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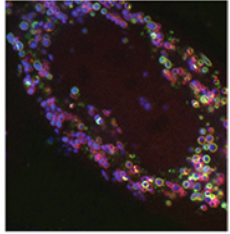
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# Heat shock response and autophagy— cooperation and control

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**Keywords:** autophagy, exercise, heat shock response, HSP70, humans, protein breakdown, protein synthesis

**Abbreviations:** AKT, v-akt murine thymoma viral oncogene homolog 1; AMPK, adenosine monophosphate-activated protein kinase; ATG, autophagy-related; BECN1, Beclin 1, autophagy related; EIF4EBP1, eukaryotic translation initiation factor 4E binding protein 1; ER, endoplasmic reticulum; FOXO, forkhead box O; HSF1, heat shock transcription factor 1; HSP, heat shock protein; HSPA8/HSC70, heat shock 70kDa protein 8; IL, interleukin; LC3, MAP1LC3, microtubule-associated protein 1 light chain 3; MTMR14/hJumpy, myotubularin related protein 14; MTOR, mechanistic target of rapamycin; NR1D1/Rev-Erb- $\alpha$ , nuclear receptor subfamily 1, group D, member 1; PBMC, peripheral blood mononuclear cell; PPARGC1A/PGC-1 $\alpha$ , peroxisome proliferator-activated receptor, gamma, coactivator 1  $\alpha$ ; RHEB, Ras homolog enriched in brain; SOD, superoxide dismutase; SQSTM1/p62, sequestosome 1; TPR, translocated promoter region, nuclear basket protein; TSC, tuberous sclerosis complex; ULK1, unc-51 like autophagy activating kinase 1.

Protein quality control (proteostasis) depends on constant protein degradation and resynthesis, and is essential for proper homeostasis in systems from single cells to whole organisms. Cells possess several mechanisms and processes to maintain proteostasis. At one end of the spectrum, the heat shock proteins modulate protein folding and repair. At the other end, the proteasome and autophagy as well as other lysosome-dependent systems, function in the degradation of dysfunctional proteins. In this review, we examine how these systems interact to maintain proteostasis. Both the direct cellular data on heat shock control over autophagy and the time course of exercise-associated changes in humans support the model that heat shock response and autophagy are tightly linked. Studying the links between exercise stress and molecular control of proteostasis provides evidence that the heat shock response and autophagy coordinate and undergo sequential activation and downregulation, and that this is essential for proper proteostasis in eukaryotic systems.

## Introduction

Protein quality control is fundamental to intracellular homeostasis. Central to this quality is a balance between protein folding

and protein degradation, the former controlled by cellular chaperones of the heat shock response,<sup>1</sup> and the latter by the ubiquitin-proteasome system,<sup>2</sup> autophagy,<sup>3</sup> and other lysosome-dependent systems.<sup>4</sup> Recent data support the idea that these systems influence each other.<sup>5,6</sup> Existing in prokaryotes and eukaryotes, the heat shock protein chaperone system of protein folding and assembly as well as regulation of degradation of denatured proteins is more evolutionarily ancient<sup>7</sup> compared to autophagy, which is exclusively a eukaryotic process. Given the greater evolutionary age of the heat shock system compared to autophagy, as well as the fact that the heat shock protein response functions in both protein conservation and degradation, a question arises of whether and how they are coordinated. Recent data<sup>5</sup> provide support for the idea that heat shock response does, in fact, exert control over autophagy.

Exercise results in widespread protein degradation followed by a similarly large scale building phase.<sup>8</sup> Thus, exercise can be used to follow the cross-regulation of protein breakdown and rebuilding, including novel regulatory paths that might exist. We propose that there is such a novel, previously unappreciated regulated crosstalk between heat shock-governed protein synthesis and folding and the protein degradation state driven by autophagy. In this review, by using the complex stress of exercise, we will discuss the model of cooperation between autophagy and heat shock response and highlight evidence suggesting an interaction and control between those 2 systems.

## Basic concepts

**The role of autophagy and heat shock response in protein homeostasis**

To be fully functional, proteins, after translation, fold into the correct 3-dimensional structure. In the crowded intracellular environment with a high risk of aggregation, a protein requires

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assistance to assume its native and functionally physiological conformation and avoid hydrophobic tangles, precipitation, and inappropriate protein interactions. In addition, intracellular problems (spontaneous transcriptional and translational errors, sudden increase in protein synthesis or excess of synthesized subunits, incorrect cellular localization, or the damaging effect of highly reactive free radicals) as well as extracellular stressors (high temperature, hypoxia, radiation, toxic chemicals, endotoxins, and osmotic pressure) can alter the folding capacity of a cell leading to translational arrest as well as the accumulation of misfolded or unfolded proteins.<sup>9-14</sup>

To insure protein homeostasis, cells employ several systems. These include intracellular removal or processing of misfolded proteins,<sup>15</sup> involving cellular chaperones, the ubiquitin-proteasome system, and autophagy. Intracellular or pericellular processing of abnormal proteins is a simple way of protein elimination, but if not controlled properly, may lead to cell death, dysregulation of homeostasis, and diseases such as Huntington,<sup>16</sup> amyloidosis,<sup>17</sup> Alzheimer,<sup>18</sup> or Parkinson.<sup>19</sup> The ubiquitin-proteasome system deals primarily with endogenous proteins. In this process, the poly-ubiquitin-protein complex binds to the regulatory unit of the proteasome, which unfolds and translocates the substrate proteins into the central chamber for proteolytic digestion.<sup>20</sup>

At basal levels or stress conditions, eukaryotic cells employ autophagy to remove misfolded proteins, large protein aggregates, and whole damaged organelles inaccessible to smaller proteolytic systems.<sup>21</sup> Under starvation conditions, autophagy represents an effective physiological response providing a biofuel from degraded macromolecules to maintain sufficient ATP production for adaptive macromolecular synthesis to survive stressful conditions.<sup>22</sup> There are 3 primary types of autophagy: chaperone-mediated autophagy, microautophagy, and macroautophagy. In chaperone-mediated autophagy, cytosolic proteins with a signature exposed pentapeptide motif (KFERQ)<sup>23,24</sup> are targeted by HSPA8/HSC70 (heat shock 70 kDa protein 8). After motif recognition by HSPA8 and subsequent binding to LAMP2A (lysosomal-associated membrane protein 2A), target proteins undergo unfolding and translocate into the lysosomal lumen where they are degraded.<sup>25</sup> During microautophagy, a small invagination of the lysosomal membrane sequestering cytosolic content is formed. After pinching off into the lysosomal lumen, the vacuole is degraded.<sup>26</sup> Macroautophagy (referred to hereafter as autophagy) can also be subdivided into several main stages. During the initial step, double- or multimembrane autophagic vacuoles called autophagosomes are formed by engulfing a portion of the cytoplasm or a damaged organelle.<sup>27,28</sup> Next, the autophagosomes fuse with lysosomes forming autolysosomes that degrade the captured material.<sup>27,29,30</sup>

Whereas autophagy is ubiquitous in eukaryotic cells,<sup>31</sup> the heat shock protein (HSP) chaperone system is a feature of both prokaryotes and eukaryotes. All living organisms employ the HSP system to convert nascent proteins into their native conformation<sup>7</sup> and to mediate the degradation of irreversibly denatured proteins that accumulate in the cells in response to various stressors. Thus, autophagy and the heat shock response represent 2 functionally distinct systems of cellular protein quality control.

