Chapter 3
Heat Shock Response and Metabolism in Skeletal Muscle

Yuki Tamura

Abstract Skeletal muscle comprises approximately 40% of the total body mass in humans. It plays important roles in locomotion, metabolism and endocrine signaling. We and others have previously described the biological responses/adaptations of skeletal muscle to heat stress, the contributions of heat shock proteins to the cellular processes underlying the muscle response to heat stress, and the therapeutic potential of manipulating heat stress and heat shock proteins in skeletal muscle. In this chapter, I briefly summarize current understanding of the heat stress-induced regulation of protein, glucose and mitochondrial metabolism in skeletal muscle. Furthermore, I overview future perspectives on studies of the heat shock response in skeletal muscle biology.

Keywords Atrophy · Glucose · Heat shock proteins · Hypertrophy · Mitochondria · Skeletal muscle

Abbreviations

AMPK	AMP-activated protein kinase
BGP-15	O-[3-piperidino-2-hydroxy-1-propyl]-nicotinic amidoxime
CaMKII	Ca2+/calmodulin-dependent protein kinase II
DEPTORDEP	domain-containing mTOR-interacting protein
FOXO	forkhead box O
GLUT	glucose transporter
HSE	heat shock element

Y. Tamura (✉)
Graduate School of Health and Sport Science, Nippon Sport Science University, Tokyo, Japan

Faculty of Sport Science, Nippon Sport Science University, Tokyo, Japan

Center for Coaching Excellence, Nippon Sport Science University, Tokyo, Japan

Research Institute for Sport Science, Nippon Sport Science University, Tokyo, Japan
e-mail: y-tamura@nittai.ac.jp

A. A. A. Asea, P. Kaur (eds.), *Heat Shock Proteins in Signaling Pathways*,
Heat Shock Proteins 17, https://doi.org/10.1007/978-3-030-03952-3_3

HSF1	heat shock factor 1
HSP	heat shock protein
IGF-1	insulin-like growth factor 1
JNK	c-Jun N-terminal kinases
LC3	microtubule-associated proteins 1A/1B light chain 3
MAPK	mitogen-activated protein kinase
MFN2	mitofusion 2
MLST8	MTOR associated protein
mTOR	mechanistic target of rapamycin
NRF	nuclear respiratory factor
PGC-1α	peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PP2A	protein phosphatase 2
PPAR	peroxisome proliferator-activated receptor
PRAS	proline-rich Akt substrate
RAPTOR	regulatory-associated protein
ROS	reactive oxygen species
UPR	unfolded protein response
VDAC	voltage-dependent anion channels

3.1 Introduction

In humans, skeletal muscle comprises approximately 40% of total body mass. It clearly plays important roles in the activities of daily life and in exercise/sport. Furthermore, it is the largest tissue regulating systemic metabolism. For example, 70–80% of circulating glucose is taken up by and metabolized in skeletal muscle (DeFronzo et al. 1981). In addition, skeletal muscle can convert kynurenine (a liver-derived molecule associated with psychological depression) into kynurenic acid, improving stress-induced depression (Agudelo et al. 2014). More generally, skeletal muscle-initiated organ-crosstalk is a research field that has expanded recently (Schnyder and Handschin 2015). For instance, muscle-derived hormone-like peptides (myokines) such as IL6, irisin and meteorin-like trigger adipose thermogenic remodeling and promote hippocampus memory formation (Schnyder and Handschin 2015). Skeletal muscle is highly plastic in response to local and systemic conditions such as the mechanical and nutritional environment. Exercise/training improves skeletal muscle mass and functions. In contrast, skeletal muscle health is impaired by disuse, injury, aging and disease. Taken together, emerging evidence strongly indicates that the maintenance or improvement of skeletal muscle mass and function could be a good therapeutic approach for improving quality of life. We and others have previously described (1) biological responses/adaptations to heat stress, (2) the contributions of heat shock proteins (HSP) to the underlying cellular processes, and (3) the therapeutic potential of targeting heat stress and HSP in skeletal muscle. In this section, I briefly summarize current understanding of the heat stress-induced regulation of protein, glucose and mitochondrial metabolism in skeletal muscle.

