Regulation of survival gene *hsp70*

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Abstract Rapid expression of the survival gene, inducible *heat shock protein 70* (*hsp70*), is critical for mounting cytoprotection against severe cellular stress, like elevated temperature. Hsp70 protein chaperones the refolding of heat-denatured peptides to minimize proteolytic degradation as a part of an eukaryotically conserved phenomenon referred to as the heat shock response. The physiologic stress associated with exercise, which can include elevated temperature, mechanical damage, hypoxia, lowered pH, and reactive oxygen species generation, may promote protein unfolding, leading to *hsp70* gene expression in skeletal myofibers. Although the pre-transcriptional activation of *hsp70* gene expression has been thoroughly reviewed, discussion of downstream *hsp70* gene regulation is less extensive. The purpose of this brief review was to examine all levels of *hsp70* gene regulation in response to heat stress and exercise with a special focus on skeletal myofibers where data are available. In general, while heat stress represses bulk gene expression, *hsp70* mRNA expression is enhanced. Post-transcriptionally, intronless *hsp70* mRNA circumvents a host of decay pathways, as well as heat stress-repressed pre-mRNA splicing and nuclear export. Pre-translationally, *hsp70* mRNA is excluded from stress granules and preferentially translated during heat stress-repressed global cap-dependent translation. Post-translationally, nascent Hsp70 protein is thermodynamically stable at elevated temperatures, allowing

for the commencement of chaperoning activity early after synthesis to attenuate the heat shock response and protect against subsequent injury. This review demonstrates that *hsp70* mRNA expression is closely coupled with functional protein translation.

Keywords Heat shock response · *hsp70* · Regulation · Skeletal muscle · Exercise · Heat stress

Introduction

Rapid expression of the survival gene, inducible *heat shock protein 70* (*hsp70*, also referred to as *hsp72*), is critical for mounting cytoprotection against severe cellular stress, like elevated temperature. The *hsp70* gene encompasses two transcripts, *hspa1a* and *hspa1b*, that contain nearly identical open reading frames in rodents, which encode a protein that shares 96.6% amino acid sequence identity with the human Hsp70 orthologue (Walter et al. 1994). Hsp70 protein chaperones the refolding of denatured peptides to minimize proteolytic degradation as a part of an eukaryotically conserved phenomenon referred to as the heat shock response (Shamovsky and Nudler 2008; Wu 1995). The physiologic stress associated with various modalities of exercise, which can include elevated temperature, mechanical damage, hypoxia, lowered pH, and reactive oxygen species generation, may also promote protein unfolding and *hsp70* gene expression in humans and animals alike (Morton et al. 2009; Noble et al. 2008). Enhanced Hsp70 protein expression is known to play a critical role in the recovery of striated muscle post-exercise (Noble et al. 2010). Although the pre-transcriptional activation of *hsp70* gene expression has been thoroughly reviewed (Akerfelt et al. 2010; Kiang and Tsokos 1998; Morimoto 1998; Shamovsky and Nudler 2008;

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Voellmy and Boellmann 2007; Wu 1995), discussion of downstream *hsp70* gene regulation is less extensive. The purpose of this brief review was to examine *hsp70* gene regulation, from activation to post-translational control in response to heat stress and exercise, with a special focus on skeletal myofibers where data are available. Heat stress, commonly defined in animal models as whole-body heating at 42°C for 15 min (also known as heat shock), represents a controlled stimulus for enhancing *hsp70* gene expression and, thus, can be used to understand some of the regulation behind the exercise-related heat shock response (Currie et al. 1988; Salo et al. 1991). Many of the studies examining the regulation of *hsp70* gene expression in response to heat stress have been conducted in vitro using mammalian cell lines or in vivo using *Drosophila*, *Saccharomyces cerevisiae*, and *Escherichia coli* as models. Studies which have specifically examined skeletal myofibers are identified below.

Pre-transcriptional regulation

It is well known that splicing of bulk precursor (pre-)mRNA (Shin and Manley 2004; Yost and Lindquist 1986) and global cap-dependent translation (Duncan et al. 1987; Van Der et al. 2009) become repressed in response to heat stress. However, enhanced *hsp70* gene expression persists in response to this condition, as initiated by the activation of heat shock factor 1 (HSF1) (Morimoto 1993) and the lesser characterized HSF2 (Ostling et al. 2007). Heat stress promotes HSF1 trans-activation and heat shock element (HSE) acquisition via nuclear translocation (Alastalo et al. 2003; Jolly et al. 2002; Sarge et al. 1993), homotrimerization (Baler et al. 1993; Westwood and Wu 1993), and enhanced phosphorylation status at serine (Ser) residues Ser230 (Holmberg et al. 2001) and Ser326 (Guettouche et al. 2005; see Akerfelt et al. 2010; Kiang and Tsokos 1998; Morimoto 1998; Shamovsky and Nudler 2008; Voellmy and Boellmann 2007; Wu 1995 for review). Calcium/phospholipid-dependent protein kinase, cAMP-dependent protein kinase (PKA; Ohnishi et al. 1998), and calcium/calmodulin-dependent protein kinase II (CaMKII; Holmberg et al. 2001) have all been implicated in enhancing HSF1 activation and *hsp70* mRNA expression.