Under cellular stress conditions, these 2 systems are likely to complement each other. A recent study<sup>5</sup> provided evidence that cells under certain conditions prioritize the HSP response over autophagy, and the heat shock response inhibits autophagy under conditions when both systems are activated.

### The role of autophagy in physiology of skeletal muscle

Growing evidence suggests that the right level of autophagy, along with the ubiquitin-proteasome system, is critical to homeostasis of skeletal muscle.<sup>32</sup> Two main approaches focusing on activation or inhibition of autophagy have been undertaken to delineate the role of autophagy in regulating the physiology of skeletal muscle.

Inhibition of autophagy in *autophagy-related (ATG) 5* and *ATG7* conditional knockout mice models leads to a small reduction in body growth, degenerative changes in muscle tissue, reduction in myofiber size, accumulation of protein aggregates, abnormal mitochondria, and reduction in muscle force leading to severe weakness.<sup>33,34</sup> Similarly, reduced autophagy in *col6a<sup>-1</sup>*/collagen VI-deficient mice results in the accumulation of dysfunctional organelles and promotes apoptosis and muscle atrophy.<sup>35</sup> Mutant mice with normal levels of basal autophagy but deficient in exercise- or starvation-induced autophagy show lower endurance, impaired glucose metabolism, and inhibited glucose uptake by skeletal muscle after a single bout of exercise. Moreover, the autophagy mutant mice lack chronic exercise-induced protection against glucose intolerance when fed a high-fat diet.<sup>36</sup> The importance of autophagy in the development of endurance capacity was further demonstrated in *becn1 (VPS30/ATG6)* heterozygous mice showing reduced basal autophagy flux, number of mitochondria, and capillary density in skeletal muscle.<sup>37</sup> Interestingly, diminished autophagy levels in sedentary *Becn1* heterozygotes does not influence the exercise performance when compared with wild-type animals, but completely prevents the development of muscle adaptation and physical endurance in response to several weeks of involuntary training among *Becn1* heterozygotes. To sum up, these studies demonstrate that autophagy plays a fundamental role in skeletal tissue homeostasis and, when deficient, leads to impaired physical performance.

Recent studies have also shown that aggravated autophagy contributes to muscle loss. In mice, activation of the FOXO (forkhead box O) transcription factors results in enhanced autophagy and lysosomal proteolysis leading to muscle atrophy.<sup>38,39</sup> Similarly, increased autophagy levels in a transgenic mouse model expressing a mutant *Sod1* (superoxide dismutase 1, soluble) gene that mediates antioxidative defense are associated with muscle atrophy and a profound reduction in muscle strength.<sup>40</sup> In centronuclear myopathy, a naturally occurring mutation leading to inactivation of MTMR14/hJumpy (myotubularin-related protein 14) activates autophagy, suggesting that aggravated autophagy is important in the etiology of centronuclear myopathy.<sup>41</sup> Excessive autophagy contributing to muscle wasting has also been shown in tumor-bearing animals,<sup>42</sup> in a systemic burn injury model in mice,<sup>43</sup> in patients with progressive stages of lung cancer cachexia,<sup>44</sup> and in chronic obstructive pulmonary disease patients.<sup>45</sup>

These studies suggest that aggravated/excessive autophagy is responsible for the loss of muscle mass, whereas defective autophagy leads to the degeneration of muscle fiber, severe reduction in muscle strength, and metabolic disorders. Future studies are needed to clearly define the role of autophagy in physiology and pathophysiology in skeletal muscle. In addition, identifying potential and effective therapeutic approaches focusing on autophagy management in disease should be a priority of the upcoming research.

### Cellular and molecular mechanisms of autophagy

Metabolic adaptations are primarily mediated by AMPK (adenosine monophosphate-activated protein kinase) and AKT/protein kinase B (v-akt murine thymoma viral oncogene homolog),<sup>46,47</sup> and both are important in autophagy regulation. AMPK controls food intake in the hypothalamus, promotes glucose and fatty acid uptake and oxidation in heart and skeletal muscle, inhibits fatty acid synthesis in adipocytes and liver, and inhibits insulin secretion in pancreatic  $\beta$  cells.<sup>48,49</sup> AKT regulates cellular metabolism through glucose uptake, glycogen synthesis, glycolysis, and protein synthesis.<sup>50</sup>

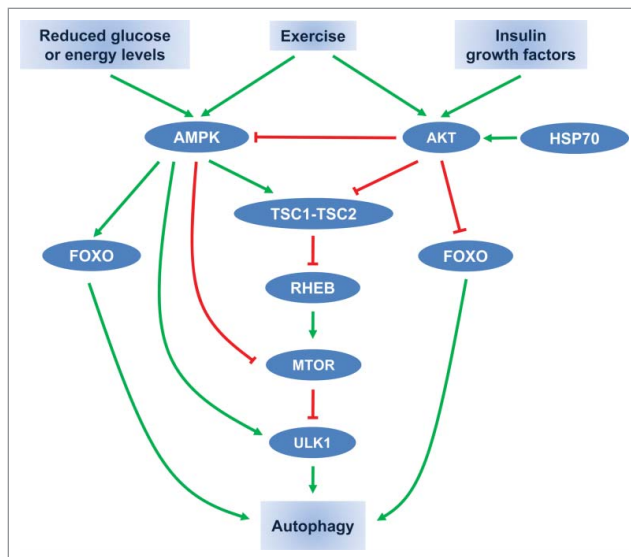
Prolonged exercise, a physiological condition represented by high energy requirements, activates both AMPK<sup>51-53</sup> and AKT,<sup>54,55</sup> that modulate the activity of TSC (tuberous sclerosis complex) consisting of the TSC1-TSC2 tumor suppressor heterodimer that is involved in autophagy regulation (Fig. 1). Downstream of TSC, a small protein, the RAS-like GTPase RHEB (Ras homolog enriched in brain), cycles between an active GTP-bound form and an inactive GDP-bound form.<sup>56</sup> Reduced glucose or energy levels increase the AMP/ATP ratio and results in the activation of AMPK and TSC.<sup>49</sup> This activation of AMPK and TSC leads to augmentation of the RHEB-GDP levels, inhibition of the mechanistic target of rapamycin (MTOR) pathway and leads to