3.1.1 Heat Shock Response and Heat Shock Proteins in Skeletal Muscle

The heat shock response and induction of HSP are believed to be essential biological processes for the maintenance of protein homeostasis (proteostasis) (Schlesinger 1990). The most well-accepted, basic role of HSP is their function as molecular chaperones. HSP helps de novo protein folding, the refolding of denaturized proteins, protein trafficking, and proteolysis. Stress-inducible HSP expression is driven via the activation of heat shock responsive transcriptional factor 1 (HSF1). Under basal conditions, HSF1 exists as monomer and in a repressed state for heat shock element (HSE) binding and transcriptional activity. In contrast, under stress conditions including heat shock, proteotoxicity or physiological stress (for example, mechanical stress, osmolality shock, energy imbalance), HSF1 forms a trimer, binds to HSE and promotes the transcription of target genes (especially HSP). Induction of the heat shock response and HSP in skeletal muscle can be triggered by exercise and drugs (for example, BGP-15, celastrol) as well as heat stress (Henstridge et al. 2014; Ma et al. 2015). Both a single bout of endurance exercise and chronic endurance training increase several types of HSP (for example, HSP72, HSP60, HSP10, HSP25) (Morton et al. 2009). Interestingly, HSP induced by a single bout of exercise return to pre-exercise level within 2–4 days (Oishi and Ogata 2012). However, elevated HSP induced by chronic endurance training does not return to pre-training levels for at least 28 days (Oishi and Ogata 2012). This suggests that the protein stability or half-life of HSP can be modulated by repeated bouts of exercise. However, the regulation of HSP protein stability is not well understood.

3.1.2 Heat Shock Response and Myofibril Remodeling

Fundamentally, skeletal muscle mass is determined by the net balance between protein synthesis and protein breakdown. Mechanistic (mammalian) target of rapamycin complex 1 (mTORC1) has been extensively studied as a key phosphokinase that controls protein synthesis. mTORC1 is a protein complex composed of mTOR, RAPTOR, MLST 8, PRAS 40 and DEPTOR. mTORC1 is activated by amino acids (especially leucine), mechanical loads, insulin and growth factors (for example, insulin-like growth factor-1 [IGF-1]). When mTORC1 is activated, it both inhibits the translation initiation inhibitor, and activates ribosomes. In recent years, ribosomal biogenesis has also attracted attention as a factor controlling skeletal muscle protein synthesis. For further details on protein synthesis in skeletal muscle, please refer to a review by Yoon (2017).

On the other hand, protein degradation mechanisms can be divided into (1) the ubiquitin–proteasome system, (2) the autophagy–lysosome system, and (3) the apoptosis system. The ubiquitin–proteasome system is a mechanism to selectively degrade proteins labeled with poly-ubiquitin chains. MuRF1 and Atrogin 1 have

been identified as the E3 ubiquitin ligases of myofibers in skeletal muscle. The autophagy–lysosomal system is a mechanism for the non-selective proteolysis of proteins following their delivery by autophagosomes to lysosomes. Interestingly, autophagy acts as double-edged sword in the regulation of skeletal muscle mass—skeletal muscle atrophy is induced by both excessive and insufficient autophagy. Although autophagy was originally discovered as a non-selective proteolysis mechanism, some types of selective autophagy are now known (for example, mitochondria-selective, "mitophagy"; described below). Apoptosis is a type of programmed cell death. Following the release of cytochrome c from the mitochondria into the cytoplasm, several steps of caspase signal transduction are activated culminating in caspase-3 cleaving genomic DNA. In recent years, the importance of mitochondria-independent apoptosis (that is, endoplasmic reticulum stress-initiated cell death) in skeletal muscle mass regulation has increasingly been recognized. These protein degradation systems can act cooperatively or independently, depending on the cellular environment. The expression of genes encoding proteolytic enzymes is controlled by the FoxO transcription factor family. For further details on proteolysis mechanisms, please refer to a review by Bonaldo and Sandri (2013).

The heat shock response and HSP affect skeletal muscle mass in the basal state and in overloading/unloading conditions. In studies using cultured cells, it has been shown that myotube diameter is decreased by HSP 72 knockdown (Gwag et al. 2015). An analysis of skeletal muscle from HSF1-deficient mice showed that the proportion of slow muscle fibers was reduced (Ohno et al. 2015). Consistent with this observation, continuous heat stress promotes the differentiation of myoblasts to slow-fiber dominant myotubes (Yamaguchi et al. 2013). There is a consensus that heat stress suppresses disuse atrophy in skeletal muscle, based on various experimental approaches. Interestingly, attenuation of skeletal muscle atrophy is also observed following relatively mild heat stress that is insufficient for HSP induction (Naito et al. 2012). This suggests that HSP72 is sufficient but not necessary for the heat stress-induced attenuation of muscle atrophy. Yoshihara and coworkers reported that transient heat stress activates the Akt/mTORC1 pathway in rat skeletal muscle. Interestingly, activation of the Akt/mTORC1 pathway by heat stress is temperature dependent (that is, higher temperature results in more activation) (Yoshihara et al. 2013). Studies on cultured cells have reported that the inhibition of mTORC1 activation by heat stress results in insufficient activation of HSF1 and HSP induction (Chou et al. 2012). Therefore, the primary significance of mTORC1 activation by heat stress is likely to be cell protection.

