The Heat Shock Connection of Metabolic Stress and Dietary Restriction

Balázs Dancsó, Zoltán Spiró, Mehmet Alper Arslan, Minh Tú Nguyen, Diána Papp, Péter Csermely, and Csaba Sőti*

Department of Medical Chemistry, Semmelweis University, Budapest, Hungary

Abstract: Molecular chaperones and the heat shock response guard and modulate protein conformation, protect proteins from misfolding and aggregation, and maintain signalling and organellar networks. Overnutrition and the metabolic syndrome represent a pro-aging condition, and dietary restriction is the most robust environmental intervention that induces longevity from yeast to mammals. In recent years a considerable effort has been made to elucidate the signaling pathways involved in metabolic signaling. Here we review the current understanding on the connection between metabolic stress, dietary restriction and the heat shock response and highlight results showing chaperone induction as a promising therapeutic strategy to promote healthy aging and to prevent metabolic disorders.

Keywords: Aging, caloric restriction, diabetes, heat shock response, resveratrol, sirtuin.

INTRODUCTION: STRESS, AGING AND THE HEAT SHOCK RESPONSE

Stress can be defined as an environmental change that induces damage at all the molecular, cellular and organismal level, respectively [1,2]. In the organisms several adaptive (stress) responses have evolved to promote survival via the acquisition of stress tolerance. If these responses can not eliminate damage, it results in a functional decline, a so-called distress, while hormesis is the induction of benefical effects by exposure to low doses of chemical or physical agents that are harmful at higher doses [3,4]. As aging can be considered as a chronic stress state [5], robust adaptive mechanisms are needed not only for instant survival but also to attain longevity.

An important target of stress at the cellular level is the proteome: during proteotoxic stress and in aging the dysbalance of protein homeostasis and the loss of both protein stability and function occur [6]; besides, protein conformational disorders such as Parkinson's, Alzheimer's, and Huntington's disease, respectively, may mimic the degenerative distress state of aging [7]. The maintenance of proteome integrity is regulated by a network of genes that link stress responses and lifespan. A key player in this regard is the chaperone network [7-10] which is responsibe to maintain and modulate protein conformation, to protect proteins from misfolding and aggregation, to promote translocation and assembly and disassembly of macromolecular complexes [11-14]. The induction of heat shock response is mediated by the heat shock transcription factor 1 (HSF1) [15]. Under normal conditions HSF1 is kept in an inactive, monomeric form by an inhibitory complex of Hsp-s. Upon proteotoxic insults, like heat shock, heavy metals and proteasome inhibitors, Hsp-s interact with denaturated and partially unfolded proteins, thus HSF1 is titrated out of the inhibitory complex. HSF1 trimerizes, becomes phosphorylated and is translocated into the nucleus, where it binds to consensus sequences of the promoter of heat shock genes (heat shock elements, HSEs). Recent evidence suggests that beyond this feedback loop translational elongation factor eEF1A and a thermometer non-coding RNA (HSR1) together participate in HSF1 activation [16,17]. According to this model, the heat shock derived translational shutdown and cytoskeletal collapse make eEF1A capable to bind the concomitantly formed HSR1. Thus the eEF1A-HSR1 complex is able to capture HSF1 released from the aforementioned chaperone complex and promotes trimerization and further activation steps, linking general translation and RNA metabolism to the heat shock response. After activation and nuclear translocation HSF1 is located within 30s in so-called stress granules [18-20]. These discrete subnuclear granules contain a plethora of proteins with unknown functions, including splicing factors suggesting a special micro-compartment for fine-tuning transcriptional responses during stress [18,21,22].

Mapping out the connection between the heat shock response and longevity has already begun with ambiguous results. The nematodal HSF1 ortholog HSF-1 overexpression induces longevity, while HSF-1 knock out shortens life-span in *C. elegans* [23,24], while mice lacking HSF1 do not display shorter lifespan [25]. Furthermore, studies in worms expressing GFP under the *hsp16.2* promoter demonstrated that the robustness of the heat shock response may predict lifespan [26]. However, a recent study using *hsp22* and *hsp70* reporter *Drosophila* strains reported a negative correlation between reporter expression and lifespan warranting further research in this direction [27].

