Published in final edited form as:

Curr Rheumatol Rep. 2012 June ; 14(3): 238–243. doi:10.1007/s11926-012-0247-5.

Endoplasmic Reticulum Stress in Skeletal Muscle Homeostasis and Disease

Sree Rayavarapu, William Coley, and Kanneboyina Nagaraju

Institute of Biomedical Sciences, The George Washington University, Research Center for Genetic Medicine, Children's National Medical Center, 111 Michigan Ave NW, Washington, DC 20010, USA

Sree Rayavarapu: srayavarapu@cnmcresearch.org; William Coley: wcoley@cnmcresearch.org; Kanneboyina Nagaraju: knagaraju@cnmcresearch.org

Abstract

Our appreciation of the role of endoplasmic reticulum(ER) stress pathways in both skeletal muscle homeostasis and the progression of muscle diseases is gaining momentum. This review provides insight into ER stress mechanisms during physiologic and pathological disturbances in skeletal muscle. The role of ER stress in the response to dietary alterations and acute stressors, including its role in autoimmune and genetic muscle disorders, has been described. Recent studies identifying ER stress markers in diseased skeletal muscle are noted. The emerging evidence for ER–mitochondrial interplay in skeletal muscle and its importance during chronic ER stress in activation of both inflammatory and cell death pathways (autophagy, necrosis, and apoptosis) have been discussed. Thus, understanding the ER stress–related molecular pathways underlying physiologic and pathological phenotypes in healthy and diseased skeletal muscle should lead to novel therapeutic targets for muscle disease.

Keywords

Skeletal muscle; Endoplasmic reticulum; Sarcoplasmic reticulum; Mitochondria; Myositis; ER stress; Autophagy; Necrosis; Apoptosis; Muscle disease

Introduction

Endoplasmic reticulum (ER) stress occurs when ER homeostasis is disrupted. Potential physiologic and pathological disruptors such as enhanced protein synthesis, accumulation of misfolded proteins, imbalance in calcium levels, deprivation of glucose or energy, ischemia, hyperhomocysteinemia, viral infections, and certain chemicals challenge the ER [1, 2]. To address these challenges, the ER employs two adaptive mechanisms: the unfolded protein response (UPR) and the ER overload response (EOR). The UPR involves the activation of three ER membrane-associated proteins, PKR-like eukaryotic initiation factor 2a kinase (PERK), inositol requiring enzyme 1 (IRE1), and activating transcription factor-6 (ATF6), and the upregulation of genes encoding ER chaperone proteins such as BiP/Grp78 and Grp94, which in turn enhance the ER's protein-folding capacity. In addition, activation of the UPR attenuates the translation machinery and reduces the protein synthetic load, preventing further accumulation of unfolded proteins in the ER. In contrast, the EOR

involves the upregulation of the nuclear factor- κ B (NF- κ B) pathway and modulation of the inflammatory response. Due to the successful activation of these adaptive mechanisms, the ER stress is resolved; should this resolution not occur, the functionally compromised cell initiates its terminal cell death mechanisms. These cell death events are mediated by transcriptional activation of the genes encoding cholesterol oxidase-peroxidase C/EBP homologous protein (also known as growth arrest and DNA damage 153 [GADD153]), a member of the CCAAT/enhancer-binding protein family of transcription factors; the mitogen-activated protein kinase c-Jun N-terminal kinase (JNK), Bcl-2 family proteins; and ER-associated caspases [3, 4].

ER stress response pathways and their involvement in the pathology of various metabolic disease states (e.g., obesity and diabetes) have been reviewed extensively elsewhere [5, 6]. In addition to metabolic diseases, ER stress has also been associated with muscle diseases such as myotonic dystrophy type 1, dysferlin-deficient muscular dystrophy, and myositis [7–11]. In this review, we focus on understanding the role of ER stress in skeletal muscle homeostasis and pathology; in addition, we offer some mechanistic explanations for the onset of ER stress and its possible relationship with other pathologic processes in diseased muscle.

