles of rats infused with TNF have reduced eIF-4E activity and reduced protein synthesis.[137] Muscle protein synthesis drops as much as 50% in septic rats.[135] Acute alcohol exposure also impairs skeletal muscle protein synthesis and $p70^{S6k}$ phosphorylation.[136,138] However, it remains to be tested whether impairment in protein synthesis is mediated by the free radicals generated under these catabolic conditions. Catabolic signaling also alters muscle-specific mRNA expression through the destabilization of MyoD protein.[140] MyoD is a muscle-specific basic helix–loop–helix transcription factor that drives expression of genes necessary for induction and maintenance of muscle cell differentiation.[30,139,140] Reduced levels of MyoD could lead to impaired myogenesis and muscle repair. Finally, growth hormone resistance and reduced insulin-like growth factor levels are a significant complication of chronic kidney disease.[217] These reductions in growth factor effectiveness may contribute to muscle wasting via reduced protein synthesis or lack of inhibition of protein degradation pathways.

INTERVENTIONS

Nutrition. Most treatments of chronic disease do little to address the underlying cachexia. Efforts are being made to find interventions specific for prevention or reduction of cachectic symptoms by promoting appetite and preserving lean body mass. Increased appetite can be effectively achieved with cannabinoids and megestrol acetate. However, these treatments have no measurable effect on lean body mass.[202] By contrast, branched-chain amino acid supplementation shows promise (Fig. 3). These essential amino acids (leucine, isoleucine, and valine) stimulate protein synthesis, inhibit protein degradation, and are an important energy source for muscle.[98,260] In animal models, they spare lean body mass during weight loss and promote muscle protein anabolism with aging.[141,224] Results from clinical trials are mixed. Some findings have shown that leucine administration improves nitrogen balance, reduces skeletal muscle catabolism, increases skeletal muscle protein synthesis, and maintains plasma amino acid concentrations.[43] Other trials, however, showed no apparent benefits.[43] The reasons for the mixed results are unclear, but branched-chain

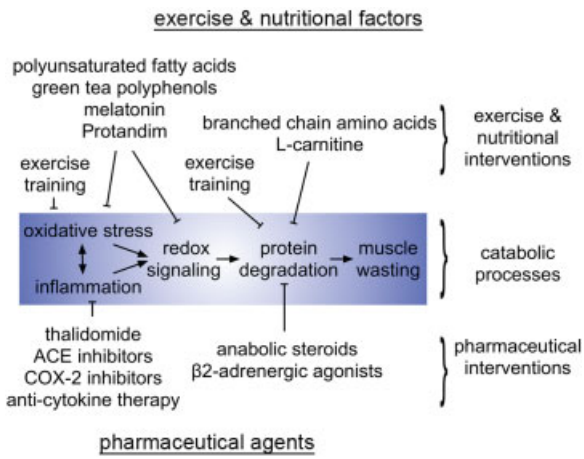

FIGURE 3. Muscle wasting interventions. Diagram shows targets of interventions to alleviate catabolic processes of muscle wasting accompanying chronic disease. **Middle**: catabolic processes; **top**: exercise and nutritional interventions mainly target redox imbalances and protein degradation; **bottom**: pharmaceutical interventions mainly target inflammation and protein degradation.

amino acid supplementation may only be effective for severe catabolic states.

Other promising dietary interventions include fish oil polyunsaturated fatty acids, melatonin, green tea extract polyphenols, and L-carnitine (Fig. 3). COPD and pancreatic cancer patients treated with fish oil capsules showed decreased inflammatory response, increased body weight, and improved strength.[25,273] Melatonin acts as a direct oxidant scavenger and stimulates the activity of glutathione peroxidase, SOD, catalase, and NOS. It has been shown to reduce oxidative stress in diabetic patients[192] and has anti-tumor and anti-cytokine effects that improve survival in patients with advanced cancer.[163] In a study of 100 patients with untreatable metastatic solid tumor,[153] melatonin decreased circulating TNF and significantly reduced weight loss. In a separate study,[208] melatonin combined with fish oil had an additive positive effect when compared with either agent taken individually; 27% of patients responded with weight stabilization or gain when treated with melatonin alone, 38% responded similarly with fish oil alone, and 63% responded to the combined treatment. Although controlled clinical studies on muscle catabolism are lacking, green tea extract improves muscle function and reduces oxidative stress in mouse models of Duchenne dystrophy.[31,57] In addition, green tea extract shows promise as a prevention for diseases where oxidative stress is a factor in the pathogenesis, such as Alzheimer's disease,[70] prostate cancer,[16] and cardiovascular disease.[241]

Reduced L-carnitine levels are associated with the development of cachexia.[262] Accordingly, clinical trials using L-carnitine supplements have been consistently positive (Fig. 3). Of 50 cancer patients treated with L-carnitine (4 g/day for 7 days), 45 showed an improvement of mood and quality of sleep and a significant reduction in their Brief Fatigue Inventory and Functional Assessment of Cancer Therapy–Fatigue scores, indicators of overall fatigue.[88] A second study demonstrated that cancer patients receiving 6 g/day of L-carnitine for 4 weeks had significantly decreased fatigue and increased lean body mass and appetite.[86] L-carnitine supplementation also significantly decreased fatigue and improved muscle mass in studies with 84 elderly subjects[209] and 122 patients with end-stage renal disease.[24]

