6-30-2014

MITOHORMESIS: PROMOTING HEALTH AND LIFESPAN BY INCREASED LEVELS OF REACTIVE OXYGEN SPECIES (ROS)

Michael Ristow
University of Jena

Kathrin Schmeisser
University of Jena

International DOSE-RESPONSE Society
www.Dose-Response.org

MITOHORMESIS: PROMOTING HEALTH AND LIFESPAN BY INCREASED LEVELS OF REACTIVE OXYGEN SPECIES (ROS)

Michael Ristow[1,2], Kathrin Schmeisser[2] □ [1] Energy Metabolism Laboratory, ETH Zürich (Swiss Federal Institute of Technology Zurich), Schwerzenbach/Zürich, CH 8603, Switzerland; [2] Dept. of Human Nutrition, Institute of Nutrition, University of Jena, Jena D-07743, Germany

□   Increasing evidence indicates that reactive oxygen species (ROS), consisting of superoxide, hydrogen peroxide, and multiple others, do not only cause oxidative stress, but rather may function as signaling molecules that promote health by preventing or delaying a number of chronic diseases, and ultimately extend lifespan. While high levels of ROS are generally accepted to cause cellular damage and to promote aging, low levels of these may rather improve systemic defense mechanisms by inducing an adaptive response. This concept has been named mitochondrial hormesis or mitohormesis. We here evaluate and summarize more than 500 publications from current literature regarding such ROS-mediated low-dose signaling events, including calorie restriction, hypoxia, temperature stress, and physical activity, as well as signaling events downstream of insulin/IGF-1 receptors, AMP-dependent kinase (AMPK), target-of-rapamycin (TOR), and lastly sirtuins to culminate in control of proteostasis, unfolded protein response (UPR), stem cell maintenance and stress resistance. Additionally, consequences of interfering with such ROS signals by pharmacological or natural compounds are being discussed, concluding that particularly antioxidants are useless or even harmful.

1. INTRODUCTION

Mitochondrial metabolism and reactive oxygen species

Mitochondria are important cell organelles that are responsible not only for the conversion of the bulk of nutritive energy, but also exert a major role in aging processes and in the development of age-related diseases. As an inevitable by-product of oxidative phosphorylation (OxPhos), mitochondria generate over 90% of all intracellular reactive oxygen species (ROS), with conversion of $0.15 – 5\%$ of total oxygen consumed by resting cells (Halliwell and Gutteridge 2007, Chance *et al.* 1979, Boveris and Chance 1973, St. Pierre *et al.* 2002). Hence, as main producers of energy and also potentially harmful ROS, mitochondria have a major impact on physiological and pathophysiological processes within the cell.

ROS formation to an extent that exceeds physiological levels and hence causes putative damage is called oxidative stress (Sies 1985). Thus, mitochondrial dysfunction implicating increased oxidative stress has been proposed to be associated with a variety of diseases like diabetes,

Address correspondence to Michael Ristow; Email: mristow@mristow.org

cancer and neurodegenerative disorders, including Alzheimer's and Parkinson's disease (Wiederkehr and Wollheim 2006, Ristow 2006, Fukui and Moraes 2008, Tatsuta and Langer 2008). Beyond that, impairment of mitochondrial activity is supposed to be a major reason for aging (Tatsuta and Langer 2008, Bratic and Larsson 2013, Trifunovic *et al.* 2004), whereas the role of ROS in this regard is still under debate. On the one hand, ROS have been implicated into cellular damage hence contributing to the aging process. On the other hand, an increasing number of studies linking improvement of mitochondrial capacity to increased lifespan and health span extension. Evidence for this dates back to the 1990s, when essential signaling roles for hydrogen peroxide were established (Barja 1993, Finkel 1998, Sena and Chandel 2012). Hence, it seems that a shift towards oxidative metabolism could delay the onset of age-related diseases and maybe aging itself.