In recent years, studies on cultured cells have been employed to clarify mechanisms underlying the beneficial effects of heat stress on muscle atrophy. Tsuchida and coworkers recently established an in vitro experimental model of the heat stress-induced attenuation of muscle atrophy (glucocorticoid-induced myotube atrophy and heat stress) (Tsuchida et al. 2017). They found that its molecular basis was the suppression of decreased mTORC1 pathway activity by glucocorticoids and the reduced expression of enzymes related to FoxO and the ubiquitin proteasome system. On the other hand, studies on rat muscles in vivo have shown that heat stress suppresses the increase in apoptosis induced by hindlimb suspension (Yoshihara

et al. 2015). Interestingly, suppression of the ubiquitin–proteasome system by heat stress was observed only in the soleus muscle (slow muscle fiber-dominant) (Yoshihara et al. 2015). This suggests that the molecular mechanism of muscle atrophy suppression by heat stress may be dependent on muscle fiber type. We have also shown that heat stress partially suppresses age-related muscle atrophy (Tamura et al. 2017). However, since this effect was characterized mainly on the basis of muscle weight, it will be necessary to support our conclusion with physiological measurements such as muscular strength and endurance.

In addition to perspectives from rehabilitation, heat stress can be an effective strategy to promote exercise/training adaptations. It is well-accepted that resistance exercise is the most effective option for inducing skeletal muscle hypertrophy and preventing disuse atrophy. It is now known that heat stress both during and after resistance exercise potentiates the activation of Akt/mTORC1 signaling (Kakigi et al. 2011). Although techniques to enhance the effect of resistance exercise have focused mainly on nutritional approaches, these results suggest that heat stress therapy could be another option.

3.1.3 Heat Shock Response and Glucose Metabolism in Skeletal Muscle

Skeletal muscle is the largest tissue which takes up and metabolizes circulating glucose. Therefore, improving the insulin sensitivity, glucose uptake, oxidation and storage capacity of skeletal muscle are promising strategies for preventing and treating type 2 diabetes. Glucose uptake in skeletal muscle can be divided into the insulin-dependent and -independent pathways. When insulin is secreted in response to elevated circulating glucose levels, it binds to the insulin receptor on the cell membrane of skeletal muscle and activates intracellular signal transduction. Subsequently, cytoplasmic glucose transporter 4 (GLUT4) translocates to the cell membrane and takes up circulating glucose. On the other hand, it has been shown that the increases in adenosine monophosphate/triphosphate and calcium concentration associated with muscle contraction activate adenosine monophosphate-activated protein kinase (AMPK). AMPK also induces the translocation of GLUT4 to the cell membrane. Therefore, as a transient cellular response, it is important to sufficiently induce the translocation of GLUT4. Based on these findings, it is considered that exercise training is the best way to reduce circulating glucose levels in healthy and diabetic individuals.

It has been reported that insulin resistance in patients with type 2 diabetes is improved by hot tub therapy (Hooper 1999). Even in studies on experimental animals, it has been shown that insulin resistance due to a high fat diet is also improved by local heat stress to skeletal muscle (Gupte et al. 2009). These authors also found that daily heat stress suppresses continuous activation of the c-Jun N-terminal kinase (JNK) signaling cascade (the JNK pathway is involved in the

development of insulin resistance) (Gupte et al. 2009). They concluded that the attenuation of JNK activation by heat stress is at least in part mediated by HSP72, based on experiments with an HSP72 inhibitor (Gupte et al. 2009). Furthermore, it has been shown that muscle-specific over-expression of HSP72 improves the insulin resistance associated with a high fat diet (Henstridge et al. 2014). Moreover, improvement of insulin resistance is also triggered by administering BGP-15, an inducer of HSP72 expression, supporting data from genetically modified animals. As described above, expression of HSP72 is also induced by endurance exercise and training. It has been shown that, when induction of HSP72 expression is attenuated by endurance exercise in a cold environment, improvements in glucose metabolism are also attenuated (Tsuzuki et al. 2017). To integrate these findings, increasing HSP72 in skeletal muscle appears to be a sufficient intervention for improving insulin resistance. In addition, we found that daily heat stress increases the GLUT4 protein content of skeletal muscle (Tamura et al. 2015). Therefore, it is thought that daily heat stress can up-regulate the de novo glucose uptake capacity of skeletal muscle.