HSF1 receives constitutive (Chu et al. 1998) and heat stress-related (Xavier et al. 2000) inhibitory phosphorylation at Ser307 via extracellular signal-regulated kinase 1/2 (ERK1/2), priming for phosphorylation at Ser303 by glycogen synthase kinase 3- β (GSK3- β ; Chu et al. 1996), and subsequent sequestration by 14-3-3 ϵ scaffolding protein (Wang et al. 2003). Hsp70 protein (Abravaya et al. 1992) and, more notably, an Hsp90 heterocomplex (Zou et al. 1998) partake in regulating *hsp70* mRNA expression by sequestering HSF1 monomers (Baler et al. 1996) and trimers (Guo et al. 2001), respectively. HSF1 is strongly believed to

undergo self-activation as Hsp70 (Morimoto 1993) and Hsp90 (Shamovsky and Nudler 2008) protein become redirected to unfolding peptides in response to heat stress. However, the precise chaperoning and phosphorylation status involved in full HSF1 transcriptional competency remains unclear.

Once activated fully, HSF is believed to trigger RNA polymerase II (Pol-II) escape from HSE promoter-paused pre-transcriptional initiation complex (PIC) to commence vigorous and synchronous elongation of *hsp70* mRNA (Fuda et al. 2009; Mason and Lis 1997). Rapid loss of nucleosomes (Petesch and Lis 2008) and hyperacetylation of chromatin at *hsp70* gene loci (Chen et al. 2002; Thomson et al. 2004) have both been proposed to play a role in attenuating barriers to elongation in response to heat stress. Association of chromatin regions with the nuclear envelope can also promote gene activation (Blobel 1985; Strambio-De-Castillia et al. 2010), as is the case with the *hsp70* gene, which requires peripheral nuclear localization for enhanced expression in response to heat stress (Kurshakova et al. 2007). Chromatin remodeling may further play an adaptive role in priming for enhanced *hsp70* mRNA expression in response to subsequent injury, as demonstrated in cardiac muscle (Tetievsky et al. 2008; Tetievsky and Horowitz 2010).

In the absence of increased body temperature, exercise can induce enhanced Hsp70 protein expression in skeletal muscle (Skidmore et al. 1995). Indeed, passive heating to 39.5 $\pm$ 0.2°C, a temperature similar to that experienced during exercise, has been shown to have no effect on Hsp70 protein expression in skeletal muscle (Morton et al. 2007). It has been shown that Hsp70 protein is expressed in accordance with exercise intensity (Milne and Noble 2002). Exercise-related, homeostatic perturbations such as mechanical stretching (Goto et al. 2003), hypoxia (Benjamin et al. 1990), lowered pH or influx of calcium ions (Mosser et al. 1990), reactive oxygen species generation (Fischer et al. 2006; Marini et al. 1996), decreased ATP pools (Benjamin et al. 1992), glycogen depletion (Febbraio et al. 2002), and elevated circulating catecholamines (Melling et al. 2006; Paroo and Noble 1999) have all been implicated in contributing to the activation of the heat shock response (see Morton et al. 2009; Noble et al. 2008 for review). As compared with the phenotypically faster contracting and more glycolytic myofibers of various skeletal muscles, slower and more oxidative myofibers have been shown to be more robustly (O'Neill et al. 2006) and rapidly responsive (Tupling et al. 2007), in terms of Hsp70 protein expression, to hindlimb overload and isometric exercise, respectively. Slow-oxidative muscles contain greater HSF1 content (Najemnikova et al. 2007) and experience more HSF1 activation post-heat stress as compared with faster glycolytic muscles (Locke and Tanguay 1996). However, it remains a topic of debate whether slower and more oxidative myofibers

experience greater *hsp70* gene expression in response to exercise as a result of preferential recruitment or a heightened sensitivity to the associated stress. Ultimately, the initial appearance of *hsp70* mRNA is most notably subject to pre-transcriptional regulation.