Free radical theories of aging

Increased formation of mitochondrial ROS was postulated to be a major cause of aging in 1956, when Denham Harman introduces his *Free Radical Theory of Aging* (FRTA) (Harman 1956). According to this concept, increased ROS formation causes an accumulation of damage in the cell within age, resulting in age-related impairment of cellular functions and ultimately death of the cell or the corresponding organism, respectively. Respiratory enzymes, which utilize oxygen to generate readily available energy, were proposed to be the main generators of ROS. Due to the fact that mitochondria are the main intracellular source of ROS, Harman extended his initial FRTA theory to the *Mitochondrial Free Radical Theory of Aging* (MFRTA) (Harman 1972). Over the last decades, significant research efforts have been invested to prove the MFRTA, however generating inconsistent and conflicting results (Perez *et al.* 2009). Accordingly, nowadays it seems to be established that enhancement of metabolic rate does not necessarily result in concomitantly increased ROS formation (Lapointe and Hekimi 2010) and that the relationship between ROS levels and aging is not linear (Delaney *et al.* 2013, Johnson *et al.* 2001, Lee *et al.* 2003, Kim and Sun 2007, de Castro *et al.* 2004). Nevertheless and supporting the MFRTA, a bulk of studies in different organisms found that reduced levels of oxidative stress result in extended lifespan (Harrington and Harley 1988, Phillips *et al.* 1989, Orr and Sohal 1994, Parkes *et al.* 1998, Melov *et al.* 2000, Moskovitz *et al.* 2001, Bakaev and Lyudmila 2002, Ruan *et al.* 2002, Ishii *et al.* 2004, Huang *et al.* 2006, Zou *et al.* 2007, Kim *et al.* 2008, Quick *et al.* 2008, Dai *et al.* 2009, Shibamura *et al.* 2009) and long-lived species seem to produce fewer ROS and accumulate less damage than short-lived organisms (Gredilla *et al.* 2001, Sanz *et al.* 2010, Sanz and Stefanatos 2008, Gruber *et al.* 2008).

M. Ristow and K. Schmeisser

As a consequence, ROS-lowering interventions were widely proposed to be a promising strategy to retard aging in humans. In this regard, natural or artificial substances that are able to scavenge ROS, so-called antioxidants, were examined intensively. In contrast to the studies in lower model organisms cited above, several prospective intervention trials did not find any health-promoting effects of antioxidant supplementation. Unexpectedly, most interventional studies found a lack of effects in humans (Greenberg *et al.* 1994, Liu *et al.* 1999, Rautalahti *et al.* 1999, Virtamo *et al.* 2000, Various 2002, Sacco *et al.* 2003, Zureik *et al.* 2004, Czernichow *et al.* 2005, Czernichow *et al.* 2006, Cook *et al.* 2007, Kataja-Tuomola *et al.* 2008, Sesso *et al.* 2008, Katsiki and Manes 2009, Lin *et al.* 2009, Song *et al.* 2009), whereas others even suggested detrimental effects on human health, for instance promotion of cancer growth or induction of diseases with negative impact on human lifespan (Albanes *et al.* 1996, Omenn *et al.* 1996, Vivekananthan *et al.* 2003, Lonn *et al.* 2005, Bjelakovic *et al.* 2007, Ward *et al.* 2007, Lippman *et al.* 2009, Schipper 2004, DeNicola *et al.* 2011, Abner *et al.* 2011). Consistently, several studies overexpressing antioxidant enzymes in mice failed to exert positive effects on lifespan or associated parameters (Jang *et al.* 2009, Muller *et al.* 2007, Perez *et al.* 2011). Accordingly, several long-lived species were found to have a relatively lower expression of antioxidant genes than short-lived ones (Brown and Stuart 2007, Lopez-Torres *et al.* 1993, Page *et al.* 2010, Page and Stuart 2012, Salway *et al.* 2011). In the fruit fly *Drosophila melanogaster*, increasing levels of mitochondria-derived ROS were found during aging, but were not altered through interventions that increase longevity (Cocheme *et al.* 2011). Finally, mice that are heterozygous for *Mclk1*, coding for a ubiquinone synthesis enzyme, showed both increased mitochondrial ROS production and extended lifespan (Liu *et al.* 2005).