Skeletal Muscle and Endoplasmic Reticulum Stress

Skeletal muscle has a specialized form of ER known as sarcoplasmic reticulum (SR). The SR is a storage depot for calcium and regulates its release during myofibrillar contraction; hence, the SR has a critical role in muscle contraction and the maintenance of muscle homeostasis. In addition, skeletal muscle plays a prominent role in the regulation of body metabolism by modulating glucose uptake. Therefore, it is important to understand the role of the ER/SR in both healthy muscle physiology and disease.

ER stress response pathways have been widely studied in pancreatic islets, liver, and adipose tissue; nevertheless, there is limited information on ER stress in muscle physiology and disease. Activation of the UPR has been reported in mouse skeletal muscle after the consumption of a high-fat diet. Mice fed a diet containing 70% fat and less than 1% carbohydrate for 6 weeks showed increased expression of BiP, IRE1 α , and membrane-bound transcription factor protease site 2 (MBTPS2) in the soleus and tibialis anterior muscles. In addition, this study showed that palmitic acid induced the UPR in a myogenic cell line (C2C12) and also decreased mTORC1 activity; however, in vivo evidence to confirm these findings is still needed [11–13]. Taken together, these results suggest that ER stress mechanisms may be one of the primary processes that respond immediately to the changed environmental cues in skeletal muscle and also indicate that these processes may directly modulate protein synthesis and in turn regulate muscle mass. Acute stress, such as longdistance running, also activates ER stress pathways in skeletal muscle, as indicated by a study in which muscle biopsies were obtained from eight males before and after a 200-km run [14•]. Expression of BiP and spliced x-box binding protein 1 (XBP1) in skeletal muscle was increased in response to running, indicating the importance of ER in skeletal muscle adaptation. The authors of this study also reported activation of other cellular mechanisms, such as oxidative stress, inflammation, and the reduced activity of the ubiquitin–proteasome pathway in the skeletal muscle of the runners. Additional evidence for the role of UPR in the adaptation of skeletal muscle to exercise was reported using specific knockout mice [15•]. This study showed that peroxisome proliferator-activated receptor- γ coactivator 1 α (PGC-1 α) mediates UPR in myotubes and skeletal muscle via the co-activation of ATF6 α . The PGC-1 α is also known to play a potential role in the regulation of several exercise-related factors of skeletal muscle. In sum, these findings highlight the importance of the ER/

SR and associated stress response mechanisms in both normal function and in the adaptation of skeletal muscle to various physiologic stressors.

Skeletal Muscle Disease and Endoplasmic Reticulum Stress

Evidence for enhanced UPR has been reported in autoimmune skeletal muscle diseases such as sporadic inclusion body myositis (sIBM). Increased expression of the ER chaperones calnexin, calreticulin, glucose regulatory protein (GRP)78, GRP94, and ERp72 was observed in the affected muscle by immunocytochemical staining; the authors further demonstrated that these ER chaperones co-immunoprecipitated and co-localized with amyloid- β [9]. More recently, our group has provided further evidence for the involvement of ER stress in the pathogenesis of other autoimmune muscle diseases, such as polymyositis (PM) and dermatomyositis (DM) [10]. Enhanced expression of *GRP78* and other ER stress-related genes, including *GADD153*, *PERK*, and *ATF3*, was observed in the myositis muscle biopsies, together with the activation of the NF- κ B pathway (EOR). Another study recently reported an increased expression of GRP94, calreticulin, and GRP75 in samples from myositis patients [16]. These patients exhibited muscle weakness and also showed myositis-specific autoantibodies, including anti-Mi-2 and anti-tRNA synthetases. More specifically, enhanced GRP94 expression was seen in the regenerating fibers of the myositis muscle, and an upregulation of calreticulin and GRP75 was observed in the myofibers that were also positive for major histocompatibility complex (MHC) class I staining. These findings suggest that muscle repair mechanisms as well as systemic immune responses are probably linked to ER stress pathways in myopathic muscle.