inhibition of cell growth and activation of autophagy.<sup>46,48,49</sup> In contrast, activated AKT directly phosphorylates TSC2 and inhibits its function.<sup>57</sup> Reduced activity of TSC2 by AKT increases RHEB-GTP levels resulting in MTOR activation<sup>58,59</sup> and autophagy inhibition. Additionally, AKT may also activate the MTOR pathway by the inhibition of AMPK-mediated phosphorylation of TSC2<sup>47</sup> and AMPK may inhibit MTOR directly by modulating its phosphorylation site.<sup>60-62</sup> Moreover, direct physical interaction between AMPK or MTOR and ULK1 (unc-51 like autophagy activating kinase 1) plays a crucial role in the regulation of mammalian autophagy.<sup>63-69</sup> Under conditions of nutrients abundance, the activated MTOR phosphorylates ULK1 and prevents its interaction with AMPK. Conversely, under starvation conditions, AMPK-induced MTOR inhibition prevents MTOR from binding to ULK1. Subsequently, AMPK directly interacts with and phosphorylates ULK1 resulting in its activation and leading to autophagy initiation.<sup>65</sup> As suggested recently, this complex modulation of ULK1 activity by AMPK and MTOR may represent the regulation of autophagy and metabolism accordingly to the availability of glucose and amino acids.<sup>63</sup>

In addition to the MTOR pathway, AMPK and AKT have been reported to control glucose metabolism and autophagy through modulation of FOXO family transcription factors. AMPK through the transcriptional activation of *Foxo3/Foxo3a* suppresses gluconeogenesis in the liver.<sup>70</sup> Interestingly, it has been recently shown that exercise-induced AKT phosphorylation suppresses the hepatic gluconeogenesis through a decreased association between FOXO1 and PPARGC1A/PGC-1 $\alpha$  (peroxisome proliferator-activated receptor, gamma, coactivator 1  $\alpha$ ).<sup>71</sup> In addition, AKT activation suppresses FOXO3 activation and autophagy independently of MTOR.<sup>39</sup> Conversely, AMPK triggers autophagy in skeletal muscle through activation of FOXO3 and interaction with ULK1.<sup>72</sup> We have shown that HSP70 exerts its inhibitory effect on autophagy via the increased AKT pathway.<sup>5</sup> To sum up, AMPK and AKT are responsible for controlling metabolic equilibrium and play a critical role in modulating skeletal muscle mass through fine adjustments of protein expression. Future studies are required to delineate the role of HSP70 and other members of the heat shock response on intracellular targets involved in autophagy regulation under physiological and pathological conditions.

### A correspondence between immune and muscle cells

Glucose is an important nutrient for contracting muscle.<sup>73</sup> During exercise glucose uptake rises significantly and reaches a peak (41% of glucose contribution in muscle metabolism) at 90 min during exercise.<sup>74</sup> This initial glucose involvement is replaced by free fatty acids whose contribution of total muscle metabolism extends to 62% at 240 min of exercise.<sup>74</sup> Muscle tissue is the main glutamine depot containing 90% of the body's glutamine reserves and during catabolic stress in humans, muscles are a primary organ of glutamine synthesis and release to the blood.<sup>75,76</sup> Glutamine is the most abundant free amino acid in the body and it is critical for the proper functioning of the immune cells that utilize it at high rates for antigen presentation and cytokines production.<sup>77,78</sup> In addition, macrophage-derived



**Figure 1.** Schematic overview of autophagy regulation by exercise, hormonal, and nutrient signals. Arrow-headed (green) lines and bar-headed (red) lines indicate activation and inhibition, respectively.



cytokine stimulates glutamine synthesis in muscle cells.<sup>79</sup> This loop of interaction between cytokines and glutamine represents cooperation and codependence between muscle and the immune system. Another link involving the immune system and insulin target cells (muscle) has been demonstrated in the development of metabolic syndrome. In this model, an attenuated autophagy by fatty acid in macrophages leads to activation and release of inflammasome and proinflammatory cytokine IL1B/IL-1 $\beta$  that in turn inhibits normal insulin signaling in liver, adipose, and muscle tissues resulting in insulin resistance.<sup>80</sup>

### **Cooperation between heat shock response and autophagy during heat stress and the unfolded protein response**

#### **Heat stress response modulates autophagy**

Heat stress denatures proteins and alters translation. It is also a potent stimulus of the heat shock response. Thus, it is not surprising that heat exerts a complex effect on autophagy. In one of the earliest studies describing the effect of a physiologically relevant increase in temperature on autophagy induction in isolated rat hepatocytes, the highest autophagy levels were detected at 37°C reflecting the normal body temperature, whereas temperature elevation to 40°C reduced the autophagic sequestration.<sup>81</sup> Later, by utilizing different cellular techniques and models, it was shown that heat stress, as high as 43°C, induces autophagy.<sup>82</sup> Heat exposure also triggers autophagy in a human hepatoma cell line,<sup>83</sup> rat cardiomyocytes,<sup>84</sup> human alveolar basal epithelial cells,<sup>5</sup> a mouse spermatocyte cell line,<sup>85</sup> and human cervical cancer cells.<sup>86</sup> Moreover, recent studies have shown that deletion of the heat shock transcription factor 1 (HSF1), increases basal autophagy levels.<sup>5</sup> Treatment with a constitutively active HSF1 mutant inhibits the basal level of microtubule-associated protein 1 light chain 3 (LC3-II) protein and prevents induction of autophagy in heat-treated cells.<sup>82</sup>

In animals, similar to cell culture studies, heat exposure upregulates autophagy proteins in the rat cerebellar Purkinje cells<sup>87</sup> and hepatocytes,<sup>88</sup> but not in the pancreatic cells.<sup>89</sup> These studies suggest that autophagy remains under regulatory control of the heat shock response, but more studies are needed to fully define the hierarchy of importance among proteins involved in autophagy regulation.