Mitochondrial hormesis (Mitohormesis): Non-linear responses to increased levels of ROS

These before-mentioned findings fundamentally questioned the FRTA, eventually requiring a modernized view concerning the putative roles of mitochondrial ROS (mtROS) generation. It has been repeatedly shown in recent years that mtROS serve as important signaling molecules mediating both cellular and systemic physiological changes, which has been summarized elsewhere (Finkel 1998, Mittler *et al.* 2011, Sena and Chandel 2012). Physiological targets for ROS are, for instance, thiol groups on cysteine residues that become oxidized and thereby altering functions of the enzymes in a signaling pathway (Finkel 2012, Rhee *et al.* 2000, Tonks 2005). However, given the fact that increased levels of oxidative damages do accumulate during the aging process, one interesting new point of view proposes that intrinsic aging is caused by an inadequate response to endogenous ROS signals (Sohal and Orr 2012).

Mitochondrial Hormesis and Lifespan

If ROS serve as signaling molecules as outlined above, it appears likely that ROS may also exert specific functions in promoting general health, and specifically lifespan. Since ROS at high doses unquestionably exert detrimental effects on cellular integrity, this insinuates that different levels of ROS, i.e. comparably low versus high amounts, may exert opposite effects on biological outcomes. In a more general sense, this kind of biphasic or non-linear response to potentially harmful substances was named "hormesis" (Southam and Ehrlich 1943). By today, the impact of hormetic effects on aging has been repeatedly proposed, with a range of stressors described (Calabrese and Baldwin 2002, Cypser and Johnson 2002, Rattan 2008, Mattson 2008, Lamming *et al.* 2004, Yanase *et al.* 1999). On a hypothetical basis the term was specified to mitochondrial hormesis or mitohormesis in 2006 (Tapia 2006), which after its experimental validation in parallel (Schulz *et al.* 2007) is repeatedly used in settings where mtROS act as sublethal stressors promoting lifespan, whereas higher doses increase lethality (Figure 1).

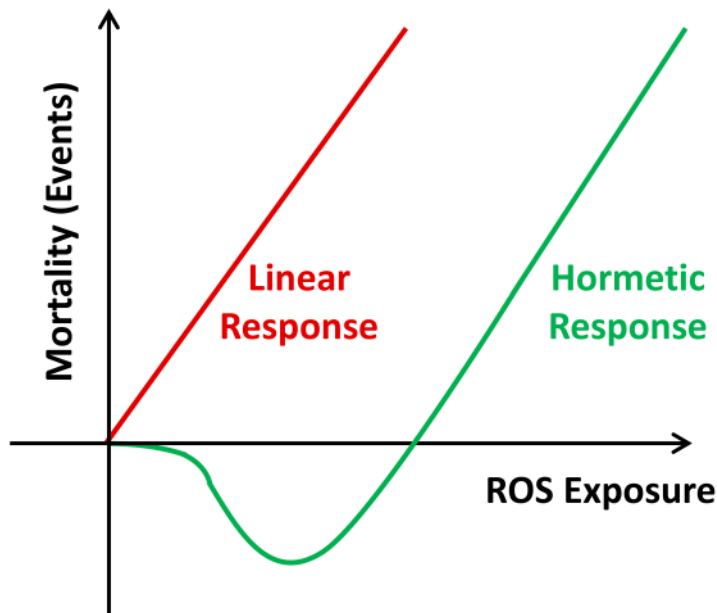**FIGURE 1.** Mitochondrial Hormesis (Mitohormesis). While the *Free Radical Theory of Aging* suggests a linear dose-response relationship between increasing amounts of ROS and oxidative stress on the one hand, and mortality events on the other (red curve), the concept of mitohormesis indicates a non-linear dose-response relationship where low doses of ROS exposure decrease mortality, while higher doses promote mortality.

M. Ristow and K. Schmeisser

Aim of the review

We here aim to summarize the wide body of published evidence that refers to the biological relevance of mitohormesis mainly in regards to regulation of stress resistance and longevity, but also affiliated areas of interest. The majority of publications in this regard does not explicitly use the term mitohormesis but rather refers to dose-dependent or non-linear, mtROS-mediated signaling processes that hence reflect typical examples of mitohormesis.

