The Role of Mitochondrial Stress in Muscle Wasting Following Severe Burn Trauma

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Increased resting metabolic rate and skeletal muscle wasting are hallmarks of the pathophysiological stress response to severe burn trauma. However, whether these two responses occur independently in burn patients or are in fact related remains unclear. In light of recent evidence demonstrating that increased proteolysis in skeletal muscle of burned patients is accompanied by mitochondrial hypermetabolism, oxidative stress, and protein damage; in this article, we discuss the evidence for a role for the mitochondrion in skeletal muscle wasting following severe burn trauma. In particular, we focus on the role of mitochondrial superoxide production in oxidative stress and subsequent proteolysis, and discuss the role of the mitochondrion as a signaling organelle resulting in protein catabolism in other cellular compartments following severe burn trauma. (J Burn Care Res 2018;39:100–108)

Skeletal muscle wasting, an undesired loss of skeletal muscle mass, is a hallmark of the long-term pathophysiological stress response to severe burn trauma, which significantly contributes to the long-term morbidity of burn survivors.[1] Patients with a ≥30% TBSA burn can lose up to 25% of their body mass in the first month post injury.[2] In the acute period post burn, muscle wasting is associated with delayed wound healing, while in the long-term, muscle wasting is associated with reduced muscle strength and function.[1] From a physiological perspective, muscle wasting in burn patients results from an increase in the rate at which muscle protein is broken down. In fact, the synthetic rate of skeletal muscle proteins is also elevated in burn survivors, which may be consequence of enhanced proteolysis increasing intracellular availability of amino acids.[3–5] However, the magnitude of this increase in muscle anabolism is lesser than that of increased protein breakdown. This results in a net loss of protein from skeletal muscle of burn patients, even when aggressive nutritional support is provided.[6]

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While our understanding of the pathophysiological stress response to severe burn trauma has significantly improved in the past few decades,[1] the mechanisms underlying chronic skeletal muscle wasting in response to burn trauma remain poorly understood, particularly at the cellular and molecular levels. Several clinical studies have been undertaken to help improve outcomes by attenuating muscle wasting in burn patients.[7–21] However, these studies have typically focused on augmenting muscle protein synthesis to better match elevated protein breakdown after burn. In our view, there is still a need to better understand the cellular mechanisms underlying burn-induced skeletal muscle proteolysis to devise new strategies that mitigate this deleterious response and hasten the recovery of burn survivors.

Hypermetabolism (increased whole body oxygen consumption) is another hallmark of the stress response to severe burn injury.[1] The destruction of the body's skin barrier and subsequent adrenergic stimulation accompanying a large burn necessitates a hypermetabolic response, which principally serves to fuel wound healing, fight infection, and maintain core temperature.[1] Whether this hypermetabolic response is linked to muscle wasting in burn patients is unclear. Hart et al[22] have previously reported a significant correlation between the degree of hypermetabolism and magnitude of amino acid loss from the leg in severely burned patients. However, because there is a clear link between the degree of injury (ie, TBSA burned)

and both hypermetabolism and muscle catabolism, it remains difficult to discern whether hypermetabolism directly contributes to muscle wasting post burn.

Skeletal muscle is a significant contributor to resting metabolic rate in both healthy individuals[23] and severely burned patients.[24] Indeed, in patients with massive burns, skeletal muscle oxygen consumption rates can double.[25] The mitochondrion is the cellular organelle responsible for the vast majority (~90%) of cellular oxygen consumption.[23] Given the central role of mitochondria in oxidative phosphorylation and thermogenesis, it is perhaps not surprising that burn patients muscle mitochondria have been estimated to consume approximately 50% more oxygen than those of an average healthy individual,[26,27] at least in the first few months post injury. While hypermetabolism, altered mitochondrial function, and muscle wasting are well-documented facets of the stress response to severe burn trauma, few studies have sought to determine the roles of hypermetabolism, and in particular mitochondrial hypermetabolism, in burn-induced skeletal muscle wasting.