OBESITY AND DIABETES AS A METABOLIC DISTRESS: THE PROTECTIVE ROLE OF MOLECULAR CHAPERONES

Overnutrition is one of the leading medical problems in the developed world. It is a result of an imbalanced diet,

*Address correspondence to this author at the Department of Medical Chemistry, Semmelweis University, Budapest, Hungary; Tel: +361-459-1500 Extn: 60129; Fax: +361-459-1500 Extn: 60147;
E-mail: csaba.soti@eok.sote.hu

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where the energy consumption is higher than the energy expenditure, and it leads to the development of the metabolic syndrome, characterized by obesity, type 2 diabetes, insulin resistance, dyslipidaemia and hypertension [28,29]. Metabolic syndrome is also a risk factor of atherosclerosis, stroke, cancer, arthritis and diabetes. Thus, the metabolic syndrome and diabetes may be perceived as a chronic metabolic distress which induces diseases and limits life expectancy.

Metabolic disturbances in diabetes induce a number of alterations in protein homeostasis. Glycation of the small chaperone α-crystallin of the lens compromises its chaperone activity and contributes to cataract formation [30]. High glucose-induced oxidative stress in the obese Zucker rat led to protein misfolding and aggregate formation could be cleared by autophagy, but not by the proteasome [31]. Elevated levels of HSF1, Hsp70 and Hsp90 that were found in the pancreas of diabetic monkeys may compensate for the altered protein homeostasis [32]. Intriguingly, decreased level of Hsp70 was found in the muscle of diabetic patients, as well as in the blood and in the liver of diabetic monkeys, where the level of HSF1 and Hsp70 and Hsp90 declined significantly [32,33] Indeed, impaired insulin signaling reduces HSF1 transactivation via the activation of glycogen synthase kinase-3 (GSK-3) and extra-cellular regulated kinase-1 (ERK-1) and c-jun N-terminal kinase (JNK) [34,35]. Decreased Hsp70 may not be able to inhibit JNK-induced inflammatory signaling, giving rise to a vicious cycle [35,36]. High glucose alters the interaction of the specific chaperone Hsp90 with two prominent clients endothelial nitric oxide synthase (eNOS) and inhibitor of kappaB kinase (IKK) providing a mechanistic basis for endothelial dysfunction [37,38]. How altered chaperone levels and function may contribute in other ways to peripheral insulin resistance, inflammation and to an altered extracellular stress signaling remains to be seen.

There are a number of experiments demonstrating the connection between diabetes and the heat shock response. Physical exercise is able to both raise chaperone levels and reverse diabetic alterations [34,35]. Besides, both the antidiabetic drug, metformin and the alkaloid, berberin promote the association of eNOS with Hsp90 and augment NO production and preserve endothelial function [39,40]. More importantly, a 41°C heat treatment once a week for 12 weeks improved glucose tolerance and reduced stress-activated signaling in rats fed by a high-fat diet suggesting a crosstalk between the development of HSF1 dependent thermotolerance and metabolic stress tolerance [41]. The chaperone co-inducer bimoclomol derivative, BRX-220 was also able to improve insulin sensitivity of both Zucker fatty diabetic rats, and streptozotocin-treated diabetic rats [42]. Finally, a recent study demonstrated that besides heat shock either overexpression or pharmacologic induction of Hsp70 by a novel chaperone co-inducer BGP-15 was sufficient to prevent the development of obesity-induced insulin resistance in fat-fed mice [43]. Strikingly, a 1-month treatment with BGP-15 significantly improved insulin sensitivity in insulin-resistant, nondiabetic human patients [44]. These protective effects may be related to an improved protein homeostasis, a more efficient modulation of signaling networks and to a better connectivity of subcellular organellar networks, such as the ER and the cytosol [8,45]. All these experiments highlight a vast therapeutic and preventive potential of chaperone induction in metabolic disorders.