Post-transcriptional regulation

mRNA is subject to extensive processing (Moore and Proudfoot 2009) and degradative (Garneau et al. 2007) pathways which interconnect with one another and translational events to regulate protein expression. Most pre-mRNAs contain introns (Hill and Sorscher 2006) which require splicing to promote nuclear export (Valencia et al. 2008) and to produce intended protein products (Nilsen and Graveley 2010; Pan et al. 2008). *hsp70* mRNA is encoded by an intronless gene (Hunt and Morimoto 1985), allowing for the circumvention of heat stress-repressed splicing (see Shi et al. 2011 for rationale). The fidelity of exon–exon junctions generated through splicing is under surveillance by an evolutionarily conserved pathway referred to as nonsense-mediated decay (Brognia and Wen 2009; Peltz et al. 1993). *hsp70* mRNA has been shown to be immune to nonsense-mediated decay as it lacks a destabilizing exon–exon junction (Behm-Ansmant et al. 2007; Maquat and Li 2001). Export of bulk mRNA to the cytoplasm involves assembly into highly structured ribonucleoprotein complexes (mRNPs) which interact with nuclear pores (Kelly and Corbett 2009; Rodriguez-Navarro and Hurt 2011). In response to heat stress, bulk mRNA has been shown to be retained in the nucleus, while *hsp70* mRNA is selectively exported (Carmody et al. 2010; Saavedra et al. 1996). Although not required for bulk mRNA export, a specific mRNP export adaptor, Thoc5, has been shown to play a crucial role in *hsp70* mRNA nuclear export post-heat stress (Katahira et al. 2009). The regulation of mRNA export and processing remains unclear post-exercise.

Bulk (Decker and Parker 1993) and *hsp70* mRNA degradation (Bonisch et al. 2007) both begin with deadenylation of poly(A)-tail, followed by cap hydrolysis and exonucleolysis. While it is unclear whether deadenylation of bulk mRNA occurs during heat stress, it has been observed that the fraction of *hsp70* mRNA containing poly(A)-tail increased and that the rapidness of *hsp70* mRNA poly(A)-tail removal decreased as the severity of heat stress increased, thus leading to the stabilization of this transcript at elevated temperatures (Dellavalle et al. 1994). AU-rich elements (ARE) found in the 3' untranslated region of select transcripts commonly mediate rapid deadenylation for fine-tuning of mRNA degradation (Chen and Shyu 1995; Garneau et al. 2007). Although *hsp70* mRNA contains an ARE (Moore et al. 1987), the 3' untranslated region of this

transcript has been demonstrated to be necessary for enhanced translation in response to heat stress (Moseley et al. 1993). With heat stress, the thermosensitive *double-stranded RNA-activated protein kinase R (pkr)* gene (Williams 1999) has been implicated in playing a role in *hsp70* mRNA stabilization via an ARE-mediated mechanism (Zhao et al. 2002). Heat stress also promotes Hsp70 protein-related sequestration of the ARE-destabilizing protein, AUF1, suppressing the degradation of ARE-containing transcripts (Laroia et al. 1999).

The spatial organization of mRNAs in the cytoplasm is important for coupling the synthesis of proteins to location of use (Martin and Ephrussi 2009; Meignin and Davis 2010). Skeletal myofibers are densely packed with the contractile apparatus consisting of myofibrils enveloped by the sarcoplasmic reticulum which contains microdomains of endoplasmic reticulum (Volpe et al. 1992), which correlate to the microfilament isotropic band (I-band; Kaakinen et al. 2008). Although subsarcolemmal localization is common to various *myosin heavy chain* mRNA isoforms and transcripts encoding proteins that are targeted to the endoplasmic reticulum, specific intermyofibrillar (Dix and Eisenberg 1988; Shoemaker et al. 1999) or I-band (Nissinen et al. 2005) organization has been observed in myofibers for these mRNA species, respectively. Enhanced *hsp70* mRNA expression has been detected early post-exercise (Locke et al. 1995; Puntschart et al. 1996) and heat stress (Currie et al. 1993) in various muscle types. However, the cytoplasmic organization of *hsp70* mRNA remains unclear in skeletal myofibers. Enhanced *hsp70* mRNA expression has been shown to be concentrated near the periphery of the slower and more oxidative myofibers of skeletal muscle post-exercise (Neufer et al. 1996). At a higher resolution, *hsp70* mRNA expression has been found to be concentrated perinuclearly in skeletal myofibers early post-exercise (unpublished observations). Ultimately, an investigation of the trafficking of *hsp70* mRNA would provide further insight into the regulation of this transcript during the exercise-related heat shock response.