2. CALORIE RESTRICTION (CR)

Calorie restriction (CR), being defined as a $10 - 50\%$ reduction of *ad libitum* calorie uptake in the absence of malnutrition, is so far the most convincing intervention to delay both aging and the occurrence of age-related diseases in a variety of organisms, as reviewed elsewhere (Fontana *et al.* 2010). The first observation that laboratory rats maintained on dietary restriction not only showed an increased lifespan, but also seem to be healthier at higher age, dates back to 1935 (McCay *et al.* 1935). Since then, it has been frequently shown that CR is capable of extending median and maximum lifespan in various species from yeast to mammals (Lin *et al.* 2004, Lin *et al.* 2002, Schulz *et al.* 2007, Iwasaki *et al.* 1988), insinuating an evolutionarily conserved mechanism, as review elsewhere (Mair and Dillin 2008).

Nevertheless, it is still a matter of debate whether CR prolongs life expectancy in humans too as it is shown that people with average body mass tend to live longest (Berrington de Gonzalez *et al.* 2010), while CR in humans rather causes severe reduction of body mass (Holloszy and Fontana 2007). However, CR in humans clearly reduces diseases associated with aging, including cardiovascular diseases, cancer, and type 2 diabetes mellitus (DM type 2) (Takemori *et al.* 2011, He *et al.* 2012, Harvey *et al.* 2012, Willette *et al.* 2012, Ryan *et al.* 2012) as well as associated risk factors known to promote the before-mentioned diseases (Larson-Meyer *et al.* 2006, Heilbronn *et al.* 2006, Lefevre *et al.* 2009). One study found that CR reduces age-related mortality (which corresponds to only 54% of deaths) in rhesus monkeys, whereas no influence on overall mortality was reported (Colman *et al.* 2009). In contrast and unlike *ad libitum* fed control animals, monkeys on CR did not show any age-related impairment in glucose homeostasis, suggesting a reduction of prevalence of metabolic disorders like DM type 2. Another recent study on the same model organism found no changes in mortality following CR, whereas beneficial effects on health and morbidity were clearly observed (Mattison *et al.* 2012). It should be noted that the two studies have used diets that differed strikingly, also in regards to carbohydrate content. Due to the fact that both studies were not finished by the time this manuscript was pre-

pared, future findings will have to show whether CR may affect overall mortality in these monkeys. Nevertheless, there is suggestive evidence that CR may also prolong life expectancy in primates and ultimately humans (Fontana *et al.* 2004, Heilbronn *et al.* 2006, Ingram *et al.* 2006, Weindruch 2006, Fontana and Klein 2007).

The concept of CR is based on an assumption postulated in the early 20th century, suggesting that there is an inverse correlation between the maximum lifespan of an organism and its metabolized nutritive energy (Rubner 1908). According to this, the *Rate of Living* hypothesis was formulated soon after by Raymond Pearl, insinuating that an increase in metabolic rate would decrease the lifespan of eukaryotes (Pearl 1928). A possible explanation for this was subsequently proposed within the FRTA by Harman, a hypothesis that became very popular and is frequently cited in aging research up to now (Harman 1956), as it is an explanation for CR which was hypothesized primarily to be a result of reduced oxidative stress and less oxidative cellular damage due to reduced metabolic rate (Sohal and Weindruch 1996).

However, more recent findings on the mechanistic basis of CR are in conflict with the FRTA. For instance, it is unclear whether CR actually does lead to a decrease in metabolic rate, i.e. oxygen consumption and/or heat production. A positive correlation for decreased metabolic rate and increase in longevity is found neither for metazoans like *Drosophila* and *C. elegans*, nor is it for mice (Hulbert *et al.* 2004, Lin *et al.* 2002, Masoro *et al.* 1982, Speakman *et al.* 2002). Rather, it has been reported that CR in *C. elegans* is associated with an increased metabolic rate (Walker *et al.* 2005, Schulz *et al.* 2007) as it is for *Drosophila* (Magwere *et al.* 2006, Piper *et al.* 2005b).