Following severe burn trauma, chronically elevated respiration rates predispose mitochondria to stress in tissues such as skeletal muscle, which can increase protein oxidation and contribute to activation of mitochondrial unfolded protein stress response (mtUPR). Indeed, due to their central role in oxidative phosphorylation, mitochondria are the principal sites of cellular reactive oxygen species (ROS) generation.[28] Increased electron transfer to support oxidative phosphorylation is accompanied by an obligatory leak of electrons from the electron transport chain at sites other than the heme domains of cytochrome C oxidase, ultimately resulting in increased formation of superoxide anions ($O_2^{\bullet-}$). Greater $O_2^{\bullet-}$ production can contribute to the inhibition of mitochondrial aconitase (mtAcn), because mtAcn is sensitive to the presence of ROS and in particular, $O_2^{\bullet-}$.[29,30] Inactivation of mtAcn has been shown to enhance hydrogen peroxide (H_2O_2) production and iron (Fe^{2+}) accumulation, which drives the Fenton reaction.[30,31] Specifically, through the Fenton reaction, mtAcn is a major source of hydroxyl radical ions ($^{\bullet}OH$), a particularly damaging ROS implicated in protein oxidation.[31,32] Therefore, persistent mitochondrial hypermetabolism in response to burn trauma increases the production of "byproducts" of electron transfer, namely $O_2^{\bullet-}$ and $^{\bullet}OH$. The continuous generation of $O_2^{\bullet-}$and $^{\bullet}OH$ endanger both the mitochondrial proteins and other structures within the cell.[2,33] Indeed, as we will discuss in detail below, this mitochondrial stress response can also be relayed to other cellular compartments, therefore contributing to increased protein damage in other parts of the cell (Figure 1).

Although mitochondria are normally capable of eliminating ROS and damaged proteins, the magnitude and persistence of the hypermetabolic stress to severe burns may overwhelm the mitochondrial quality control system.[28,34] In the present review, we discuss recent data regarding the response of skeletal muscle mitochondria to hypermetabolism in burn patients, and the role of mitochondrial stress in skeletal muscle catabolism. Moreover, we propose a hypothesis whereby mitochondrial hypermetabolism and subsequent oxidative stress contributes to muscle wasting in patients with severe burns. Finally, we will briefly discuss the utility of strategies aimed at mitigating muscle wasting in response to severe burn trauma by blunting oxidative stress.

BURN TRAUMA INDUCES MITOCHONDRIAL STRESS IN SKELETAL MUSCLE

Increased $O_2^{\bullet-}$ and $^{\bullet}OH$ production in skeletal muscle of burn patients predisposes mitochondrial proteins to proteotoxic stress.[2] Accumulation of damaged and/or misfolded proteins results in mitochondrial dysfunction, as seen in skeletal muscle of burn patients,[26,27] which may in turn potentiate further ROS production. A mtUPR is activated when proteotoxic stress exceeds protein-folding capacity of chaperones. A nuclear response is then initiated to import new replacement proteins to re-establish homeostasis within the mitochondrial protein-folding environment.[2,35,36]

In response to mitochondria proteotoxic stress, several regulatory transcription factors such as C/enhancer-binding protein (EBP) homologous protein (CHOP) and CCAAT/EBP β (C/EBPβ) are activated.[37,38] CHOP is induced early during mitochondrial stress, because it contributes to the transcription of heat shock protein (HSP60) to prevent aggregation of oxidatively damaged and unfolded proteins.[37,39] Along with the upregulation of CHOP and C/EBPβ, elevated c-jun n-terminal kinase 2 (JNK2) and activator protein-1 (AP-1) has been reported in response to mitochondrial stress in vitro.[37,38] The ultimate goal of the activation of these transcription factors is to increase the production of nuclear-encoded mitochondrial chaperones, such as HSP60 and HSP10. Increased production of these chaperones facilitates the assembly of new proteins in the mitochondria to meet increased protein demands in the face of greater protein misfolding and degradation.[2,37,39]