#### **Interactions between the heat shock response and autophagy during the unfolded protein response**

Besides hyperthermia, conditions generating the unfolded protein response upregulate both the heat stress response and autophagy. Treatment with a highly selective, reversible inhibitor of the 26S proteasome, bortezomib, resulting in mitochondrial dysregulation and endoplasmic reticulum (ER) stress triggers autophagy and the cellular chaperone HSP70 in melanoma cell lines.<sup>90</sup> Similarly, exposure to the histone deacetylase inhibitor panobinostat activates the heat stress response and ER stress and leads to an increased accumulation of unfolded proteins resulting in autophagy induction.<sup>91</sup> In 2 independent cell

culture studies, HSP70 and HSF1 were shown to be required in autophagosomes formation. In mouse embryonic fibroblasts, panobinostat-induced formation of autophagic vesicles was prevented by HSP70 knockout,<sup>92</sup> whereas, in human breast adenocarcinoma cells, exposure to the chemotherapeutic agent carboplatin increased autophagy as indicated by an increase in LC3 punctate structures and LC3 and ATG7 protein expression that was prevented by knockdown of HSF1.<sup>93</sup> It was also reported that silencing of TPR (translocated promoter region, nuclear basket protein) a component of the nuclear pore complex leading to a significant reduction in nuclear pore numbers results in a significant increase in autophagy that is associated with an increase in heat stress response in HeLa cells (see a comprehensive diagram illustrating the intracellular mechanisms regulating autophagy in translocated promoter region, nuclear basket protein-depleted cells).<sup>94</sup> In mouse with progression of Alzheimer-like deficits, the autophagy-activating agent rapamycin (an inhibitor of mTOR) results in HSF1 activation and HSPs overexpression in the brain. Rapamycin-fed animals express a reduced amyloid- $\beta$  content in the brain, demonstrating that rapamycin treatment improves protein homeostasis by removing damaged proteins through autophagy and fixing unfolded proteins via increased chaperone activity.<sup>95</sup> Although the exact role and relationship between autophagy and the heat stress response under stressful conditions remains to be determined, they cooperate in maintaining cellular homeostasis by facilitating appropriate folding of partially unfolded proteins or removing irreversibly damaged proteins to help the cell in coping with the cellular stress.<sup>86,88,96</sup>

### **Cooperation between the heat shock response and autophagy during exercise in animals and in humans**

#### **The effect of exercise on muscle growth**

Muscle growth is only possible when protein synthesis exceeds protein breakdown, meaning there is a positive anabolism. Resistance exercise is important and well known in development of muscle mass (hypertrophy). In humans, resistance exercise increases protein synthesis<sup>97-106</sup> and improves protein balance during the recovery phase in the skeletal muscle,<sup>8,107,108</sup> but not during acute bouts of resistance exercise.<sup>109</sup> Similar to resistance exercise, low intensity aerobic training<sup>110</sup> causes a significant increase in fractional synthetic rate in the leg muscle. In contrast, in female deltoid muscle, neither resistance nor swimming exercise, when performed separately, had a significant effect on net muscle protein synthesis, but when combined stimulated increased muscle protein synthesis above baseline levels.<sup>111</sup> Similarly, there was no change in protein synthesis or protein breakdown in vastus lateralis shortly after an acute bout of resistance exercise.<sup>112</sup> Interestingly, the effect of exercise on protein synthesis seems to depend on the type, or protein measurement (mixed vs. myofibrillar), and training status of the subjects (trained vs. untrained). In response to acute resistance exercise, there was a significant increase in mixed protein synthesis in untrained

subjects but not in the trained athletes:<sup>113</sup> however, the myofibrillar protein synthesis rate was elevated in both untrained and trained subjects in response to resistance exercise.<sup>114,115</sup>

The effect of the training protocol and muscle protein synthesis is documented in exercise literature as well. Both resistance<sup>116-118</sup> and endurance<sup>119</sup> exercise training result in a marked increase in skeletal muscle protein synthesis rate. However, a 12-wk regimen of high-intensity resistance exercise did not alter the whole body protein synthesis.<sup>120</sup>

The role of autophagy and other lysosome systems in exercise-induced muscle growth remains to be determined.

### Exercise and HSP70 protein expression in animals

Heat shock proteins comprise a family of chaperones, whose expression is induced in response to a wide variety of physiological and environmental insults, including high temperature, oxidative stress, heavy metal exposure, and ionizing radiation.<sup>121-123</sup> The primary function of these heat shock proteins is to fold nascent proteins and refold denatured proteins after cellular stress.<sup>7,124,125</sup> The heat shock proteins also modulate physiology of a single cell or whole organism by regulating signaling pathways,<sup>126</sup> cell survival,<sup>127</sup> tight junction permeability,<sup>128-130</sup> cytokine expression,<sup>131</sup> and protein degradation.<sup>25,132</sup>

HSP70 is the most highly conserved member in the HSP family and has been studied in the response to acute exercise or exercise training in animals. Brief (5 min) eccentric exercise produces no increase in HSP70 protein expression in the muscle tissue,<sup>133</sup> but longer and more exhaustive treadmill running<sup>134,135</sup> or eccentric exercise<sup>136,137</sup> results in a significant increase in HSP70 protein expression in cardiac and skeletal muscles. Elevated HSP70 levels are also observed in lung and kidney in response to strenuous endurance exercise.<sup>138</sup>

Findings on aerobic training on muscle HSP70 protein expression are conflicting. A high-intensity aerobic exercise protocol involving treadmill running (5 d) elevated HSP70 protein expression in both cardiac<sup>135</sup> and skeletal muscle.<sup>139</sup> Conversely, no increase in HSP70 was observed in animals exposed to either the continuous (low intensity and longer duration) or to the intermittent exercise protocol (high intensity and short duration).<sup>136,140</sup>

In conclusion, exercise (acute or training) raises the HSP70 levels but the magnitude of the response depends on the intensity<sup>141</sup> and type of exercise.<sup>138</sup>