DIETARY RESTRICTION IS AN INDUCER OF LONGEVITY AND OF THE HEAT SHOCK RESPONSE

Dietary (caloric) restriction, a moderate (30-40%) reduction of caloric intake with maintained nutrient supply is the most robust intervention that induces longevity from yeast to mammals. Dietary restriction also decreases the incidence of age-related diseases, such as cancer, diabetes, cardiovascular and neurodegenerative diseases by inducing changes in metabolism, protein biogenesis and turnover as well as by evoking resistance to a variety of stresses [46,47]. Thus, dietary restriction may emerge as a hormetic metabolic stress that activates various defense mechanisms to promote longevity.

Early studies showed that dietary restriction was able to restore the age-induced loss of Hsp70 transcription via the preservation of HSF1 activation in rat hepatocytes [48,49]. As a functional consequence, dietary restriction highly improved thermotolerance and was able to rescue 100% vs 50% of old rats subjected to hyperthermia [50]. These findings have been recapitulated in rat intestine, neural tissue, skeletal muscle and in heart myocardium, suggesting that a more efficient heat shock response induced by dietary restriction may improve muscle and neuronal function, protect from muscle cell loss and importantly may exert cytoprotection against ischemic episodes [51-55]. A small, but significant cytoprotection from heat stress could be transferred with blood serum to HepG2 cells by culturing them in serum obtained from human subjects undergoing caloric restriction, however, this study found no difference in basal Hsp70 levels [56]. Using transcriptional profiling, independent studies demonstrated a better maintenance of stress responses including chaperones both in liver and in muscle, respectively, of caloric restricted primates [57,58]. This effect was reflected in an efficient protection in both nematode and mouse models of misfolding models of neurodegenerative disorders [59,60]. Similarly to food restriction, the mimetic 2-deoxyglucose was shown to induce chaperones and protect neuronal cells from excitotoxic, oxidative and proteotoxic injury [61,62]. Intriguingly, 2-deoxyglucose blunted the Hsp70 induction and thermotolerance of prostate cancer cells suggesting that an otherwise hormetic intervention may induce a distress in the already stressed tumor cells and providing one plausible mechanism for the potent antitumor effect of dietary restriction and fasting [63]. Since an increased protein turnover is implicated in the 'cleansing' effects of dietary restriction, and chaperones are known to play an important role both in proteasomal degradation and in chaperone-mediated autophagy, it would be worth studying their crosstalk to gain a better understanding on the interplay between these processes [52,55,64-67].

THE HEAT-SHOCK RESPONSE IN THE DIETARY RESTRICTION-RELATED SIGNALING NETWORK

In recent years evidence has been accumulated that dietary restriction is not only a simple consequence of restriction of fuel and metabolism but initiates a highly regulated and orchestrated process that drives energy allocation from

reproduction to self maintenance during low food availability. Due to its versatility, short lifespan and ease of genetic manipulations much of the understanding has been obtained in the nematode *C. elegans*. Here we will mainly rely on data from worms and supplement it with findings from higher organisms.

A major endocrine sensor of food supply is insulin signaling. Reduction in insulin signaling extends life span in various organisms [68,69]. The essential role of HSF-1 and the chaperone-network in this pathway has been proven in the nematode *Caenorhabditis elegans*, acting in concert with the forkhead transcription factor FoxO/*daf-16* [24,70]. Consequently, insulin-signaling mutations delay the onset of polyglutamine toxicity in worms [71].