Pre-translational regulation

The 5' cap structure of bulk mRNA acts as a pivotal site for controlling global translation initiation (Gebauer and Hentze 2004). In response to heat stress, initiation of global cap-dependent translation becomes repressed via suppression of the activity of eukaryotic translation initiation factors eIF4E (Duncan et al. 1987; Gingras et al. 1999; Vries et al. 1997) and eIF2 (Scheper et al. 1997; Van Der et al. 2009; Williams 1999). Exercise-related perturbations to intracellular energy content, such as activation of the AMP-activated kinase (Ponticos et al. 1998; Wojtaszewski et al. 2000), have been

demonstrated to suppress eIF4E activity, with concomitant reduction in global protein synthesis in skeletal muscle (Bolster et al. 2002; Dreyer et al. 2006). *hsp70* mRNA is preferentially translated during globally repressed cap-dependent translation via an internal ribosome entry site (IRES; Hernandez et al. 2004; Rubtsova et al. 2003), which is a secondary-structured region within the 5' untranslated region of select transcripts which recruits the ribosome directly to an internal position on the mRNA (Spriggs et al. 2008). *hsp70* mRNA is also preferentially translated via ribosomal shunting (Yueh and Schneider 2000), which involves ribosomal circumvention of the inhibitory structure within the 5' untranslated region of select transcripts (Chappell et al. 2006). It remains a topic of debate whether *hsp70* mRNA is translated through an IRES, a shunting mechanism, or a hybrid of both.

Heat stress also promotes polysome disassembly and shuttling of stalled translation pre-initiation complexes and bulk mRNA to triage centers known as stress granules (Anderson and Kedersha 2008; Kedersha et al. 1999). *hsp70* mRNA is selectively excluded from stress granule assembly, which acts to promote its preferential translation in response to heat stress (Kedersha and Anderson 2002). Ultimately, enhanced Hsp70 protein expression has been observed in skeletal muscle early after heat stress (Oishi et al. 2002) and exercise (Skidmore et al. 1995). On these grounds, the argument is made that the appearance of *hsp70* mRNA strongly supports protein translation.

Post-translational regulation

The native state of Hsp70 protein is thermodynamically stable well above temperatures experienced during heat stress (Fuertes et al. 2004; Montgomery et al. 1993). Hsp70 protein contains an ATPase and the substrate-binding domain, which cooperate with one another and with cofactors and co-chaperones to chaperone the refolding of a vast array of clients through bind–release cycling (Mayer and Bukau 2005; Schlecht et al. 2011). Hsp70 protein bind–release cycling is regulated by members of the diverse HSP40 family which are involved in the capture of specific clients via the stimulation of ATPase activity (Glover and Lindquist 1998), while various nucleotide exchange factors, including those of the BAG family (Kabbage and Dickman 2008; Takayama et al. 1997) are involved in the dissociation of specific clients via the stimulation of ADP release (Kampinga and Craig 2010). ATPase activity results in the transient autophosphorylation of Hsp70 protein (McCarty and Walker 1991; Wu et al. 2004). Enhanced Hsp70 protein expression has been observed with concomitant elevation in its phosphorylated state early after exercise in skeletal (Hernando and Manso 1997) and cardiac muscles (Melling

et al. 2009). Hsp70 protein can be phosphorylated in vitro by cAMP-dependent protein kinase (PKA), inhibiting its ability to enhance calcineurin activity (Lakshmikuttyamma et al. 2004). However, the physiologic relevance of Hsp70 ATPase domain-independent phosphorylation by upstream kinases remains unclear.

Enhanced Hsp70 protein expression is involved in the attenuation of the heat shock response (Abravaya et al. 1992) through inhibitory interaction with HSF1 transactivation domain (Akerfelt et al. 2010; Shi et al. 1998). In addition, enhanced Hsp70 protein expression provides cytoprotection to skeletal (Lepore et al. 2000) and cardiac muscles (Karmazyn et al. 1990) against subsequent injury (see Kregel 2002; Noble et al. 2010 for review). Enhanced Hsp70 protein expression localized to myofibrils (Paulsen et al. 2009) and increased binding to the sarcoplasmic/endoplasmic reticulum calcium ATPase 1a (SERCA1a) pump (Tupling et al. 2004) have been implicated in preserving function in response to exercise or heat stress, respectively. Enhanced Hsp70 protein has also been shown to play a role in preventing stress granule assembly (Gilks et al. 2004; Kedersha and Anderson 2002). Furthermore, Hsp70 protein interacts with ubiquitin ligase protein C-terminus of Hsc70-interacting protein to target those clients which cannot be refolded efficiently for proteasomal degradation (Hohfeld et al. 2001; Stankiewicz et al. 2010). Finally, Hsp70 protein plays a role in activating proliferative pathways (Song et al. 2001) and suppressing apoptotic cascades (Giffard et al. 2008; Mosser et al. 2000) by mediating the conformation of clients involved in signal transduction. Taken together, enhanced Hsp70 protein expression attenuates the heat shock response and minimizes reactivation following subsequent injury through cytoprotective function at a multitude of levels within the skeletal myofiber. Hsp70 protein presumably engages in these same activities post-exercise to provide the protection that is observed in response to physical activity.