### Exercise-induced HSP70 protein expression in humans

Our studies were among the first to show the effect of acute exercise on HSP70 protein expression in human peripheral white blood cells. Ryan et al. showed that treadmill exercise results in no apparent increase in HSP70 protein expression in human leukocytes.<sup>142</sup> Similarly, 2 50-min bouts of moderate intensity aerobic exercise<sup>143,144</sup> do not affect HSP70 levels in peripheral blood mononuclear cells (PBMCs). In our recent studies, strenuous treadmill running (rectal temperature of 40°C) produces a time-dependent increase in HSP70 protein expression in peripheral leukocytes, but the difference did not reach statistical significance.<sup>5</sup> Similarly, a short (4 min) bout of “all-out” cycling results

in a nonsignificant increase in HSP70 protein expression in monocytes and lymphocytes.<sup>145</sup> On the contrary, running in a hot environment (40°C) with body temperature exceeding 39°C results in a significant increase in HSP70 in PBMCs within 1 h after exercise<sup>146</sup> following an increase in *HSP70* gene<sup>147</sup> and transcript expression.<sup>148,149</sup>

Exhaustive endurance exercise has been consistently shown to trigger heat stress response in human leukocytes. In subjects who completed a half marathon (21.1 km) with an increased plasma creatine kinase activity indicating exercise-induced skeletal muscle damage and rectal temperature reaching 44°C, there is a post-exercise increase in HSP70 protein expression in monocytes and granulocytes that remains elevated for up to 1 d post-exercise.<sup>149,150</sup> Similarly, exhaustive treadmill exercise,<sup>148,151</sup> strenuous cycling,<sup>152,153</sup> or repeated sprint cycle exercise<sup>154</sup> augments HSP70 protein expression in leukocytes that lasts up to 48 h post exercise.

In skeletal muscle, moderate<sup>155</sup> or high intensity exercise<sup>156</sup> does not alter HSP70 protein expression within 3 h after cessation of exercise, despite the fact that *HSP70* mRNA levels are upregulated 4 min post exercise<sup>156</sup> and stay elevated 3 h after exercise termination.<sup>156,157</sup> However, a significant effect of exercise on HSP70 protein expression in human skeletal muscle has been observed as early as 8 h post exercise<sup>158</sup> and expression remains elevated up to 7 d after exercise termination.<sup>158-166</sup>

When examining exercise training effects on HSP70 protein expression in humans, it has been shown that a 7-d heat acclimation protocol consisting of 2 50-min exercise bouts in a warm environmental chamber elevates subjects' core temperature to  $\geq 39^\circ\text{C}$  and results in a significant increase in HSP70 protein expression in peripheral leukocytes at 4-h post-exercise.<sup>144</sup> Similarly, a 10-d acclimation program involving treadmill walking or running in a hot environment augments HSP70 content in peripheral blood mononuclear cells.<sup>143,167,168</sup> Elevation of HSP70 in response to high-intensity and long-term training is also found after an 11-d training program, but not in response to short or moderate intensity exercise.<sup>146,169-172</sup>

Besides exercise intensity, training status and the type of exercise seem to exert considerable effect on HSP70 expression. In untrained subjects, 5-8 wk of triceps brachii training produce a significant increase in HSP70,<sup>173</sup> whereas 12 wk of concentric contraction of biceps brachii decrease HSP70 protein expression in trained athletes.<sup>174</sup> Taken together, exhaustive endurance (acute or training) exercise triggers a heat stress response in peripheral leukocytes as well as in skeletal muscles, but the magnitude of HSP70 expression depends on exercise intensity and training status.<sup>175</sup> Future studies are needed to clearly determine the minimum amount of physical activity for increased heat stress response.

### Exercise modulates autophagy in animals

Most scientific interest in autophagy and exercise has been observed in the last 4 y, despite the fact that the first study showing upregulated autophagy levels in response to exercise was published 3 decades ago.<sup>176</sup> In these older studies, strenuous physical exercise associated with the appearance of necrotic fibers in skeletal muscle results in the most pronounced changes in autophagy

levels between 2 and 7 d after exercise and returns to baseline within 2 wk after exertion. Recently these results were confirmed in mice performing a short but more strenuous exercise.<sup>177</sup> Even low intensity aerobic exercise (10 m/min for 90 min), however, augments autophagy in the gastrocnemius muscle, and this effect is more pronounced in the fasted than in a fed state, suggesting that a decreased INS/insulin-AKT pathway in the fasted state exerts a less evident inhibitory effect on autophagy.<sup>178</sup>

It has also been shown that exercise-induced autophagy is not limited to skeletal muscle, and that it is also upregulated in adipose tissue, pancreatic  $\beta$  cells, and the brain.<sup>36,179</sup>

Deficiency of NR1D1/Rev-Erb- $\alpha$  (nuclear receptor subfamily 1, group D, member 1), a nuclear receptor involved in controlling hepatic lipid and glucose metabolism results in dysfunctional mitochondria, their reduced biogenesis, and increased mitochondrial clearance via autophagy, as well as reduced exercise capacity. By contrast, pharmacological activation of NR1D1 with a synthetic ligand, SR9009, improves mitochondrial function and exercise endurance,<sup>180</sup> suggesting that autophagy represents an important adaptive mechanism in the maintenance of cellular homeostasis under stress conditions.

The effect of exercise training on autophagy regulation seems to be multifactorial, and appropriate autophagy levels are fundamental for the well-being of an organism. Under basal conditions, the highest autophagy levels are observed in tonic, oxidative muscles (soleus). In plantaris muscle composed of both glycolytic and oxidative fibers, intermediate autophagy levels are observed; the lowest levels of autophagy proteins are present in glycolytic white vastus lateralis. Voluntary exercise training does not enhance already high basal autophagy levels in oxidative soleus muscle, but enhances basal autophagy flux in plantaris muscle.<sup>37</sup> Besides skeletal muscle, aerobic training upregulates autophagy proteins (BECN1, ATG7, and LC3) in aortic and cardiac tissues.<sup>181,182</sup> Moreover, it seems that autophagy also depends on the type of exercise. A 5-wk swimming program decreases gene expression of autophagy proteins (LC3), whereas 5 wk of wheel running increases *Lc3* mRNA in the gastrocnemius.<sup>183</sup>

Autophagy is responsible for the removal of dysfunctional proteins, but uncontrolled and exceptionally upregulated autophagy may be harmful and lead to deleterious consequences. In rats, exposure to an effective antitumor agent, doxorubicin, results in cardiotoxicity that is associated with an increased oxidative stress and the upregulation of cellular proteolytic systems, including autophagy. Although aerobic training exerts no significant change on autophagic genes and proteins in control animals, it prevents doxorubicin-induced cardiac muscle damage and significantly reduces autophagy proteins.<sup>184</sup> Similarly, transient middle cerebral artery occlusion leads to neurological dysfunctions and increases LC3 accumulation in the peri-infarct region. Physical exercise training improves neurological function and inhibits autophagosome accumulation in this region.<sup>185</sup> In rats, pharmacologically induced diabetes results in increased muscle atrophy, reduction in diameter of the muscle fibers, and increased autophagy. Exercise training reverses these changes, increases muscle mass, and reduces autophagy levels.<sup>186</sup> In mice with

experimentally induced myopathy and increased autophagy proteins (LC3-II and SQSTM1/p62), 6 wk of exercise training prevents these changes leading to an improvement in muscle function and a decrease in atrophy.<sup>187</sup>