Pharmaceutical Agents. In addition to dietary interventions, certain pharmaceuticals have been tested for effective prevention of wasting (Fig. 3). Anabolic steroids (oxandrolone and nandrolone) have shown positive effects on muscle mass in patients with HIV infection, COPD, and cancer. Angiotensin-converting enzyme (ACE) inhibitors (captopril and enalapril) reduce weight loss, perhaps as a consequence of decreased circulating TNF.[5,289] The β_2-adrenergic agonist formoterol alleviates cachectic symptoms in tumor-bearing rats and mice. The mechanism appears to be through stimulation of skeletal muscle protein synthesis and inhibition of the ubiquitin–proteasome pathway.[229] However, there are few clinical trials showing efficacy in humans. Several positive studies have shown that patients with chronic heart failure treated with salbutamol for 3 weeks[99] or clenbuterol for 3 months[74] recovered more skeletal muscle mass and strength than the placebo group. In addition, clenbuterol improved rehabilitation time of strength recovery in patients undergoing knee surgery.[165] Cyclooxygenase-2 (COX2) inhibitors have been effective in animal models of cancer cachexia. Inhibition of COX2 by celecoxib or meloxican reversed tumor-induced wasting in colon 26 and adenocarcinoma murine models, respectively.[53,112] In these models, the inhibitors reduced both circulating levels of inflammatory cytokines and protein degradation.

Anti-Cytokine Therapy. Because inflammatory cytokines are important mediators of muscle wasting in chronic disease, it is plausible that anti-cytokine antibodies could prove an effective treatment. Anti–IL-6 therapy reduced fever and cachexia in a single trial of patients with HIV/AIDS-related lymphoma.[61] However, in the majority of clinical trials, anti-cytokine therapies have been ineffective.[222] Positive responses have been seen in animal models of cancer where anti-TNF and anti-IFN antibodies partially reverse protein turnover and decrease levels of ubiquitin–proteasome components.[48,156,171]

In contrast, the immunomodulatory drug thalidomide possesses powerful anti-TNF properties and selectively destabilizes TNF mRNA[185] (Fig. 3). A recent clinical trial of patients with advanced pancreatic cancer showed significant attenuation of loss of muscle mass and improvement of physical function with thalidomide.[85] These patients gained or maintained weight and arm muscle mass, whereas the placebo group lost 4 kg in weight and 8 cm^3 in arm muscle mass. A smaller 2-week trial also showed that thalidomide attenuated weight loss and loss of lean body mass in patients with esophageal cancer.[121]

Combination Therapy. Combination therapy has resulted in encouraging patient responses. For example, based on published and clinical observations, Mantovani et al.[167] developed an anti-inflammatory/antioxidant cocktail that included omega-3 fatty ac-

ids (eicosapentaenoic acid and docosahexaenoic acid), medroxiprogesterone acetate, α-lipoic acid, carbocysteine lysine salt, vitamin E, vitamin A, vitamin C, and the COX2 inhibitor celecoxib. Twenty-five patients with cancer cachexia were treated with this combination for 4 months. This regimen resulted in a significant increase in lean body mass and a significant decrease in ROS, IL-6, and TNF, and quality of life comprehensively improved.

An interesting approach yet to be tested for treatment of muscle wasting was recently shown to be effective in reducing plasma lipid peroxidation in humans. The goal of the study was to increase endogenous levels of antioxidant enzymes.[189] Because of their greater antioxidant capacity, it was suggested that increases in enzyme activity will be more effective than antioxidant supplements. The investigators used a combination of plant extracts that included milk thistle, green tea, and turmeric (Protandim). These extracts individually are reported to increase SOD and catalase activity while decreasing plasma lipid peroxidation. The Protandim was given to healthy human subjects. After 30 days, markers of lipid peroxidation declined 40% ($P < 0.0001$). After 120 days, erythrocyte SOD increased 30% ($P < 0.01$) and catalase increased 54% ($P < 0.002$).

Exercise. Last but not least, exercise is a critical therapy for alleviating muscle protein loss in many conditions including cancer, heart failure, and rheumatoid arthritis[8,106,168] (Fig. 3). The negative effects are few and the benefits are consistent and improve a patient's physical function and quality of life.[6] Exercise-induced increases in muscle mass result in greater strength and reduced susceptibility to fatigue. In addition, exercise reduces inflammatory responses, enhances the activity of antioxidant enzymes, and increases insulin sensitivity, thereby decreasing muscle protein degradation. Endurance training was found to decrease levels of catabolic cytokines in the quadriceps muscle of patients with chronic heart failure.[46] Progressive resistance training in rheumatoid arthritis patients, 2.5 times per week for 12 weeks, added approximately 1 kg in lean body mass, with the majority of that affecting leg mass.[168] Finally, colorectal cancer survivors, who increased their cardiovascular fitness through moderate exercise three times per week, significantly increased their quality of life.[49] Consequently, if tolerated, exercise should be included in nutritional or drug treatment strategies.

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