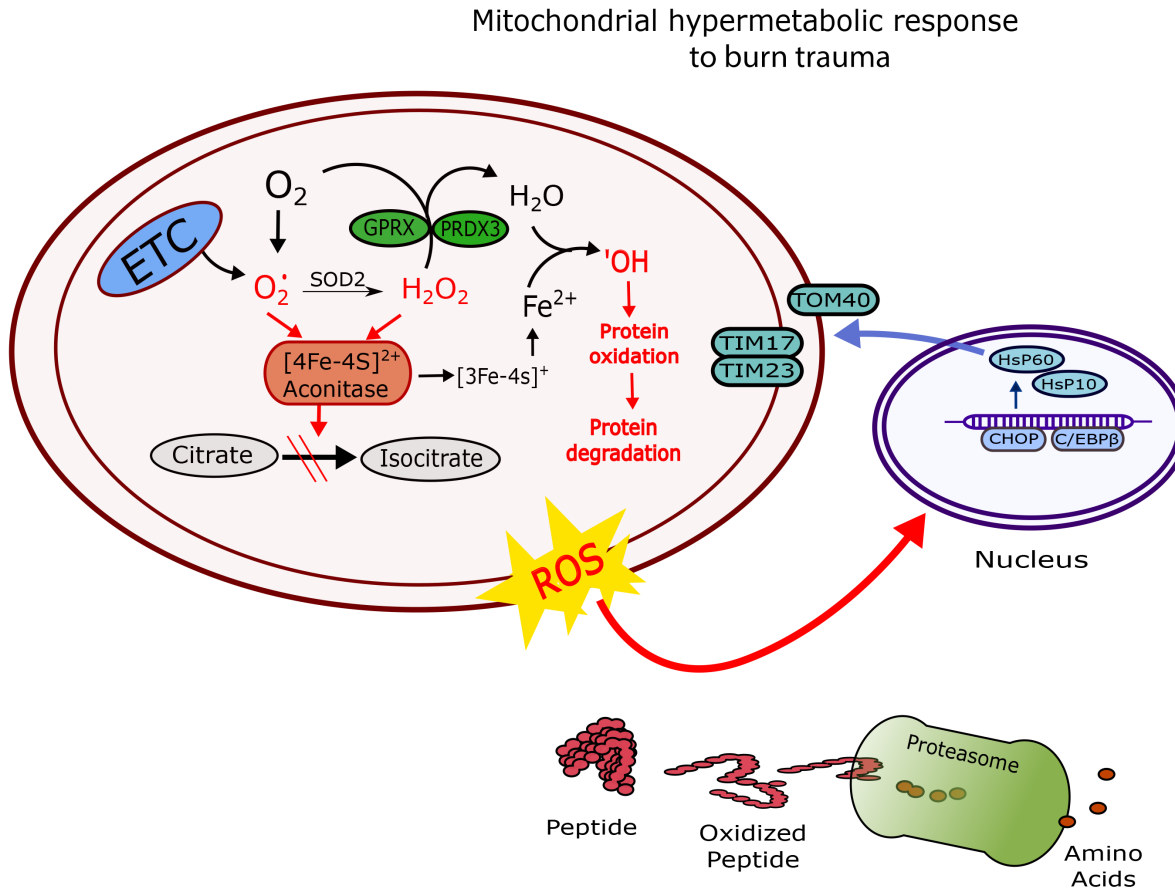

Figure 1. Schematic overview of the mitochondrial stress response to burn trauma in skeletal muscle. ETC, electron transport chain; $O_2^{\bullet-}$, Superoxide ion; $^{\bullet}OH$, hydroxyl ion; PRDX3, thioredoxin-dependent peroxide reductase; GPRX, glutathione peroxidase; HSP, heat shock protein; TOM, translocase of the outer membrane; TIM, translocase of the inner membrane; CHOP, C/enhancer-binding protein homologous protein; C/EBPβ, CCAAT/enhancer-binding protein β.

Interestingly, we have recently shown increased mRNA expression and protein concentrations of a number of mediators of the mtUPR response in skeletal muscle of severely burned patients.[2] Specifically, we reported the increased transcription of JNK2, Lon peptidase 1 (LONP1), c-JUN, CHOP, C/EBPβ, C/EBPα, HSP60, ATP-dependent Clp protease (CLpP), JUNB, and Activating transcription factor 6 (ATF6) mRNA, and elevated relative protein expression of LONP1, CHOP, and HSP90 in muscle of burn patients. This mtUPR was accompanied by a concurrent increase in whole body hypermetabolism, skeletal muscle mitochondrial hypermetabolism, oxidative stress, and marked skeletal muscle catabolism.[2] Collectively these data suggest that mtUPR is activated in skeletal muscle of burn patients in response to hypermetabolism and increased oxidative stress, and likely functions to prevent mitochondrial protein aggregation, dysfunction, and ultimately, mitophagy. However, it is important to note that while HSP60, CLpP, and LONP1 are specific to the mitochondrion, the majority of the transcription factors induced in skeletal muscle following burn trauma are not. Thus, while these data support the notion that a mitochondrial stress response is mounted in skeletal muscle of severely burned individuals, they also suggest a more global stress response that likely effects multiple cellular organelles.