On the other hand, it has been shown that skeletal muscle glucose uptake is also promoted immediately after a single heat stress treatment. Since increased HSP72 was not observed in this context, it appears that an HSP72-independent pathway also contributes to improved glucose metabolism (Koshinaka et al. 2013). This and other studies employed an isolated skeletal muscle model (an ex vivo model) to interrogate the direct role of skeletal muscle in glucose uptake. It has been shown that a single bout of heat stress increases glucose uptake in isolated skeletal muscle (Goto et al. 2015). Interestingly, there is an additive effect of heat stress and insulin on glucose uptake. Goto et al. have shown that AMPK is activated by heat stress, and pharmacological inhibition of AMPK prevents the promotion of glucose uptake by heat stress (Goto et al. 2015). However, the effects of heat stress on AMPK activity are controversial. For example, it has been shown that AMPK inactivation is observed when heat stress is applied to various cultured cells, including skeletal muscle cells (Wang et al. 2010). The molecular mechanism of this effect has been shown to involve an increase in the phospholipid, PP2A (a component of the cell membrane). AMPK inactivation by heat stress has also been shown to be an essential response for the induction of HSP72. We have confirmed that AMPK is inactivated by heat stress in mouse skeletal muscle (Tamura et al. 2014). Overall, the effect of heat stress on AMPK activity is more likely attributable to differences in heat stress conditions, such as temperature and time, rather than to in vitro, ex vivo and in vivo differences such as humoral factors. In addition, as for the physiological significance of inducing HSP expression, there may be different molecular mechanisms depending on the temperature range. AMPK has been shown to be involved in various biological processes such as mitochondrial biogenesis (described below) and is positively involved in autophagic regulation (Sanchez et al. 2012). Therefore, it is important to better understand how the response of AMPK is affected by different experimental conditions. To summarize this section, several lines of evidence indicate that heat stress can be an effective alternative strategy for diabetic patients with low physical fitness.

3.1.4 Heat Shock and Mitochondrial Biogenesis/Turnover in Skeletal Muscle

Mitochondria are organelles responsible for energy production. In particular, improving the content and function of mitochondria in skeletal muscle contributes to improved exercise performance at sub-maximal intensity through sparing glycogen (Fitts et al. 1975). Furthermore, mitochondria trigger and/or mediate various biological processes and signal transduction pathways by buffering intracellular Ca2+ concentrations, producing reactive oxygen spices (ROS), and regulating apoptotic cell death. Recent emerging evidence demonstrates that decreased and/or dysfunctional mitochondria in skeletal muscle cause skeletal muscle atrophy with disuse and aging, and systemic metabolic disease with the dysfunction of other organs affected through neural or circulating factors (Tezze et al. 2017). In this section, we outline our recent findings on heat stress and mitochondrial adaptation in skeletal muscle. For further information on heat stress and mitochondrial adaptation, please also refer to our recent review (Tamura and Hatta 2017). For more general information about the adaptive mechanism and biological significance of mitochondria in skeletal muscle, see recent reviews by Hood and coworkers (Tryon et al. 2014; Carter et al. 2015; Hood et al. 2015, 2016; Kim et al. 2017).

Mitochondrial content is determined by the net balance between mitochondrial biogenesis and breakdown (mitophagy). Mitochondrial biogenesis can be divided into three steps: (1) transcription of mitochondria-related genes, (2) translation of mitochondria-related gene products, and (3) the processing of mitochondrial-related proteins by post-translational modification and transport, folding and assembly. Among these steps, the transcription process has been most extensively studied. It is accepted that PGC-1α plays important roles in the transcription of mitochondria-related genes. PGC-1α acts as a transcriptional booster, cooperating with transcription factors (for example, NRF1/2, p53, PPARs). Mitochondria-related genes are encoded by both nuclear and mitochondrial DNA. In the basal state, PGC-1α is mainly localized in the cytosol. However, when PGC-1α is activated, it translocates into the nucleus and mitochondria, and then promotes the transcription of mitochondria-related genes. PGC-1α activation has been shown to be induced following activation of upstream factors such as AMPK, p38 MAPK, CaMKII and mTORC1. In contrast, the mechanisms involved in the translation and subsequent processing of mitochondria-related gene products are not well understood. Importantly, this limitation is common in mitochondrial biology, and does not apply only to skeletal muscle.