Since increased metabolic rates are necessarily linked to increased mitochondrial metabolism, it appears likely that these lifespan-extending processes may precipitate into increased production of ROS as an inevitable by-product of mitochondrial metabolism, as shown e.g. for glucose restriction (Schulz *et al.* 2007) and discussed in more detail below, reflecting a CR-associated prime example of mitohormesis.

3. MITOHORMETIC MECHANISMS OF ADAPTIVE RESPONSES

Notably, it was repeatedly reported that CR is capable of inducing stress defense mechanisms, particularly those which are involved in the detoxification of ROS, such as radical-scavenging enzymes and phase I and II biotransformation response enzymes, reflecting a number of putative mitohormetic responses (Koizumi *et al.* 1987, Semsei *et al.* 1989, Rao *et al.* 1990, Pieri *et al.* 1992, Youngman *et al.* 1992, Xia *et al.* 1995, Masoro 1998, Barros *et al.* 2004, Mahlke *et al.* 2011, Qiu *et al.* 2010, Rippe *et al.* 2010, Sreekumar *et al.* 2002, Park *et al.* 2012, Schulz *et al.* 2007, Zarse *et al.* 2012, Schmeisser *et al.* 2013b).

M. Ristow and K. Schmeisser

The independent observations of increased mtROS levels on the one hand and the induction of stress defense on the other, notably both in states of CR, raised the possibility that an initial induction of mtROS induce stress defense mechanisms culminating in secondarily decreased mtROS levels, as experimentally shown recently in a time-resolved manner (Zarse *et al.* 2012): In states of glucose restriction due to a constitutive genetic defect in the insulin/IGF-1 receptor DAF-2, a global decrease of mtROS levels in the steady-state was found. However, when analyzing an acute disruption of the same genetic pathway, a transient increase of mtROS was observed that secondarily induced defense mechanisms, ultimately reducing ROS levels in the steady state (Figure 2A). Blocking the initial ROS signal accordingly abrogated the induction of stress defense, as well as the steady-state reduction of ROS levels (Figure 2B). This indicates that the mitohormetic ROS signal is typically transient, and is reduced or even abolished in the steady-state due to an adaptive up-regulation of antioxidant enzymes and more globally stress defense. In other words, transiently increased ROS levels act to induce a vaccination-like response within the individual cell to lead to reduced ROS levels and better stress defense in the steady state (Figure 3).

This subsequent decrease in ROS due to an adaptive increase of detoxifying mechanisms has often been misinterpreted as being the primary result of CR, which as outlined above is not the case. Rather, a clear causal relationship between primarily enhanced ROS formation and activation of ROS defense mechanism under conditions of CR was described (Agarwal *et al.* 2005), which manifests the hypothesis that CR is an essential trigger of mitohormetic mechanisms as shown thereafter (Schulz *et al.* 2007). Moreover, carbonyl concentrations reflecting oxidative protein damage were found to be increased in the brains of mice shortly after initiation of CR, whereas steady-state concentrations were significantly lower than those of control group (Dubey *et al.* 1996). Furthermore, levels of F2-isoprostane, reflecting oxidized lipids, were found to be decreased in obese woman under modest calorie restriction after 5 days of intervention (Buchowski *et al.* 2012). According to this, adaptive response mechanisms seem to be likely the reason for the beneficial effects initiated by CR, which is also supported by more recent research (Schulz *et al.* 2007, Sharma *et al.* 2010, Zuin *et al.* 2010, Rattan and Demirovic 2010, Mesquita *et al.* 2010), also in a time-resolved manner (Zarse *et al.* 2012). In rodents that are exposed to CR for instance, an induction of antioxidant defense capacities has been frequently shown (Koizumi *et al.* 1987, Semsei *et al.* 1989, Rao *et al.* 1990, Pieri *et al.* 1992, Youngman *et al.* 1992, Xia *et al.* 1995, Masoro 1998, Barros *et al.* 2004, Mahlke *et al.* 2011, Qiu *et al.* 2010, Rippe *et al.* 2010, Sreekumar *et al.* 2002). Additionally, glucose restriction in yeast not only promotes lifespan but also decreases ROS levels although respiration was increased (Barros *et al.* 2004). In conflict with
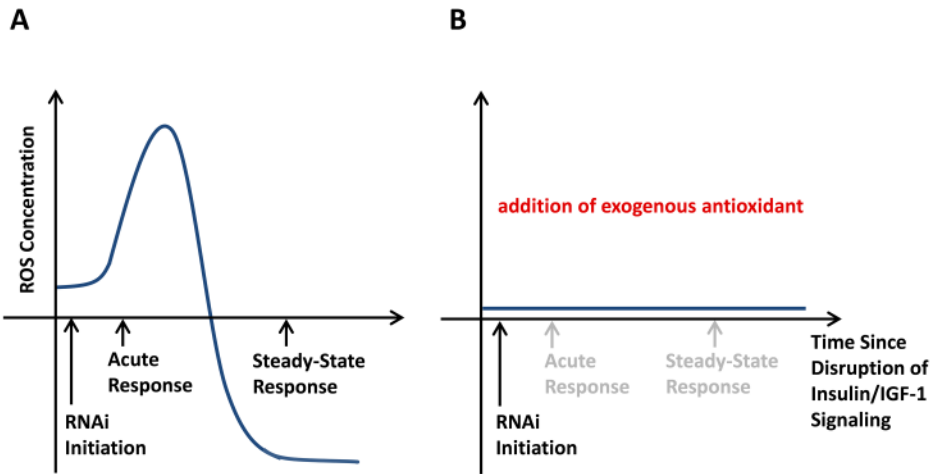
Mitochondrial Hormesis and Lifespan