Perspectives

This review has consolidated the various levels of transcriptional and translational regulations governing *hsp70* gene expression in response to exercise and heat stress per se with a special focus on skeletal myofibers (see Fig. 1 for review). In summary, while heat stress represses general gene expression, enhanced expression of survival transcript, *hsp70*, specifically prevails as HSF1 sustains transactivation and HSE acquisition under these conditions. Heat stress promotes architectural changes to the chromatin at *hsp70* gene loci, which serve to epigenetically upregulate expression. Pre-transcriptional regulation of HSF1 seems to exert the greatest control over the heat shock response as the appearance of

Fig. 1 At rest, global intron splicing, (as coupled with *Pol-II*), and cap-dependent translation (80S) proceed at basal rates in the skeletal myofiber. Under these conditions, the *hsp70* gene nuclear factor, *HSF1*, activity is negatively regulated in both the nucleus and cytoplasm via constitutive phosphorylation (black beads) by *pERK1/2*, *GSK-3 β* , and other kinases? and via sequestration by *Hsp70*, *Hsp90*, and other binding proteins (BP?). In this state, *HSF1* sustains transactivational inhibition, causing *Pol-II* to remain in a promoter-paused state (tethered to PIC), thus suppressing downstream *hsp70* mRNA and protein expression. In response to heat stress, global intron splicing (as coupled with *Pol-II*) and cap-dependent translation (80S) become impaired. Under these conditions, *HSF1* becomes activated via homotrimerization, gain in phosphorylative status (white beads) via *CAMKII* and other kinases?, and transactivation upon binding to the HSE promoter. In doing so, activated *HSF1* promotes *Pol-II* escape from PIC and, thus, vigorous

increase in *hsp70* mRNA transcriptional rate. Heat stress promotes hyperacetylation of the *hsp70* gene (*CH₃COR*), which enhances *HSF1* access to the HSE. Accumulation of *hsp70* mRNA is thought to result in protein production. Post-transcriptionally, *hsp70* mRNA concentrates near the nucleus and circumvents heat stress-related nuclear retention of bulk mRNA, degradation as afforded by extension of poly(A)-tail (AAA), and destabilization via protection by PKR. Pre-translationally, *hsp70* mRNA avoids inclusion into stress granules and is preferentially translated via an IRES. Post-translationally, nascent *Hsp70* protein localizes to SERCA1a calcium pump and myofibrils in the cytoplasm and commences chaperoning activity early after synthesis as coupled with ATP hydrolysis to promote the refolding of denatured peptides. The role of exercise? in inducing *hsp70* mRNA and protein expression by the aforementioned mechanisms remains unclear in the skeletal myofiber. For definition of terms, please see the main text

hsp70 mRNA thereafter strongly supports functional protein production. Post-transcriptionally, intronless *hsp70* mRNA circumvents a host of decay pathways as well as heat stress-repressed pre-mRNA splicing and nuclear export to become available for translation. Pre-translationally, *hsp70* mRNA is excluded from stress granules and preferentially translated during heat stress-repressed global cap-dependent translation. Post-translationally, nascent *Hsp70* protein is thermodynamically stable at elevated temperatures, allowing for the commencement of chaperoning activity early after synthesis to attenuate the heat shock response and protect against subsequent injury. Taken together, elevated *hsp70* mRNA

abundance is thought to be closely coupled with functional protein accumulation.

Given the extensive capillarization and proximity of neighboring myofibers in a skeletal muscle, the elevated temperature associated with exercise is thought to pose homogenous heat stress to all myofibers (Watkins et al. 2007). However, exercise promotes a more robust (O'Neill et al. 2006) and rapid (Tupling et al. 2007) *Hsp70* protein expression in the phenotypically slower contracting and more oxidative myofibers of the skeletal muscle. This differential *Hsp70* protein expression suggests that the physiologic stress associated with myofiber recruitment during exercise, and the

resulting elevated temperatures as a by-product of contraction, may, collectively be responsible for enhanced *hsp70* gene expression in response to exercise.

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