MITOCHONDRIAL STRESS: TRANSMISSION TO THE CELL CYTOSOL

Cellular ROS are predominantly produced within the mitochondrion.[28] A potentially deleterious outcome of prolonged mitochondrial hypermetabolism following burn trauma is the generation and transduction of mitochondrial ROS into the cell cytosol; a concept supported by the recent study by Maharjan et al,[40] who demonstrated that the transmission of mitochondrial stress to the cell cytosol is feasible.

These researchers further showed that treating cells with mitochondrial-targeted antioxidants and antioxidant enzymes attenuated cellular damage and protected cellular integrity.[40] Furthermore, Kirstein et al[41] demonstrated the transduction of redox state and peroxide between tissue (neurons and muscle) and between organelles (endoplasmic reticulum [ER] and cytosol) in vitro and in vivo. Collectively, these studies suggest that mitochondrial ROS production can result in oxidative damage in other cellular compartments/organelles.

In the skeletal muscle of patients with severe burns, we have recently reported profound oxidative stress, induction of cytoprotective transcription factors, antioxidants, and cytosolic proteasomes (i.e., the 26S proteasome).[2] Interestingly, we also reported higher mRNA level of nuclear factor erythroid 2-related factor 2/nuclear factor (erythroid derived 2)-like 2 (NFE2L2) and NFE2L1 transcription factors.[2] NFE2L2 is known as a transcription factor responsible for protection of cells from oxidative stress.[2,42,43] Activation of NFE2L2 protects cells from mitochondrial ROS by up regulating nuclear respiratory factor1 (NrF1) and peroxisome proliferator-activated receptor γ co-activator 1α.[43] Cell in the cytoplasm, NFE2L2 dissociates from kelch-like ECH-associated protein 1 (KEAP1) in the presence of oxidative stress to activate antioxidant defense transcription factors and ubiquitin proteasome pathways, which facilitates the neutralization of excess oxidants and the degradation of denatured proteins, respectively.[44–46] Elevated mRNA levels of both NFE2L2 and KEAP1 in skeletal muscle of patients with burns provide evidence that oxidative stress is transmitted from the mitochondrion to the cell cytosol.[28]

The degradation of damaged proteins is performed by the proteasomes in the cell cytosol, a process which can be induced by oxidative stress.[47] In agreement with Majetschak et al,[48] who reported higher levels of 20S proteasomes in the plasma of patients with severe burns, we recently demonstrated the upregulation of proteasomes in skeletal muscle of severely burned individuals, which was accompanied by the accumulation of damaged proteins, indicating greater protein oxidation and degradation in skeletal muscle of burn patients.[2] Collectively, these data are consistent with the hypothesis that hypermetabolism-induced mitochondrial ROS can be transmitted to the cytosol, resulting in protein damage and breakdown.

The above observation may have important physiological implications. Specifically, skeletal muscle wasting in response to severe burns has long been thought to function to provide substrate (amino acids) for other important processes in the body (i.e., the acute phase response and wound healing), suggesting that the process of skeletal muscle protein wasting post burn is not futile or inefficient, and likely serves an important function in the healing process. Thus, attempting to block this response may in fact be facile if adequate counter measures to support the bodies' enhanced demand for amino acids are not provided. However, if a portion of muscle proteolysis following burn trauma results from the oxidative damage of cytosolic proteins, then this component of the proteolytic response to burns may indeed be wasteful, and therefore could represent a potential target for further therapeutic manipulation. Crucially, this would not carry the same constraints as strategies targeting proteolysis per se.