To address the mechanism of dietary restriction a number procedures have been developed in *C. elegans*. All of them induce a further life extension of already long-lived insulin signaling mutants suggesting that the effects of dietary restriction involve different mechanism apart form insulin-like signaling. A dilution of the food source bacteria from 10^{11} to 10^{8} *E. coli*/ml on solid agar extended lifespan of worms by 20-30%. Despite an increased stress resistance, the *C. elegans* HSF1 ortholog *hsf-1* was dispensable, however, it fully depended on the AMP-dependent protein kinase AMPK/*aak-2* and on FoxO/*daf-16* [72,73]. A similar longevity by the dilution of the bacterial food peptone was also mediated by *daf-16*, however, the contribution of *hsf-1* is, as yet, unknown [74]. The reduction of pharynx pumping rate by a genetic mutation (*eat-2*) depends on the mitochondrial gene *clk-1* while *daf-16*- and *hsf-1* are indispensable, moreover, the necessity of *clk-1* has been shown in the bacterial dilution protocol, too [24,73,75]. Yet, bacterial dilution combined with *eat-2* mutation produced a synergistic longevity [73]. Separate studies from two labs employed liquid medium, where diluting bacteria extended lifespan which was also largely *daf-16*-independent, however, depended on neuroendocrine signals by either the transcription factors FoxA/*pha-4* or Nrf2/*skn-1*, respectively [76,77]. Notably, *pha-4* also seemed to mediate the longevity of *eat-2* mutants [76]. The involvement of the heat shock response in these models has not been addressed. Dietary restriction in *Drosophila* appeared to be FoxO-independent [78]. The results highlighted above argue that a partial reduction of food source in invertebrates is heterogeneous intervention targeting various nodes of a highly connected signaling network and draws attention to the careful design and interpretation of research in mammalian models.

After reaching the adult stage, *C. elegans* displays a robust 50% increase in lifespan either in axenic medium almost devoid of calories or even in the total absence of the food source *E. coli* [79-81]. The life extending mechanism of these interventions is totally different from a partial food reduction, since *(i)* serial dilution of bacteria on the plates below a threshold (cca. 10^{7} *E. coli*/ml) killed worms within two days [73], *(ii)* the longevity by bacterial deprivation was independent on FoxO/*daf-16* and AMPK/*aak-2* [80], *(iii)* the presence of metabolically active live bacteria, or their product prevented the food deprivation-induced longevity [79,82]. Indeed, both the longevity induced as well as a potent protection in several proteotoxic models by bacterial deprivation required *hsf-1* [60]. It may be hypothesized that beyond the optimum food supply that finely tunes metabolism a signal produced by live microorganism exerts a constitutive inhibition on stress responses and HSF-1. Further research is necessary to reveal the nature and the pathway of the inhibition. For a summary of genes involved in dietary restriction-induced longevity please refer to Table **1**.

Another important nutrient sensor is the target of rapamycin (TOR) kinase which is activated by both nutrient supply and insulin. Inhibition of TOR in wild type and in *eat-2* mutant worms induces longevity by activating translation and inhibiting autophagy [66,83]. Reduction of translational output *per se* induces thermotolerance and longevity, the latter being additive to that of both insulin-like and *eat-2* mutants [83,84]. Similarly, both insulin-like and *eat-2* mutants require autophagy for their longevity, however, activation of autophagy is not sufficient to extend lifespan [66,67]. Though there is no direct evidence on the role of the protea-

Table 1. Requirement of Genes for Longevity in Various Dietary Restriction (Mimetic) Interventions *C. elegans*. See the text for details and for references. * B. Dancsó and C. Sőti, unpublished results, ** Tóth ML, Dancsó B, Csermely P and Sőti C, submitted manuscript