An integral ER membrane protein that is highly induced under stress, homocysteine-induced ER protein (Herp), has been found to co-localize with amyloid- β and GRP78 in sIBM muscles and in ER stress-induced culture myotubes [17,18]. Herp plays a role in maintaining ER Ca^{2+} homeostasis and regulating mitochondrial function in the brain. Induction of Herp improves the ER folding capacity and alleviates protein overload; it also contributes to ERAD and prevents apoptosis triggered by ER stress [19]. Even though an explicit role for Herp in sIBM pathology was not clearly indicated by the study of Nogalska et al. [17], its induction can be hypothesized as a compensatory mechanism to improve ER function in affected muscle fibers. Another study has reported aberrant expression of ER-bound RING finger protein 5 (RNF5/RMA1) in sIBM muscles; RNF5 is involved in muscle organization and the recognition of misfolded proteins [20]. All these studies clearly suggest that ER stress response pathways are activated and involved in pathogenesis in myositis muscle; however, the cause-and-effect relationship between ER stress and myofiber damage in inflammatory myopathies is not yet completely clear.

Major Histocompatibility Class I and Endoplasmic Reticulum Stress

One of the characteristics of PM, DM, and inclusion body myositis (IBM) is the upregulation of MHC class I on the skeletal muscle fibers. It is generally thought that this aberrant MHC class I expression leads to antigen processing and presentation, resulting in a dysregulated autoimmune response (both T cell and B cell) against self-antigens [21–23]. Nevertheless, there is emerging evidence from our group and others that nonimmune (ER stress, autophagy, tumor necrosis factor [TNF]- α -related apoptosis-inducing ligand [TRAIL]) mechanisms are also potential mediators of pathology in myositis. More detailed information on the pathophysiology of these diseases is provided in recent reviews on the topic [24–26]. Development of myofiber degeneration and muscle weakness in response to muscle-specific expression of MHC class I molecules in a transgenic murine model has indicated that these molecules have a direct role in mediating muscle pathology [27]. Furthermore, the demonstration of striking upregulation of MHC class I antigens with

surface as well as internal reactivity (reticular pattern), and their co-localization with the ER marker calnexin in human myositis biopsies has confirmed that MHC molecules can play a critical role in mediating ER stress in myopathic muscle [10, 28]. It is interesting that only wild-type MHC molecules, and not the glycosylation mutants (degradable forms), can induce the expression of GRP78 in C2C12 muscle cells; this result indicates that the aberrant expression of wild-type MHC molecules on skeletal muscle facilitates the induction of ER stress responses [10]. This study not only demonstrated an activation of the UPR but also of the EOR (NF- κ B pathway) in both myositis patient samples and a transgenic murine model, indicating that the induction of ER stress can in turn regulate inflammatory mechanisms in the affected muscle. Another study has demonstrated that conditional expression of MHC class I molecules in younger muscle (21-day-old mice) induces a rapid onset of the disease in the skeletal muscle, indicating an effect of age on the disease phenotype [29]. More importantly, genes involved in protein folding (e.g., ER chaperones, calreticulin) are rapidly upregulated in younger MHC class I-induced skeletal muscle, indicating that younger muscle is more sensitive to protein overload than adult skeletal muscle. This study further suggests that disruption of ER homeostasis via upregulation of MHC class I may be one of the initial mechanisms involved in myofiber damage. Other than the aforementioned studies, there is little evidence available to date to explain how ER stress pathways are activated in myositis muscle. However, in the case of sIBM, it is thought that the abnormal accumulation of intracellular inclusions (amyloid- β or phosphorylated tau) that are characteristic of the disease may be the reason for the enhanced UPR in affected muscle [9]. It has also been reported that activation of ER stress pathways in sIBM increases β -site amyloid- β precursor protein, cleaving enzyme 1 (BACE1) mRNA, and noncoding BACE1 antisense transcripts [30]. However, the specific role of amyloid- β and BACE1 in the pathogenesis of sIBM muscle is not yet clear. Taken together, these findings indicate that MHC class I molecules may contribute to ER stress in myopathic muscle by disrupting ER homeostasis. However, more evidence is required to connect the unusual MHC class I expression on affected myofibers to the induction of ER stress in myositis.