INCREASED MITOCHONDRIAL PROTEIN TURNOVER IN SKELETAL MUSCLE OF BURN SURVIVORS

The integrity of mitochondrial proteins is of obvious importance. Mitochondria exposed to unabated ROS will accumulate damaged proteins, ultimately impairing their function. Thus, mitochondria must protect their proteins from the potentially harmful effects of ROS. Mitochondria use various means to ensure the quality of their protein components.[49,50] However, proteasomes responsible for the degradation of oxidative damaged and misfolded proteins are present only in the cell cytosol.[51] Subsequently, mitochondria are equipped with specialized proteolytic systems responsible for the degradation of damaged mitochondrial proteins before they aggregate and cause dysfunction.[50]

The mitochondrial AAA protease family of proteases, LONP1, YME1 Like 1 ATPase (YME1L1), and CLpP, play critical roles in mitochondrial protein turnover.[5,10] LONP1 facilitates the degradation of oxidized and misfolded proteins within the mitochondrial matrix, while YME1L1 is localized in the mitochondrial inner membrane, where it carries out a similar function to LONP1.[49,51,52] CLpP also resides within the mitochondrial matrix.[52] CLpP is also responsible for the degradation of misfolded proteins and participates in the activation of mtUPR within the mitochondrial matrix.[53]

LONP1 and CLpP are responsible for selective degradation of mitochondrial matrix proteins, preventing the aggregation of damaged proteins.[54,55] Bezawork-Geleta et al[55] tracked the fate of ornithine transcarbamylase (OTC-Δ), a mitochondria UPR^{mt}-specific protein, in mammalian cells to determine the role of CLpP and LONP1 in the degradation of unfolded mitochondrial proteins.[39] Their data

demonstrated that LONP1 plays a more important role in degrading OTC-Δ, suggesting that LONP1 may be a more important player in mitochondrial protein degradation.[55] Furthermore, in addition to degrading unfolded proteins, LONP1 has been shown to degrade oxidatively damaged mitochondrial proteins such as aconitase.[29,32] However, we should note that while CLpP may not play as an important role in degrading OTC-Δ, it may be critical for the removal of other damaged mitochondrial proteins.[56,57] Indeed, Zhao et al[39] demonstrated that CLpP protein is upregulated following accumulation of unfolded protein in mammalian cells.

In addition to LONP1 and CLpP, YME1L1, which is localized within the mitochondrial intermembrane space, plays an important role in mitochondrial protein turnover. Protein quality control in this compartment of the mitochondrion is of paramount importance, particularly when considering that it is the site of electron transfer and oxidative phosphorylation. Accordingly, the phospholipid membranes and the transmembrane protein complexes that reside within them are particularly susceptible to oxidative damage. The role of YME1L1 in protein turnover in the mitochondrial intermembrane space is well documented.[58,59] A recent report by Rainbolt et al[58] demonstrated that oxidative stress reduces YME1L1 levels and function, which sensitizes cells to oxidative stress. Furthermore, the loss of YME1L1 in mouse embryonic fibroblast cells results in elevated mitochondrial fragmentation and leads to significant increased mitochondrial fusion,[59] suggesting a critical role for YME1L1 in mitochondrial proteostasis and function.

Recently, we reported that the expression of YME1L1, LONP1, and CLpP were upregulated in skeletal muscle of patients with severe burns.[2] Furthermore, we found that LONP1 protein abundance was about 60% higher in burn patients skeletal muscle compared with healthy controls.[2] Interestingly, we report here that LONP1 mRNA levels are positively correlated with increased leak of mitochondrial respiration in skeletal muscle of burn patients (Figure 2), supporting an association between hypermetabolism and mitochondrial protein turnover. We hypothesize that the significant increase in transcription of these mitochondrial proteases reflects an adaptive response to prevent aggregation of damaged proteins within the mitochondrion. Collectively, these data suggest that persistent mitochondrial hypermetabolism seen in patients with severe burns results in oxidative stress, induction of mitochondrial proteases, and increased mitochondrial protein breakdown in skeletal muscle.

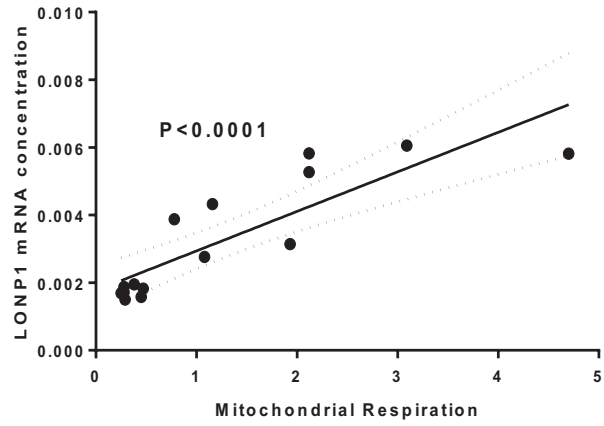

Figure 2. The relationship between Lon peptidase 1 (LONP1) transcription and mitochondrial hypermetabolism in skeletal muscle of patients with severe burns. Greater mitochondrial hypermetabolism in response to burns is associated with greater transcription of the mitochondrial peptidase LONP1. Raw data were originally published in reference 1.