Intervention	**Genes (human ortholog)**						
	***daf-16* (FoxO)**	***aak-2* (AMPK)**	***hsf-1* (HSF1)**	***clk-1* (CLK1)**	***skn-1* (Nrf2)**	***pha-4* (FoxA)**	***sir-2.1* (SirT1)**
Bacterial dilution	yes	yes	no	Yes	no	no	no
Peptone dilution	yes	yes	?	?	?	?	?
Pharynx pumping (eat-2)	no	no	no	Yes	?	yes	yes/no
Liquid DR #1	no	?	?	?	yes	?	?
Liquid DR #2	partial	partial	?	?	?	yes	?
Bacterial deprivation	no	*no	yes	?	?	?	*no
Resveratrol	yes/no	yes	**yes	?	?	?	yes

somal system in dietary restriction, a close relationship can be suspected. A proper protein homeostasis seems to be a critical determinant in longevity and closely connected to the mechanism of dietary restriction. Namely, translation modulates protein output, molecular chaperones guard protein conformation and protein disposal clears the damaged and unnecessary proteins and provides fuel from intrinsic stores to build new proteins, elements of an adaptive response.

HSF1 and chaperones are involved in several physiological and housekeeping processes like signaling and immunity, however, the exact contribution of their significance related or unrelated to protein homeostasis has not been addressed. Taking use of the poikilothermic nature of *C. elegans* we investigated the effect of dietary deprivation on the lifespan of wild type and *hsf-1* loss-of function animals at temperatures below and above the ambient 20ºC. Fig. (**1**) shows that decreasing temperature progressively lengthens the lifespan of both the wild type and *hsf-1* worms to a similar extent (to 280% mean lifespan at 15ºC) suggesting that at the temperatures tested there is a uniform need of *hsf-1* for survival. Besides, dietary deprivation progressively extends the lifespan of wild type worms with increasing temperature. However, this effect is completely abolished in *hsf-1* mutants. These data indicate that either the effect of dietary deprivation is independent of the protein homeostatic burden or HSF-1 mediates the longevity effect via both protein-maintenance and independent means. Indeed, it has been shown that HSF1 regulates 3% of the genome in yeast and supports such core cellular functions as cell size, translation and ribosome biogenesis as well as glucose metabolism in mammalian tumor cell lines [85,86]. It may well be, that HSF1 orchestrates a network that optimizes fuel utilization and overall cellular and organismal functions in the postmitotic worm to attain efficient self maintenance and longevity. However, the mechanisms and the gene network involved remains to be identified.

RESVERATROL AND SIR2 ARE ACTIVATORS OF HSF1

The plant polyphenol resveratrol recapitulates the dietary restriction-induced longevity of yeast, invertebrates and mice on a high-fat diet (but not on a normal diet) [87-91]. Other studies, nevertheless, could not show an increased longevity upon resveratrol treatment in invertebrate and normal fed mouse trials [92,93]. Resveratrol has been shown to act via the Sir2 (silent information regulator) sirtuin family of NAD^+-dependent protein deacetylases in a FoxO/*daf-16*-independent manner [88,94]. Sir2 deacetylates a number of key regulatory proteins including FoxO, PPARγ, and its activator PGC-1α and, responsible for survival under stress and the metabolic change [95-97]. Genetic activation of Sir2/*sir-2.1* induces a lifespan extension in worms and mice overexpressing the major mammalian ortholog SirT1 show reduced energy expenditure, improved metabolism and protection from diabetes [98-100]. Sir2/*sir-2.1* seems to mediate some forms of dietary restriction including the *eat-2* mutation in *C. elegans* and SirT1 is required for dietary restriction-induced physical activity in mice [101-103]. However, in other studies dietary restriction by *eat-2* by bacterial dilution or by bacterial deprivation did not depend on Sir2 [73,80,83].