The content of mitochondria is determined not only by mitochondrial biogenesis but also by mitochondrial degradation. The cellular machinery of mitochondrial breakdown (mitochondrial selective autophagy—mitophagy) has been a rapidly growing research field in recent years (Drake and Yan 2017). There are several mitophagic pathways, but here, we briefly discuss Parkin-mediated mitophagy. Dysfunctional and unhealthy mitochondria produce high levels of ROS and impair

cellular processes and integrity. Therefore, it is necessary to remove dysfunctional mitochondria from cells. The mitochondrial E3 ubiquitin ligase, Parkin, translocates from the cytosol to the mitochondrial outer-membrane in response to a decrease in mitochondrial membrane potential and the accumulation of oxidative stress. Parkin promotes the poly-ubiquitination of mitochondrial outer-membrane proteins (for example, VDAC, Mfn2). The poly-ubiquitin chain is then recognized by p62/SQSTM1, which is known as an autophagic substrate and an adapter protein for autophagosomes. LC3-II, a key autophagosome molecule, recognizes p62/SQSTM1 and targets the bound mitochondria for breakdown, transport to lysosomes, and finally, degradation.

Liu and Brooks first demonstrated that heat stress increases mitochondrial content in cultured cells (Liu and Brooks 2012). Furthermore, we have recently reported that heat stress-induced mitochondrial biogenesis is observed in mouse skeletal muscle (Tamura et al. 2014). To explore the significance of our observation in vivo, we have also investigated heat stress interventions as post-exercise therapy. We found that heat stress after exercise has additive effects with endurance training on enhancing mitochondrial biogenesis (Tamura et al. 2014). Interestingly, this additive effect of heat stress depends on the in vivo environment. It has been shown that a high-fat diet increases mitochondrial content in skeletal muscle (Hancock et al. 2008). However, it has also been found that the mitochondrial biogenesis associated with a high-fat diet disappears when mice are subjected to heat stress (Gupte et al. 2009). We have also examined the mechanism by which mitochondrial biogenesis is induced by heat stress. We found that a single bout of heat stress increased PGC-1α protein content in nuclear and mitochondrial fractions (unpublished observations). We have confirmed that heat stress acutely increases the mRNA level of mitochondria-related genes (unpublished observations), consistent with the translocation of PGC-1α. We interpret these observations as heat stress activating the transcriptional step of mitochondrial biogenesis in a PGC-1α-centered manner.

We next examined the mechanism underlying PGC-1α activation by heat stress. We found that p38 MAPK and mTORC1 are activated by heat stress (Tamura et al. 2014). Interestingly, a pioneering study by Liu and Brooks showed that the activation of mitochondrial biogenesis by heat stress is mediated by activation of AMPK (Liu and Brooks 2012). However, as described above, AMPK was inactivated in our study. Therefore, we suggest that various factors contribute to mitochondrial biogenesis induction by heat stress. In addition, mechanisms underlying mitochondrial biogenesis might involve not only the repeated transient activation of PGC-1α, but also a stable increase in PGC-1α content. We have confirmed that the content of PGC-1α mRNA is increased by heat stress (unpublished observations). Interestingly, it has recently been clarified that HSF1 functions as a transcription factor for PGC-1α (Ma et al. 2015). Also, in a study of the liver, it was shown that liver mitochondria are decreased following knockout of HSF1 (Qiao et al. 2017). Therefore, the heat shock response and oxidative energy metabolism are much more closely-linked than conventional understanding would suggest. It has been reported that the over-expression of HSP72 in skeletal muscle increased mitochondrial content. Interestingly, overexpression of HSP72 does not alter the amount of

PGC-1α (Henstridge et al. 2014). Moreover, an HSP72 knockout mouse displays abnormal mitochondria (Drew et al. 2014). Therefore, it will be necessary in the future to carefully study the control of protein transport and folding for mechanistic insights into the contribution of HSP72.

Based on our findings showing that heat stress increases mitochondrial content, we examined whether heat stress also counteracts the mitochondrial loss associated with skeletal muscle disuse. Reduction and dysfunction of mitochondria in skeletal muscle have also been shown to cause muscle atrophy following disuse (Powers et al. 2012). We examined whether heat stress can suppress the decrease of mitochondria caused by experimental muscle disuse (sciatic nerve resection; denervation). As expected, we found that heat stress partially suppressed the decrease in mitochondrial content and skeletal muscle atrophy caused by denervation (Tamura et al. 2015). Although we initially thought that PGC-1α-mediated mitochondrial biogenesis could have contributed to this effect, we did not obtain any results supporting this possibility. On the other hand, since mitophagy is activated by denervation, we decided to study the effect of heat stress on mitophagy. Interestingly, heat stress attenuated the activation of mitophagy induced by denervation. We next tested a molecular mechanism potentially underlying the contribution of heat stress. It was revealed that mitochondrially localized Parkin, the state of mitochondrial poly-ubiquitination, and the amount of p62 bound to mitochondria were all increased by denervation, but these increases were attenuated by heat stress.