Mitochondrial Abnormalities in Myositis and the Link to Endoplasmic Reticulum Stress

Skeletal muscle has an elevated demand for energy; therefore, mitochondria are key organelles in this tissue because of their role in energy production. Mitochondria regulate critical aspects of muscle function, including energy metabolism and calcium homeostasis. They are also the source of reactive oxygen species that can stimulate cell-signaling pathways or damage muscle proteins and thereby regulate apoptotic and necrotic death pathways. The skeletal muscle ER makes intimate contact with mitochondria in specialized areas called mitochondria-associated ER membranes (MAM). This interaction may play a critical role in cellular homeostasis by regulating calcium exchange and protein transport [31]. This interaction has also been shown to play a role in amplifying the cell death cascade and has been described in cardiac muscle. The opening of mitochondrial permeability transition pore stimulated by SR-mitochondrial calcium cross-talk may play a major role in causing cardiac myocyte death [32]. Also, there is evidence that mitochondrial oxidative stress and its interplay with the ER plays a major role in the pathogenesis of certain neurodegenerative diseases [33]. On the other hand, mitochondrial abnormalities also have been observed in myositis patients (IBM) [34]. A more recent study has assessed mitochondrial function in DM biopsies using histologic and biochemical techniques. The percentages of cytochrome c oxidase (COX)-negative fibers and succinic dehydrogenase (SDH)-hyperreactive fibers were found to be higher in DM patients than in healthy individuals. However, other parameters, such as the oxidation rates of various substrates and enzymatic activities of the electron transport chain and adenosine triphosphate (ATP) ase,

did not differ significantly between groups; the authors therefore concluded that the overall function of the electron transport chain is not altered in DM muscle [35]. Another study also reported abnormal SDH and COX histochemical activity in DM muscle and further noted that these changes were characteristic of the atrophic perifascicular fibers in the affected muscle. However, these changes in SDH and COX were not observed in myofibers that had atrophied as a result of denervation, indicating that these changes are specific to DM pathology [36]. One study reported that a series of patients with PM also show mitochondrial pathology in muscle and that alterations in autophagic degradation pathways may be a common pathogenic mechanism in both PM with mitochondrial pathology and in IBM patients [37]. Thus, these findings indicate that mitochondria modulate myositis pathology; however, further studies are required to specifically determine how ER stress pathways and mitochondria work together to cause myofiber damage in myositis. A clear understanding of the interplay between the SR and mitochondria may provide important insights into myopathic muscle diseases.

Cross-Talk Among Endoplasmic Reticulum Stress, Autophagy, and Inflammation

Increasing evidence for cross-talk between the ER stress response and autophagy has recently become available. One study has shown that basal autophagy degrades endogenous ER degradation-enhancing α mannosidase like protein 1 (EDEM1) in nonstressed cells when it reaches the cytosol, indicating a link between these two processes [38]. Specific factors initiating myofiber damage and death are not yet well-defined; nevertheless, it is known that multinucleated myotubes are relatively resistant to classic apoptosis. Autophagic cell death pathways recently have been shown to play a role in muscle fiber damage in myositis muscle via the activation of TRAIL. TRAIL is a type II transmembrane protein that is expressed on a variety of cells and can induce NF- κ B activation upon binding to its receptor [39]. TRAIL has also been implicated in tissue remodeling and lumen formation and induces caspase 3-independent autophagic cell death [40]. We have proposed that TRAIL and NF- κ B may modulate both inflammation and the cell death pathways of myositis [41•].