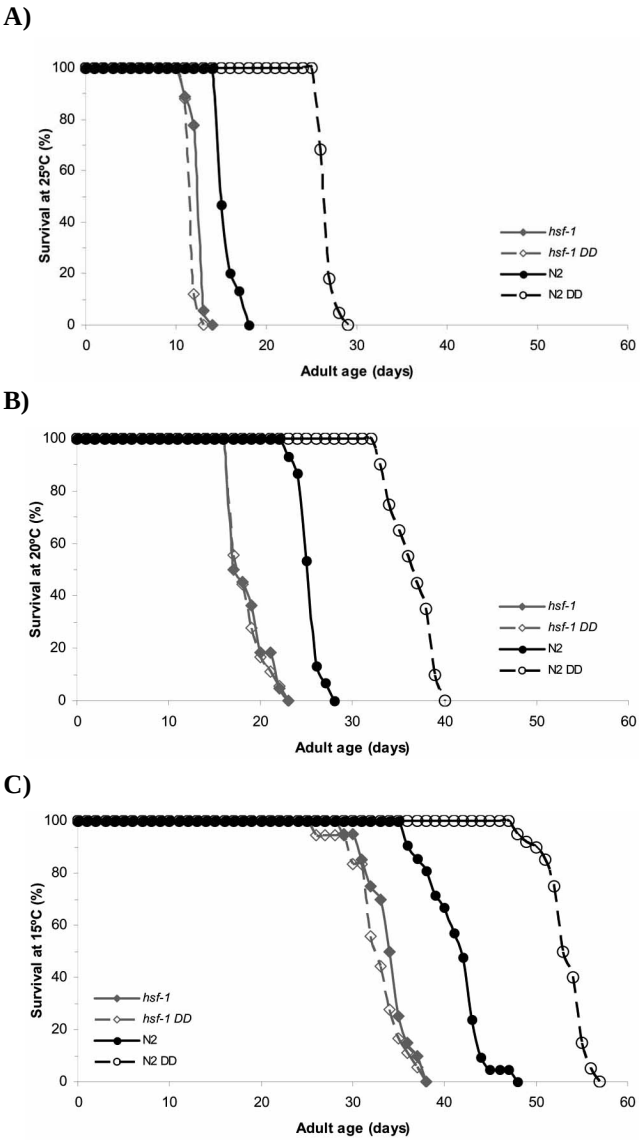

Fig. (1). HSF-1 mediates dietary deprivation-induced life-span extension at various temperatures. Survival curves of wild type (N2) and *hsf-1(sy441)* loss of function nematodes at 25ºC **(A)**, 20ºC **(B)** or 15ºC **(C)** in the presence (closed symbols) or absence (dietary deprivation, DD, open symbols) of the food source, *E. coli*. Synchronized strains were grown on NGM plates containing 50 μM FudR (5-fluoro-2'-deoxyuridine). DD was initiated at day 4 of adulthood. Animals that crawled off the plate, exploded, bagged, or became contaminated were removed from the evaluation process. The figure shows representative curves of 3 independent experiments.

Both resveratrol and Sir2/SirT1 were protective in misfolding neurodegenerative models suggesting an improved protein homeostasis [104,105]. As a potential mechanism, we have shown that resveratrol specifically induces the heat shock response and protects various mammalian cells against heat stress and proposed a Sir2-dependent modulation of HSF1 [106]. Recently this has been experimentally demonstrated by showing that SirT1 deacetylates HSF1 and prolongs its binding to the heat shock promoter [107]. However, the exact contribution of the heat-shock response to resvera-

trol-induced longevity remained unknown. Recent results from our lab show that HSF-1 mediates resveratrol-induced longevity in a manner dependent on Sir-2.1 in *C. elegans* (Tóth ML, Dancsó B, Csermely P and Sőti C, submitted manuscript, Table **1**). These findings link the metabolic and proteotoxic stress responses in longevity regulation in invertebrates. How this interaction modulates aging in mammals remains to be determined.

SUMMARY AND PERSPECTIVES

The observations presented in this review demonstrate an intimate connection between metabolic disturbances, dietary restriction and protein homeostasis with a special emphasis on the HSF1-orchestrated heat shock response. Most experiments elucidating the dietary restriction-induced longevity regulation have been performed in invertebrates and analyzing one or two components of the signaling pathways. Future studies employing systems biology and mammalian models will reveal the topology of the signaling network and the place of HSF1 in response of dietary restriction. This may lead to the development of novel strategies to attain the final goal of healthy aging and to prevent or heal civilization diseases.

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