However, this result should be interpreted carefully. If the mitochondria to be broken down are not degraded, the attenuation of mitochondrial clearance by heat stress is not always preferable (because unhealthy mitochondria would accumulate). Therefore, we decided to evaluate mitochondrial oxidative stress, because oxidative stress and mitochondrial dysfunction can be both cause and consequence, forming a vicious circle. Although mitophagy is a quality control mechanism at the organelle level, in recent years, the mitochondrial unfolded protein response (UPR^{mt}) has received attention as a quality control mechanism at the molecular level. We have also examined the mitochondrial stress response and the response of mitochondrial proteases from the viewpoint of the UPR^{mt}. As a result, both mitochondrial oxidative stress and mitochondrial proteases were increased by denervation, but it became clear that heat stress improves than rather worsens the UPR^{mt} (Tamura et al. 2015, Tamura et al. unpublished observations). Therefore, we consider that the primary effect of heat stress on denervated mitochondria is to improve mitochondrial health. Subsequently, the need to degrade mitochondria is reduced. In recent years, attention has been paid to the function and dynamics of HSP in mitochondrial health. Over-expression of mitochondrial HSP in skeletal muscle has been shown to suppress mitochondrial dysfunction (Sarangi et al. 2013). It has also been shown that HSP72, which was considered to be a cytoplasmic HSP, translocates to mitochondria in response to mitochondrial stress, interacting with parkin (Drew et al. 2014). These observations suggest that an HSP-centered, dynamic mitochondrial quality control mechanism is becoming more important to our understanding of mitochondrial and muscle biology.

3.2 Conclusions

I believe that more attention should be paid to the physiological roles of the HSF1-dependent heat shock response and HSP other than their function as molecular chaperones. In recent years, roles of the transcription factor, HSF1 other than HSP synthesis have received the most attention (Li et al. 2017; Gomez-Pastor et al. 2017). In addition, the regulation of HSF1 activity has been examined in the past from the perspectives of the content and post-translational modification of HSF1. It is also necessary to pay attention to the epigenetic regulation of HSF1 transcriptional activity, such as changes in the chromatin structure of HSF1 target genes. We have recently performed transcriptome and bioinformatics analyses to discover novel responses to heat stress in skeletal muscle. We detected the activation of pathways other than HSF1–HSP (unpublished observation). Overall, searching for new targets regulated by HSF1 and integrating our understanding of heat shock responses other than HSF1 will be necessary in the future.

Acknowledgements Yuki Tamura is the recipient of a post-doctoral fellowship from the Japan Society for the Promotion of Science, Tokyo, Japan.

References

Agudelo LZ, Femenía T, Orhan F, Porsmyr-Palmertz M, Goiny M, Martinez-Redondo V et al (2014) Skeletal muscle PGC-1α1 modulates kynurenine metabolism and mediates resilience to stress-induced depression. Cell 159(1):33–45

Bonaldo P, Sandri M (2013) Cellular and molecular mechanisms of muscle atrophy. Dis Model Mech 6(1):25–39

Carter HN, Chen CCW, Hood DA (2015) Mitochondria, muscle health, and exercise with advancing age. Physiology 30(3):208–223

Chou S-D, Prince T, Gong J, Calderwood SK (2012) mTOR is essential for the proteotoxic stress response, HSF1 activation and heat shock protein synthesis. PLoS One 7(6):e39679

DeFronzo RA, Alvestrand A, Smith D, Hendler R, Hendler E, Wahren J (1981) Insulin resistance in uremia. J Clin Investig 67(2):563–568

Drake JC, Yan Z (2017) Mitophagy in maintaining skeletal muscle mitochondrial proteostasis and metabolic health with aging. J Physiol. https://doi.org/10.1113/JP274337

Drew BG, Ribas V, Le JA, Henstridge DC, Phun J, Zhou Z et al (2014) HSP72 is a mitochondrial stress sensor critical for Parkin action, oxidative metabolism, and insulin sensitivity in skeletal muscle. Diabetes 63(5):1488–1505