An association between accumulation of mutant proteins and induction of ER stress pathways was also reported in dysferlin-related dystrophic muscle diseases. Examination of muscle biopsies from dysferlin-deficient patients revealed the presence of dysferlin expressing tubular aggregates and the induction of ER stress in the affected skeletal muscle. Dysferlin-deficient muscle showed enhanced expression of ER chaperones (GRP78 and GRP94) when compared with control muscle [7]. These authors have proposed that the tubular aggregates seen in the skeletal muscle of dysferlin-deficient patients are probably derived from SR and that muscle tissue undergoes ER stress as a result of a disturbance in intra-sarcoplasmic Ca^{+2} homeostasis. Another group subsequently demonstrated that wild-type dysferlin localizes to the ER/Golgi, becomes associated with retrotranslocon, Sec61 α , and VCP (p97), and is degraded by the ER-associated degradation system with involvement of ubiquitin/proteasome, whereas mutant dysferlin aggregated in the ER and induced eukaryotic translation initiation factor 2 α phosphorylation, LC3 conversion, and autophagosome formation. These findings suggest that accumulation of mutant dysferlin in ER results in activation of autophagic pathways and ER stress-mediated cell death mechanisms [42]. Taken together, these findings suggest that interplay exists between ER stress and autophagy and that these pathways together play an important role in myofiber damage in skeletal muscle diseases.

ER stress mechanisms have been associated with the activation of inflammatory responses in many cellular models, including skeletal muscle. Pathways such as NF- κ B, JNK, reactive

oxygen species, interleukin-6, and TNF- α have been shown to be activated by ER stress mechanisms [43–45]. Specifically, the IRE1 α branch of the UPR activates NF- κ B and JNK [45]. In endothelial cells, the UPR is induced by oxidized lipids and in turn enhances inflammatory gene expression that is dependent on ATF4 and XBP1 [46]. An association of ER stress with the inflammatory response is also evident from studies indicating that single nucleotide polymorphisms in the *XBP1* gene are associated with human inflammatory bowel disease [47]. ER stress and NF- κ B activation have also been demonstrated in myositis skeletal muscle, with the translocation of NF- κ B p65 from cytosol to nucleus being observed in affected muscle, but not in control muscle [10]. Thus, several lines of cross-talk exist between ER stress pathways and inflammatory responses in different tissues and diseases.

Conclusions

The evidence accumulated thus far indicates that ER stress is an adaptive mechanism in skeletal muscle during exercise and diet alteration. However, this phenomenon becomes pathological in situations in which an uncontrolled ER stress leads to cross-talk with mitochondria and formation of autophagosomes, initiating an activation of inflammatory and cell death pathways (autophagy, necrosis, and apoptosis) in the skeletal muscle (Fig. 1). The relative contribution of these pathways to muscle fiber damage is still unclear. A systematic approach in which these pathways are genetically or pharmacologically blocked should elucidate their relative contributions to the disease process in muscle disorders and help us design therapeutic strategies to reduce fiber damage and improve muscle function.

Acknowledgments

Dr. Nagaraju is supported by a grant from the National Institutes of Health (RO1-AR050478 and AR050478-06S1). The authors wish to thank Dr. Debbie McClellan for editorial help.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. Kaufman RJ. Stress signaling from the lumen of the endoplasmic reticulum: coordination of gene transcriptional and translational controls. *Genes Dev.* 1999; 13:1211–1233. [PubMed: 10346810]
2. Mori K. Tripartite management of unfolded proteins in the endoplasmic reticulum. *Cell.* 2000; 101:451–454. [PubMed: 10850487]
3. Matsumoto M, Minami M, Takeda K, Sakao Y, Akira S. Ectopic expression of CHOP (GADD153) induces apoptosis in M1 myeloblastic leukemia cells. *FEBS Lett.* 1996; 395:143–147. [PubMed: 8898082]
4. Nakagawa T, Zhu H, Morishima N, Li E, Xu J, et al. Caspase-12 mediates endoplasmic-reticulum-specific apoptosis and cytotoxicity by amyloid-beta. *Nature.* 2000; 403:98–103. [PubMed: 10638761]
5. Hotamisligil GS. Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. *Cell.* 2010; 140:900–917. [PubMed: 20303879]
6. Hetz C, Martinon F, Rodriguez D, Glimcher LH. The unfolded protein response: integrating stress signals through the stress sensor IRE1 α . *Physiol Rev.* 2011; 91:1219–1243. [PubMed: 22013210]
7. Ikezoe K, Furuya H, Ohyagi Y, Osoegawa M, Nishino I, et al. Dysferlin expression in tubular aggregates: their possible relationship to endoplasmic reticulum stress. *Acta Neuropathol.* 2003; 105:603–609. [PubMed: 12664320]