There is growing evidence suggesting that exercise, through the activation of previously suppressed autophagy, may provide beneficial effects. In dystrophic mice, voluntary exercise improves markers of oxidative capacity and autophagy levels, suggesting that exercise-induced autophagy levels account for exercise benefits.<sup>188</sup> It has been reported that mutation in the *Col6a<sup>-/-</sup>/collagen VI* gene results in skeletal muscle myopathy that is characterized by myofiber degeneration and decrease in muscle strength.<sup>189</sup> The *Col6a<sup>-/-</sup>* mutant mice fail to trigger autophagy in response to exercise and this appears to worsen the dystrophic condition in the mice.<sup>177</sup> Long-term resistance training (9 wk) prevents age-related muscle atrophy and is associated with increased autophagy levels in rat gastrocnemius muscles.<sup>190</sup> Similarly, regular aerobic exercise prevents an age-related decrease in autophagy proteins (BECN1 and ATG7), suggesting that exercise plays an important role in skeletal muscle remodeling through the modulation of the degradation of the crucial muscle proteins.<sup>191,192</sup> Taken together, these studies demonstrate the requirement of autophagy in exercise-mediated development of skeletal muscle adaptation and physical endurance. They also suggest that exercise by controlling autophagy adjusts its intensity to the appropriate levels. Future studies are needed to show that autophagy contributes to the beneficial effect of exercise in disease prevention and life-span extension.

### Exercise modulates autophagy in humans

Recently, studies have shown that 1 h of aerobic exercise (70–80% of  $\text{VO}_2$  max) in a warm (30°C) environment results in a significant increase in autophagy in peripheral leukocytes.<sup>5</sup> Interestingly, glutamine supplementation resulting in an increase in HSP70 protein expression prevents this exercise-induced increase in autophagy, suggesting that autophagy remains under inhibitory control of the heat stress response. In human skeletal muscles, ultra-endurance running (149 km for more than 18 h) produces a significant increase in autophagy proteins (LC3-II and ATG12). These changes correlate with low plasma insulin levels, reduced activation of AKT, FOXO3, MTOR, and EIF4EBP1 (eukaryotic translation initiation factor 4E binding protein 1) and concurrent upregulation of AMPK.<sup>193</sup> Conversely, a single bout of resistance exercise has no effect<sup>112</sup> or reduced autophagy levels in both older and younger adults<sup>194</sup> in skeletal muscle. Similar to resistance training, a short (20 min) sub-maximal aerobic exercise (cycle ergometer corresponding to 81%  $\text{VO}_2$  max) exerts no significant effect on autophagy regulation in human skeletal muscle.<sup>195</sup> Finally, future research is needed to investigate the effect of exercise (intensity and type) on autophagy regulation in humans and to determine the role of autophagy under physical performance. A key question is to identify, besides exercise, optimal strategies including nutritional modifications that help autophagy work more effectively.



## Autophagy and heat shock – cooperation through the complex stress of exercise

### Model of control

The heat shock response was fully functional during the evolution of the system of autophagy. In addition, heat shock both manages denatured polypeptides and is essential for protein translocation, multimer assembly, refolding, and protein synthesis. Finally, cells must constantly switch between damaged protein clearance and rebuilding. These principles argue for a cooperative interaction between these 2 protein management systems, heat shock response and autophagy, where one exerts either activation or inhibitory control over the other. A recent study<sup>5</sup> suggests that this is indeed the case and that the heat shock response regulates autophagy. Single gene overexpression of the HSP70 protein, the main executor of the heat shock response, inhibits starvation- or rapamycin-induced autophagy. In addition, under control conditions, HSF1, the central regulator of the heat shock response, negatively regulates autophagy.<sup>5</sup> The molecular basis for modulation of autophagy by heat shock response includes activation of the AKT-MTOR pathway.

Additional evidence from blockage with other proteostasis pathways supports the above view. Pharmacologically induced proteasome inhibition upregulates autophagy in mouse cardiomyocytes,<sup>196</sup> human prostate cancer cells,<sup>197</sup> and human breast cancer cells.<sup>198</sup> In mouse fibroblasts, autophagy is activated by selective blockage of chaperone-mediated autophagy.<sup>199</sup> Similarly, knockdown of an essential autophagy gene (*ATG5*) results in upregulation of chaperone-mediated autophagy in mouse embryonic fibroblasts.<sup>200</sup> Inhibition of the proteasome by using MG132 activates autophagy in mouse embryonic fibroblasts through a downregulation of the AKT-TSC-MTOR pathway.<sup>201</sup> Similarly, inhibition of the HSP70-dependent proteasomal pathway by methylene blue enhances degradation of androgen receptor through induction of autophagy, suggesting that the level of the heat shock response affects the activity of autophagy.<sup>202</sup> Pretreatment with a chemical chaperone, 4-phenylbutyric acid, prevents an ER stress-induced decrease in the MTOR pathway and results in autophagy inhibition. In colorectal cancer cells, transient knockdown of HSP70 expression (siRNA) potentiates, whereas HSP70 overexpression (adenovirus to express HSP70) prevents, an increase in autophagy induced by the pro-apoptotic agent OSU-03012.<sup>203</sup> Moreover, mild heat preconditioning associated with HSP70 overexpression inhibits heat-induced autophagy and this effect is diminished by HSP70 inhibition with triptolide pretreatment.<sup>84</sup> The above studies indicate that the heat shock response and autophagy are linked and that autophagy remains under regulatory control of the heat shock response. In addition, we propose that HSP70 itself acts as a part of the intracellular control mechanism, switching the cell from the degradation phase to the building and protein synthesis phase.