Fitts RH, Booth FW, Winder WW, Holloszy JO (1975) Skeletal muscle respiratory capacity, endurance, and glycogen utilization. Am J Phys 228(4):1029–1033

Gomez-Pastor R, Burchfiel ET, Thiele DJ (2017) Regulation of heat shock transcription factors and their roles in physiology and disease. Nat Rev Mol Cell Biol. https://doi.org/10.1038/nrm.2017.73

Goto A, Egawa T, Sakon I, Oshima R, Ito K, Serizawa Y et al (2015) Heat stress acutely activates insulin-independent glucose transport and 5′-AMP-activated protein kinase prior to an increase in HSP72 protein in rat skeletal muscle. Physiol Rep 3(11):e12601

Gupte AA, Bomhoff GL, Swerdlow RH, Geiger PC (2009) Heat treatment improves glucose tolerance and prevents skeletal muscle insulin resistance in rats fed a high-fat diet. Diabetes 58(3):567–578

Gwag T, Park K, Park J, Lee JH, Nikawa T, Choi I (2015) Celastrol overcomes HSP72 gene silencing-mediated muscle atrophy and induces myofiber preservation. J Physiol Pharmacol 66(2):173–283

Hancock CR, Han DH, Chen M, Terada S, Yasuda T, Wright DC, Holloszy JO (2008) High-fat diets cause insulin resistance despite an increase in muscle mitochondria. Proc Natl Acad Sci 105(22):7815–7820

Henstridge DC, Bruce CR, Drew BG, Tory K, Kolonics A, Estevez E et al (2014) Activating HSP72 in rodent skeletal muscle increases mitochondrial number and oxidative capacity and decreases insulin resistance. Diabetes 63(6):1881–1894

Hood DA, Tryon LD, Vainshtein A, Memme J, Chen C, Pauly M et al (2015) Exercise and the regulation of mitochondrial turnover. Prog Mol Biol Transl Sci 135:99–127

Hood DA, Tryon LD, Carter HN, Kim Y, Chen CC (2016) Unravelling the mechanisms regulating muscle mitochondrial biogenesis. Biochem J 473(15):2295–2314

Hooper PL (1999) Hot-tub therapy for type 2 diabetes mellitus. N Engl J Med 341(12):924–925

Kakigi R, Naito H, Ogura Y, Kobayashi H, Saga N, Ichinoseki-Sekine N et al (2011) Heat stress enhances mTOR signaling after resistance exercise in human skeletal muscle. J Physiol Sci 61(2):131–140. https://doi.org/10.1007/s12576-010-0130-y

Kim Y, Triolo M, Hood DA (2017) Impact of aging and exercise on mitochondrial quality control in skeletal muscle. Oxidative Med Cell Longev 2017. https://doi.org/10.1155/2017/3165396

Koshinaka K, Kawamoto E, Abe N, Toshinai K, Nakazato M, Kawanaka K (2013) Elevation of muscle temperature stimulates muscle glucose uptake in vivo and in vitro. J Physiol Sci 63(6):409–418

Li J, Labbadia J, Morimoto RI (2017) Trends Cell Biol. https://doi.org/10.1016/j.tcb.2017.08.002

Liu CT, Brooks GA (2012) Mild heat stress induces mitochondrial biogenesis in C2C12 myotubes. J Appl Physiol 112(3):354–361

Ma X, Xu L, Alberobello AT, Gavrilova O, Bagattin A, Skarulis M et al (2015) Celastrol protects against obesity and metabolic dysfunction through activation of a HSF1-PGC1α transcriptional axis. Cell Metab 22(4):695–708

Morton JP, Kayani AC, McArdle A, Drust B (2009) The exercise-induced stress response of skeletal muscle, with specific emphasis on humans. Sports Med 39(8):643–662

Naito H, Yoshihara T, Kakigi R, Ichinoseki-Sekine N, Tsuzuki T (2012) Heat stress-induced changes in skeletal muscle: heat shock proteins and cell signaling transduction. J Phys Fit Sports Med 1(1):125–131

Ohno Y, Egawa T, Yokoyama S, Nakai A, Sugiura T, Ohira Y et al (2015) Deficiency of heat shock transcription factor 1 suppresses heat stress-associated increase in slow soleus muscle mass of mice. Acta Physiol 215(4):191–203

Oishi Y, Ogata T (2012) Skeletal muscle fiber plasticity: heat shock proteins and satellite cell activation. J Phys Fitness Sports Med 1(3):473–478