8. Ikezoe K, Nakamori M, Furuya H, Arahata H, Kanemoto S, et al. Endoplasmic reticulum stress in myotonic dystrophy type 1 muscle. *Acta Neuropathol.* 2007; 114:527–535. [PubMed: 17661063]
9. Vattemi G, Engel WK, McFerrin J, Askanas V. Endoplasmic reticulum stress and unfolded protein response in inclusion body myositis muscle. *Am J Pathol.* 2004; 164:1–7. [PubMed: 14695312]
10. Nagaraju K, Casciola-Rosen L, Lundberg I, Rawat R, Cutting S, et al. Activation of the endoplasmic reticulum stress response in autoimmune myositis: potential role in muscle fiber damage and dysfunction. *Arthritis Rheum.* 2005; 52:1824–1835. [PubMed: 15934115]
11. Deldicque L, Hespel P, Francaux M. ER stress in skeletal muscle: origin and metabolic consequences. *Exerc Sport Sci Rev.* 2011
12. Deldicque L, Cani PD, Philp A, Raymackers JM, Meakin PJ, et al. The unfolded protein response is activated in skeletal muscle by high-fat feeding: potential role in the downregulation of protein synthesis. *Am J Physiol Endocrinol Metab.* 2010; 299:E695–E705. [PubMed: 20501874]
13. Deldicque L, Bertrand L, Patton A, Francaux M, Baar K. ER stress induces anabolic resistance in muscle cells through PKB-induced blockade of mTORC1. *PLoS One.* 2011; 6:e20993. [PubMed: 21698202]
14. Kim HJ, Jamart C, Deldicque L, An GL, Lee YH, et al. Endoplasmic reticulum stress markers and ubiquitin-proteasome pathway activity in response to a 200-km run. *Med Sci Sports Exerc.* 2011; 43:18–25. [PubMed: 20473228] This article demonstrates that ER stress pathways are enhanced in skeletal muscle in response to long-distance running.
15. Wu J, Ruas JL, Estall JL, Rasbach KA, Choi JH, et al. The unfolded protein response mediates adaptation to exercise in skeletal muscle through a PGC-1 α /ATF6 α complex. *Cell Metab.* 2011; 13:160–169. [PubMed: 21284983] This article highlights the importance of the PGC-1 α /ATF6 α complex in the adaptation of skeletal muscle to exercise.
16. Vitadello M, Doria A, Tarricone E, Ghirardello A, Gorza L. Myofiber stress-response in myositis: parallel investigations on patients and experimental animal models of muscle regeneration and systemic inflammation. *Arthritis Res Ther.* 2010; 12:R52. [PubMed: 20334640] This article substantiates that ER stress pathways are enhanced in the myositis muscle.
17. Nogalska A, Engel WK, McFerrin J, Kokame K, Komano H, et al. Homocysteine-induced endoplasmic reticulum protein (Herp) is up-regulated in sporadic inclusion-body myositis and in endoplasmic reticulum stress-induced cultured human muscle fibers. *J Neurochem.* 2006; 96:1491–1499. [PubMed: 16441512]
18. Kokame K, Agarwala KL, Kato H, Miyata T. Herp, a new ubiquitin-like membrane protein induced by endoplasmic reticulum stress. *J Biol Chem.* 2000; 275:32846–32853. [PubMed: 10922362]
19. Chan SL, Fu W, Zhang P, Cheng A, Lee J, et al. Herp stabilizes neuronal Ca²⁺ homeostasis and mitochondrial function during endoplasmic reticulum stress. *J Biol Chem.* 2004; 279:28733–28743. [PubMed: 15102845]
20. Delaunay A, Bromberg KD, Hayashi Y, Mirabella M, Burch D, et al. The ER-bound RING finger protein 5 (RNF5/RMA1) causes degenerative myopathy in transgenic mice and is deregulated in inclusion body myositis. *PLoS One.* 2008; 3:e1609. [PubMed: 18270596]
21. Tournadre A, Lenief V, Miossec P. Expression of Toll-like receptor 3 and Toll-like receptor 7 in muscle is characteristic of inflammatory myopathy and is differentially regulated by Th1 and Th17 cytokines. *Arthritis Rheum.* 62:2144–2151. [PubMed: 20309865]
22. Pandya JM, Fasth AE, Zong M, Arnardottir S, Dani L, et al. Expanded T cell receptor V β -restricted T cells from patients with sporadic inclusion body myositis are proinflammatory and cytotoxic CD28null T cells. *Arthritis Rheum.* 62:3457–3466. [PubMed: 20662057]
23. Fasth AE, Dastmalchi M, Rahbar A, Salomonsson S, Pandya JM, et al. T cell infiltrates in the muscles of patients with dermatomyositis and polymyositis are dominated by CD28null T cells. *J Immunol.* 2009; 183:4792–4799. [PubMed: 19752224]
24. Rayavarapu S, Coley W, Nagaraju K. An update on pathogenic mechanisms of inflammatory myopathies. *Curr Opin Rheumatol.* 2011; 23:579–584. [PubMed: 21960036]
25. Nagaraju K, Lundberg IE. Polymyositis and dermatomyositis: pathophysiology. *Rheum Dis Clin North Am.* 2011; 37:159–171. v. [PubMed: 21444017]