DOES MITOCHONDRIAL PROTEIN DEGRADATION IMPACT CYTOSOL PROTEIN TURNOVER IN SKELETAL MUSCLE OF BURN PATIENTS?

The increased mitochondrial protein turnover in skeletal muscle of burn patients may have important implications for protein homeostasis in the rest of the cell. Since ~98% of mitochondrial proteins are encoded in the nucleus and thus synthesized outside of the mitochondrion,[35,49,50,61–63] mitochondrial and cytosolic protein turnover are closely linked, where increased mitochondrial protein degradation must be met by an increase in synthesis and transport of new proteins into mitochondria. Indeed, the vast majority of proteins that constitute the electron transport chain are imported from the cell cytosol.[64] Thus, the maintenance of the mitochondrial protein pool is heavily dependent on the nucleus and protein availability within the cell cytosol.[35,65] Therefore, it is logical to suppose that increased stress-induced mitochondrial protein degradation in skeletal muscle of burn patients likely contributes to skeletal muscle wasting by diverting resources away from the synthesis of myofibrillar proteins.

Transport of mitochondrial proteins depends on loosely assembled nuclear-encoded proteins from the cell cytosol.[62,66] The specialized translocase complex on the outer mitochondrial membrane that interacts with newly synthesized preproteins is known as the translocase of the outer membrane (TOM) complex.[66] After translocation of the preproteins through the TOM complex, they proceed into the

mitochondrial matrix by interacting with and moving through the inner mitochondrial membrane via the translocase of inner membrane (TIM) complex.[62,66,67] Besides these translocase protein complexes, translocation of the preproteins through the inner membrane space also depends on the presence of HSP70, co-chaperone Mge1, ATP hydrolysis, and an appropriate mitochondrial membrane potential.[66] In the mitochondrial matrix, processing peptidases selectively remove presequence amino acids and the proteins are folded into mature peptides with or without the help of chaperones.[62,66]

In line with increased expression of mitochondrial proteases and increased mitochondrial protein degradation, we found that mitochondrial membrane translocase proteins (TOM40, TIM23, and TIM17), responsible for protein transport into the mitochondria, were also upregulated in skeletal muscle of burn patients.[2] We suggest that increased protein expression of TOM and TIM translocases supports greater protein transport from the cell cytosol into mitochondria to replace the damaged proteins that are removed by mitochondrial proteases. However, this increased demand for new proteins by mitochondria poses a threat to proteostasis in the cell cytosol. Furthermore, efflux of ROS from the mitochondria of burn patients also results in damage to cytosol proteins, leading to their degradation by the proteasomes (Figure 1). Indeed, recent studies have demonstrated increased protein damage and activation of proteosomes in skeletal muscle of burn patients.[2,48] Thus, oxidative stress in response to severe burns likely results in protein degradation in both the mitochondrion and cytosol of skeletal muscle. Furthermore, the reliance of the mitochondrion on the cell cytosol for the bulk of its newly synthesized protein may constitute a double hit on cytosolic amino acids stores.

Most data on the impact of severe burn trauma on skeletal muscle protein turnover have assayed amino acid flux into and out of bound proteins within a mixed muscle homogenate. The prevailing opinion is that the net efflux of amino acids from these bound proteins largely originates from the contractile myofibrilar protein pool. Because myofibrilar protein represents the bulk of the total protein pool within skeletal muscle, this is most likely true. However, the mitochondrial protein pool represents ~5% of the protein pool in skeletal muscle,[68] and may have a greater turnover rate than that of contractile proteins.[69] Thus, increased damage to the mitochondrial protein pool may significantly influence intracellular amino acid utilization in skeletal muscle of burn patients. While skeletal muscle contractile proteins likely represent an amino acid reservoir used to buffer circulating amino acid levels in patients recovering from burns,[6] our new data suggest that increased mitochondrial protein turnover likely places additional demands on the skeletal muscle protein pool, contributing to muscle protein wasting following severe burn trauma.