Powers SK, Wiggs MP, Duarte JA, Zergeroglu AM, Demirel HA (2012) Mitochondrial signaling contributes to disuse muscle atrophy. Am J Physiol Endocrinol Metab 303(1):E31–E39

Qiao A, Jin X, Pang J, Moskophidis D, Mivechi NF (2017) The transcriptional regulator of the chaperone response HSF1 controls hepatic bioenergetics and protein homeostasis. J Cell Biol 216(3):723–741

Sanchez AMJ, Candau RB, Csibi A, Pagano AF, Raibon A, Bernardi H (2012) The role of AMP-activated protein kinase in the coordination of skeletal muscle turnover and energy homeostasis. Am J Physiol Cell Physiol 303(5):C475–C485

Sarangi U, Singh MK, Abhijnya KVV, Prasanna Anjaneya Reddy L, Siva Prasad A, Pitke VV et al (2013) Hsp60 chaperonin acts as barrier to pharmacologically induced oxidative stress mediated apoptosis in tumor cells with differential stress response. Drug Target Insights 2013(7):35–51

Schlesinger MJ (1990) Heat shock proteins. J Biol Chem 265(21):12111–12114

Schnyder S, Handschin C (2015) Skeletal muscle as an endocrine organ: PGC-1α, myokines and exercise. Bone 80:115–125

Tamura Y, Hatta H (2017) Heat stress induces mitochondrial adaptations in skeletal muscle. J Phys Fit Sports Med 6(3):151–158

Tamura Y, Matsunaga Y, Masuda H, Takahashi Y, Takahashi Y, Terada S et al (2014) Postexercise whole body heat stress additively enhances endurance training-induced mitochondrial adaptations in mouse skeletal muscle. Am J Physiol Regul Integr Comp Physiol 307(7):R931–R943

Tamura Y, Kitaoka Y, Matsunaga Y, Hoshino D, Hatta H (2015) Daily heat stress treatment rescues denervation-activated mitochondrial clearance and atrophy in skeletal muscle. J Physiol 593(12):2707–2720

Tamura Y, Matsunaga Y, Kitaoka Y, Hatta H (2017) Effects of heat stress treatment on age-dependent unfolded protein response in different types of skeletal muscle. J Gerontol A Biol Sci Med Sci 72(3):299–308

Tezze C, Romanello V, Desbats MA, Fadini GP, Albiero M, Favaro G et al (2017) Age-associated loss of OPA1 in muscle impacts muscle mass, metabolic homeostasis, systemic inflammation, and epithelial senescence. Cell Metab 25(6):1374–1389

Tryon LD, Vainshtein A, Memme JM, Crilly MJ, Hood DA (2014) Recent advances in mitochondrial turnover during chronic muscle disuse. Integr Med Res 3(4):161–171

Tsuchida W, Iwata M, Akimoto T, Matsuo S, Asai Y, Suzuki S (2017) Heat stress modulates both anabolic and catabolic signaling pathways preventing dexamethasone-induced muscle atrophy in vitro. J Cell Physiol 232(3):650–664

Tsuzuki T, Kobayashi H, Yoshihara T, Kakigi R, Ichinoseki-Sekine N, Naito H (2017) Attenuation of exercise-induced heat shock protein 72 expression blunts improvements in whole-body insulin resistance in rats with type 2 diabetes. Cell Stress Chaperones 22(2):263–269

Wang T, Yu Q, Chen J, Deng B, Qian L, Le Y (2010) PP2A mediated AMPK inhibition promotes HSP70 expression in heat shock response. PLoS One 5(10):e13096. https://doi.org/10.1371/journal.pone.0013096

Yamaguchi T, Omori M, Tanaka N, Fukui N (2013) Distinct and additive effects of sodium bicarbonate and continuous mild heat stress on fiber type shift via calcineurin/NFAT pathway in human skeletal myoblasts. Am J Physiol Cell Physiol 305(3):C323–C333

Yoon MS (2017) mTOR as a key regulator in maintaining skeletal muscle mass. Front Physiol 8:00788

Yoshihara T, Naito H, Kakigi R, Ichinoseki-Sekine N, Ogura Y, Sugiura T, Katamoto S (2013) Heat stress activates the Akt/mTOR signalling pathway in rat skeletal muscle. Acta Physiol 207(2):416–426

Yoshihara T, Sugiura T, Yamamoto Y, Shibaguchi T, Kakigi R, Naito H (2015) The response of apoptotic and proteolytic systems to repeated heat stress in atrophied rat skeletal muscle. Physiol Rep 3(10):e12597