### Exercise as a model

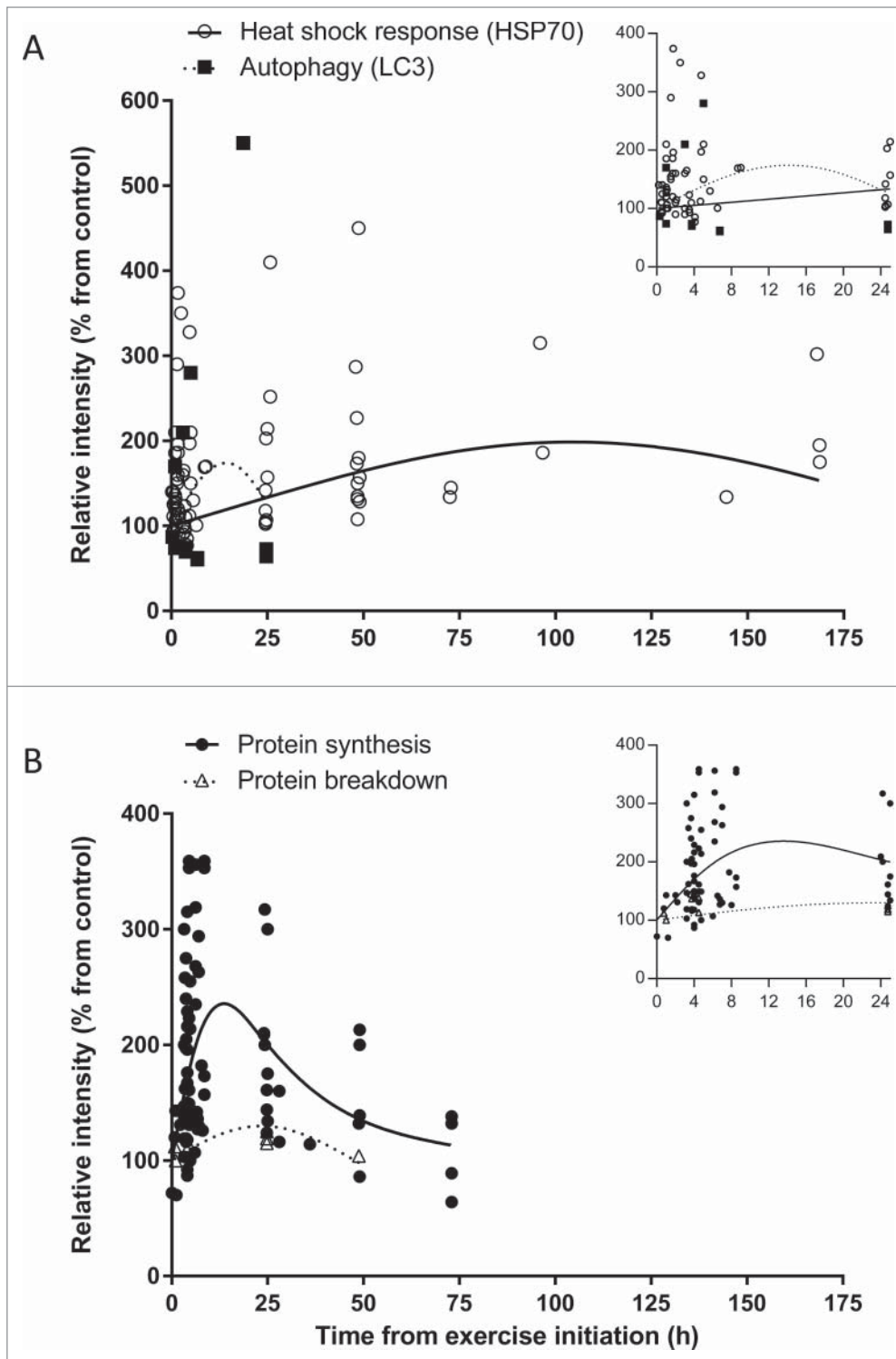
The genesis of our hypothesis of heat shock regulatory control over autophagy was grounded in part upon the concept that cells

must constantly switch between protein breakdown/clearance and rebuilding. Nowhere is this better demonstrated than in the complex stress of exercise. Consistent with cell-based studies of heat shock regulation of autophagy, it has been demonstrated that glutamine supplementation as a heat shock activator prior to exercise results in a significant increase in HSP70 protein expression in human PBMCs. This pre-exercise increase in HSP70 prevents the expected increase in autophagy in response to exercise in human subjects.<sup>5</sup>

The responses of skeletal muscle to exercise provide an example of physiological adaptations to constantly changing physical activity of an organism. At the cellular level, changes in intracellular temperature, pH, and energy status during exercise pose homeostatic challenges. In addition, the adaptation to work also poses significant challenges to the systems involved in breakdown, transport, and synthesis of proteins. In this regard, the skeletal muscle tissue is highly regulated by protein turnover comprised of degradation and rebuilding of the muscle fibers. In response to decreased mechanical stress, skeletal muscle tissue undergoes rapid atrophy characterized by the loss of mass and size.<sup>204,205</sup> On the other hand, mechanical stimulation of the tissue leads to increased mitochondrial content,<sup>206</sup> improved insulin sensitivity,<sup>207</sup> enhanced muscle strength, and increased size.<sup>208</sup> During catabolic conditions, muscle proteins are catabolized to maintain gluconeogenesis in the liver,<sup>209</sup> but excessive degradation of the muscle tissue may be extremely damaging for the organism, leading to muscle wasting and even death. In patients with lung cancer cachexia, enhanced autophagy has been shown to increase muscle proteolysis, suggesting that impaired or exaggerated autophagy in the muscle tissue plays a role in the etiology of pathological conditions and is responsible for the damage of the muscle tissue.<sup>42,44</sup>

The immediate post-exercise phase is characterized by increases in catabolic signals such as IL6/interleukin 6 and protein turnover. In healthy, active human subjects, infusion of recombinant IL6 causes a significant increase in the net release of amino acids from the muscle.<sup>210</sup> IL6, among other pro-inflammatory cytokines, has also been implicated in the development of a cachectic conditions in skeletal muscles<sup>211</sup> and is also responsible for activation of autophagy in cell culture models.<sup>212</sup>

We propose that recovery from and adaptation to exercise represents a single, unified physiological response resulting from cooperation between autophagy and the heat shock response, 2 protein management systems. In this model, the initial phase of exercise-induced damage activates protein turnover to recycle and reclaim amino acids and to remove damaged proteins. This phase is mediated by a host of factors that drive autophagy. Turnover must be stopped to allow for repair. This protein synthesis and protein folding is regulated by heat shock proteins. When the cellular response to exercise is seen as a continuous process of coordinated breakdown and repair, this concept, coupled with the evidence that HSP70 may control autophagy,<sup>5</sup> supports a model in which HSP control of autophagy is the mechanism by which the organism adapts to exercise. During this collaboration, autophagy and HSP function in concert in order to build muscle and create the adaptation. We propose that HSP serves as a