26. Zong M, Lundberg IE. Pathogenesis, classification and treatment of inflammatory myopathies. *Nat Rev Rheumatol*. 2011; 7:297–306. [PubMed: 21468145]
27. Nagaraju K, Raben N, Loeffler L, Parker T, Rochon PJ, et al. Conditional up-regulation of MHC class I in skeletal muscle leads to self-sustaining autoimmune myositis and myositis-specific autoantibodies. *Proc Natl Acad Sci U S A*. 2000; 97:9209–9214. [PubMed: 10922072]
28. Englund P, Nennesmo I, Klareskog L, Lundberg IE. Interleukin-1 α expression in capillaries and major histocompatibility complex class I expression in type II muscle fibers from polymyositis and dermatomyositis patients: important pathogenic features independent of inflammatory cell clusters in muscle tissue. *Arthritis Rheum*. 2002; 46:1044–1055. [PubMed: 11953983]
29. Li CK, Knopp P, Moncrieffe H, Singh B, Shah S, et al. Overexpression of MHC class I heavy chain protein in young skeletal muscle leads to severe myositis. Implications for juvenile myositis. *Am J Pathol*. 2009
30. Nogalska A, Engel WK, Askanas V. Increased BACE1 mRNA and noncoding BACE1-antisense transcript in sporadic inclusion-body myositis muscle fibers—possibly caused by endoplasmic reticulum stress. *Neurosci Lett*. 2010; 474:140–143. [PubMed: 20236612]
31. Dorn GW 2nd, Scorrano L. Two close, too close: sarcoplasmic reticulum-mitochondrial crosstalk and cardiomyocyte fate. *Circ Res*. 2010; 107:689–699. [PubMed: 20847324]
32. Ruiz-Meana M, Abellan A, Miro-Casas E, Agullo E, Garcia-Dorado D. Role of sarcoplasmic reticulum in mitochondrial permeability transition and cardiomyocyte death during reperfusion. *Am J Physiol Heart Circ Physiol*. 2009; 297:H1281–H1289. [PubMed: 19684187]
33. Henchcliffe C, Beal MF. Mitochondrial biology and oxidative stress in Parkinson disease pathogenesis. *Nat Clin Pract Neurol*. 2008; 4:600–609. [PubMed: 18978800]
34. Schroder JM, Molnar M. Mitochondrial abnormalities and peripheral neuropathy in inflammatory myopathy, especially inclusion body myositis. *Mol Cell Biochem*. 1997; 174:277–281. [PubMed: 9309700]
35. Miro O, Casademont J, Grau JM, Jarreta D, Urbano-Marquez A, et al. Histological and biochemical assessment of mitochondrial function in dermatomyositis. *Br J Rheumatol*. 1998; 37:1047–1053. [PubMed: 9825742]
36. Alhatou MI, Sladky JT, Bagasra O, Glass JD. Mitochondrial abnormalities in dermatomyositis: characteristic pattern of neuropathology. *J Mol Histol*. 2004; 35:615–619. [PubMed: 15614615]
37. Temiz P, Weihl CC, Pestronk A. Inflammatory myopathies with mitochondrial pathology and protein aggregates. *J Neurol Sci*. 2009; 278:25–29. [PubMed: 19101700]
38. Le Fourn V, Gaplovskaya-Kysela K, Guhl B, Santimaria R, Zuber C, et al. Basal autophagy is involved in the degradation of the ERAD component EDEM1. *Cell Mol Life Sci*. 2009; 66:1434–1445. [PubMed: 19266160]
39. Kim YS, Schwabe RF, Qian T, Lemasters JJ, Brenner DA. TRAIL-mediated apoptosis requires NF- κ B inhibition and the mitochondrial permeability transition in human hepatoma cells. *Hepatology*. 2002; 36:1498–1508. [PubMed: 12447876]
40. Mills KR, Reginato M, Debnath J, Queenan B, Brugge JS. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is required for induction of autophagy during lumen formation in vitro. *Proc Natl Acad Sci U S A*. 2004; 101:3438–3443. [PubMed: 14993595]
41. Alger HM, Raben N, Pistilli E, Francia D, Rawat R, et al. The role of tumor necrosis factor- α -related apoptosis-inducing ligand (TRAIL) in mediating autophagy in myositis skeletal muscle: a potential non-immune mechanism of muscle damage. *Arthritis Rheum*. 2011 This article demonstrates that autophagic pathways are enhanced in the myopathic muscle and highlights the role of a nonimmune mechanism in myofiber damage in myositis.
42. Fujita E, Kouroku Y, Isoai A, Kumagai H, Misutani A, et al. Two endoplasmic reticulum-associated degradation (ERAD) systems for the novel variant of the mutant dysferlin: ubiquitin/proteasome ERAD(I) and autophagy/lysosome ERAD(II). *Hum Mol Genet*. 2007; 16:618–629. [PubMed: 17331981]
43. Hu P, Han Z, Couvillon AD, Kaufman RJ, Exton JH. Autocrine tumor necrosis factor α links endoplasmic reticulum stress to the membrane death receptor pathway through