THERAPEUTIC STRATEGIES TO BLUNT MITOCHONDRIAL STRESS IN BURN-INDUCED HYPERMETABOLISM WASTING

Modulating oxidative stress may be a plausible approach to blunt hypermetabolism and skeletal muscle protein losses following severe burn trauma. Interestingly, a growing body of evidence suggests that uncoupled mitochondrial respiration may be an important component of the hypermetabolic stress response to severe burns.[26,27,70–74] Increased uncoupled respiration is mediated by mitochondrial uncoupling proteins. Of interest, UCP2 and UCP3, both of which are expressed in skeletal muscle, have been postulated to play a role in reducing mitochondrial ROS production.[75] This suggests that greater uncoupled mitochondrial respiration in tissues such as skeletal muscle may be a protective response aimed at reducing ROS production. Either way, modulating ROS production and/or providing exogenous antioxidants compounds to mop up excess ROS may hold value in terms of reducing hypermetabolism and attenuating oxidative stress and protein damage in skeletal muscle (and other tissues following major burn trauma).[76,77]

A hurdle to this approach is the need to develop antioxidants that can penetrate the mitochondrial matrix to help directly mop up the excess mitochondrial ROS. Indeed, the outer mitochondrial membrane is made up of a phospholipid bilayer with a membrane potential of approximately of ~150 mV.[78,79] As a result, antioxidant molecules need to be lipid soluble and positively charged to enter into the mitochondrial membrane space or matrix.[79] Interestingly, despite the obvious role of mitochondria in oxidative stress following burn trauma, data on mitochondrial-targeted antioxidants in burn patients are scarce, perhaps owing to the difficultly in providing antioxidant therapy that will reach the mitochondrion. A report by Carter et al[80] showed that mitochondrial-targeted antioxidant peptide SS-31 ameliorated burn-induced insulin resistance. In addition, Righi et al[34] demonstrated that SS-31 blunted hypermetabolism and improved mitochondrial redox status and coupling post burn. These

studies suggest that this mitochondrial-specific antioxidant has the potential of restoring mitochondrial function post burn. Human trials on SS-31 and other similar compounds are eagerly awaited.

As mentioned previously, we recently demonstrated that nuclear factor erythroid 2-related factor 2 mRNA was elevated following burn trauma but interestingly, its relative protein abundances were in fact lower in burn patients compared with healthy adults.[2] In response to accumulation of oxidized proteins and/or stress, transcription factors such as the NFE2L2 are activated,[42] resulting in the transcription of a battery of cytoprotective genes. The low expression of this NRF2 protein in skeletal muscle of burn patients suggests that therapeutic administration of this protein might help ameliorate the effect of oxidative stress in burn patients. An interesting study by Nelson et al[60] showed that administration of protandim, a synergetic activator of NRF2, to healthy human subjects increased superoxide dismutase protein 100-fold.[81] The therapeutic advantage of NRF2 is that it has the capacity to induce several cytoprotective genes including membrane transporters.[42] This might provide a potential therapeutic drug to help protect both the mitochondrial and cytoplasmic proteins in burn patients but remains to be tested.

SUMMARY

Because burn-induced skeletal muscle wasting contributes significantly to morbidity, it is imperative to understand the molecular mechanisms underlying this response to devise novel treatment solutions. Recent data suggest a link between hypermetabolism and skeletal muscle wasting following burn trauma. Specifically, hypermetabolism at the level of the mitochondrion results in oxidative stress. Mitochondrial hypermetabolism may place a significant burden on the skeletal muscle protein pool of burn survivors by i) causing damage to and degradation of proteins in the mitochondrion and thus increasing the protein demands of the mitochondria to replace nuclear-encoded proteins critical to mitochondrial function; and ii) the transmission of oxidative stress to the cell cytosol and resultant protein damage and proteolysis. Of potential clinical importance, unlike muscle wasting to support processes such as wound healing, oxidative damage induced turnover of protein confers little benefit to the patient (other than the need to remove and replace damaged proteins). Thus, this mechanism of skeletal muscle protein damage secondary to mitochondrial hypermetabolism represents a new target for therapeutic interventions aimed at blunting two of the greatest problems facing burn survivors: hypermetabolism and muscle wasting.

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