**Figure 2.** Time-course effect of acute exercise on (A) heat shock response (HSP70) and autophagy (LC3), and (B) protein synthesis and protein breakdown in humans based on acute exercise trials listed in **Tables S1-4**. Each dot represents 1 measurement. In both panels (A and B) the X-axis represents the time from the start of exercise, that is the sum of times in hours representing duration of exercise and collection time post-exercise; in panel (A), the Y-axis represents relative intensity of HSP70 protein expression (**Table S1**) or LC3 protein expression (**Table S2**); in panel (B), the Y-axis represents relative intensity of protein synthesis (**Table S3**) or protein breakdown (**Table S4**). (Insets) Expanded views of the first 25-h time point. Axes titles removed for clarity. The X-axis represents time from the start of exercise in hours, and the Y-axis represents relative intensity (% from control). In the (A) inset the Y-axis scale was truncated to improve clarity.

switch that turns off autophagy and allows the organism to shift from reclamation to building.

### The combined activities of autophagy and the heat shock response in exercise adaptation

We undertook an analysis of the temporal relationship between the heat shock response, represented by changes in HSP70 protein expression, and autophagy, represented by changes in LC3 following exercise. We conducted a systematic search of PubMed focusing on the terms “exercise, autophagy, HSP70, protein synthesis, protein breakdown, and humans.” Four measures (autophagy, heat shock response, protein synthesis, and breakdown) have been included in the analysis presented in **Figure 2** in support of this model. In our analysis, we collected and analyzed 1) 22 publications (with a total of 231 subjects) studying the effect of acute exercise on HSP70 protein expression in humans; 2) 5 publications (with a total of 70 subjects) examining the effect of acute exercise on autophagy activation; 3) 20 publications (with a total of 204 subjects) investigating the effect of acute exercise on protein synthesis in humans, and 4) 6 publications (with a total of 61 subjects) testing the effect of acute exercise on protein breakdown in humans. The following inclusionary and exclusionary criteria were used in our analysis: exercising human (both females and males) subject studies were used regardless of 1) age of participants, 2) training status of subjects, 3) exercise intensity (low, moderate, or high), 4) type of exercise (aerobic [running, cycling, or rowing] or resistance), 5) collected tissue (muscle tissue or white blood cells), 6) protein measurement (western blot analysis, flow cytometry, or immunostaining). Only studies with

calculated relative protein intensity of LC3 (marker of autophagy) or HSP70 (marker of the heat stress response) were used in the analysis, followed by normalization to the control, pre-exercise, or baseline values and set to 100%. For resistance exercise, when duration of exercise was not provided, only time after exercise was used for the analysis, otherwise time from the initiation of the exercise was used. Due to exceptionally high (1000–3200 fold increase with standard error reaching  $\pm 3000$  compared with a combined average of  $164 \pm 1$  in other studies) HSP70 protein expression, a study by Khassaf et al.<sup>160</sup> was excluded from the analysis. We used linear and nonlinear regression analyses to describe relationships between time since initiation of exercise and HSP70 protein expression, autophagy, synthesis, and breakdown. Analyses accounted for random study effects, but did not weight study effect sizes by their precision, as variance estimates were not available for all studies. Prior to analyses, effect sizes on the percent scale were log-transformed ( $\ln[\text{Effect\_Size}/100]$ ) to improve normality of residual errors and homogeneity of variances. Models did not include an intercept, which constrained fitted models to predict 100% response at the initiation of exercise. Nonlinear regression with study random effects was used to analyze synthesis rate data. In addition we conducted exploratory analyses to assess whether trajectories differed with respect to whether measurements were made on skeletal muscle or on PBMCs.

Time since initiation of exercise explained significant amounts of variation in HSP70 ( $P < 0.001$ ), protein synthesis ( $P < 0.001$ ), and protein breakdown ( $P = 0.01$ ), but not for autophagy ( $P > 0.15$ ). As shown in Fig. 2, the analysis of human exercise studies demonstrates that autophagy represented by LC3 protein expression has only been measured  $\leq 24$  h after completion of exercise with 8 out of 12 points showing reduced expression shortly after exercise. Overall, a quadratic polynomial model shows a peak 1.75-fold increase in LC3 protein expression during the initial, degradation phase of exercise, about 14 h from the start of exercise. However, the relationship between time and autophagy appears to be different for PBMCs and muscle. Three points with increasing expression  $< 8$  h after exercise initiation were measured in PBMCs by Dokladny et al.,<sup>5</sup> whereas 8 of 9 skeletal muscle observations had reduced expression. Given the limited number of autophagy measurements analyzed, additional studies are needed to assess autophagy measured in PBMCs and skeletal muscle. In contrast to the apparent initial increase and decline in autophagy within 24 h, cellular HSP70 levels rise to peak levels at about 105 h after exercise initiation ( $\sim 2$ -fold increase when compared with pre-exercise values) and then decline. These changes in autophagy and HSP70 levels correlate

with changes in measures of protein breakdown and protein synthesis. In response to one bout of exercise, the rate of protein breakdown shows a modest change since exercise began increasing, to about 30% above baseline at about 24 h and then decreasing. Protein synthesis rate increased about 2-fold in the first 8 hours after initiation of exercise and gradually approached baseline after 24 h. Peak synthesis rate was predicted to be between 8 and 12 h; however, we found no studies with measurements in this range and therefore additional research is needed to determine the peak and duration of increased synthesis rate.

## Conclusions

In the present review, we proposed a model of cooperation and control between autophagy and the heat shock response during exercise in humans. Our model has been supported by the direct cellular data of the effect of exercise on heat shock response and autophagy in humans. The model shows that autophagy is primarily upregulated in the initial degradation phase of exercise, whereas heat shock response is mainly activated in the building and protein synthesis phase of exercise. The model also suggests that heat shock response represented by HSP70 is an intracellular control mechanism switching the cell from the initial degradation phase (autophagy) to the building and protein synthesis phase. More studies are needed to fully determine the relationship between exercise and autophagy in exercising humans and animals and also to delineate the role of the heat shock response in regulation of other proteolytic systems in cell culture models, animals, and humans. As more research occurs and data accumulate, refinement of this model may help us understand the factors and conditions influencing the interactions between various intracellular systems responsible for maintaining protein homeostasis.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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## Supplemental Material

Supplemental data for this article can be accessed on the publisher's website.

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