- IRE1 α mediated NF- κ B activation and down-regulation of TRAF2 expression. *Mol Cell Biol.* 2006; 26:3071–3084. [PubMed: 16581782]
44. Malhi H, Kaufman RJ. Endoplasmic reticulum stress in liver disease. *J Hepatol.* 2011; 54:795–809. [PubMed: 21145844]
45. Urano F, Wang X, Bertolotti A, Zhang Y, Chung P, et al. Coupling of stress in the ER to activation of JNK protein kinases by transmembrane protein kinase IRE1. *Science.* 2000; 287:664–666. [PubMed: 10650002]
46. Gargalovic PS, Gharavi NM, Clark MJ, Pagnon J, Yang WP, et al. The unfolded protein response is an important regulator of inflammatory genes in endothelial cells. *Arterioscler Thromb Vasc Biol.* 2006; 26:2490–2496. [PubMed: 16931790]
47. Kaser A, Lee AH, Franke A, Glickman JN, Zeissig S, et al. XBP1 links ER stress to intestinal inflammation and confers genetic risk for human inflammatory bowel disease. *Cell.* 2008; 134:743–756. [PubMed: 18775308]

Fig. 1.

The endoplasmic reticulum (ER) stress response in healthy and diseased skeletal muscle. Nonpathological ER stress situations (e.g., exercise) are unlikely to induce pathological inflammation; in such cases, the ER stress response serves as an adaptive mechanism in skeletal muscle. In contrast, when ER stress becomes excessive and/or uncontrolled (mainly in pathological situations such as myositis), the resulting cross-talk with mitochondria leads to cell death (autophagy, necrosis, and apoptosis) and also initiates pathological inflammatory responses in the affected skeletal muscle, causing myofiber degeneration and disease progression