FIGURE 2. Lifespan-promoting ROS signaling can occur transiently and hence requires time-resolved quantification. A) Disruption of the insulin/IGF-1 receptor, named DAF-2, in *C. elegans* extends lifespan. The constitutive *daf-2* mutant exhibits reduced ROS levels. This has led to the conclusion that impairing DAF-2 primarily causes reduced ROS levels. However, as recently published (Zarse *et al.* 2012), the opposite is the case: When studying the acute effects of an RNAi-mediated *daf-2* knockdown, a transient increase in ROS production was observed ("acute response"). As shown in the publication (Zarse *et al.* 2012), this ROS signal induces various endogenous ROS defense mechanisms that ultimately reduce ROS levels. This leads to a persistent reduction of ROS levels in *daf-2* RNAi-treated worms in the steady state. This also exemplifies that quantifying ROS at an inappropriate time point may lead to opposing results: ROS determined during the acute response against RNAi would indicate *increased* levels, while ROS determined three days later during the steady-state would indicate *reduced* levels. B) Exogenously added antioxidants prevent the acute induction of a ROS signal (Zarse *et al.* 2012). The lack of this ROS signal leads to a complete lack of the original adaptive response shown in panel A. This causes higher steady-state ROS levels than in the absence of exogenous antioxidants which only can be explained in the framework of mitohormesis, while the linear dose-response would consider this phenomenon as paradoxical.

these findings, subsequent studies using the same models and interventions rather reported an increase in ROS production paralleled by enhanced respiration and elevated antioxidant enzyme activity (Schulz *et al.* 2007, Sharma *et al.* 2010, Zuin *et al.* 2010, Agarwal *et al.* 2005, Kharade *et al.* 2005, Piper *et al.* 2006). This suggests a relationship between increased respiration, ROS generation and the upregulation of ROS defense mechanisms, which in the end mediates longevity. Furthermore, lifespan-extending mutations in *C. elegans* are commonly associated with increased stress resistance and often also with increased metabolic activity (Lithgow *et al.* 1995, Vanfleteren and De Vreese 1995, Honda and Honda 1999, Murphy *et al.* 2003, Houthoofd *et al.* 2005, Dong *et al.* 2007).

As mentioned before, CR is able to delay the onset of a broad range of age-related diseases such as cancer, DM type 2, nephropathy, cataracts, hyperlipidemia, and hypertension (Fishbein 1991, Weindruch and Walford 1988). Therefore it seems possible, that the lifespan-extending effect of CR is linked to promotion of mean lifespan due to prevention of
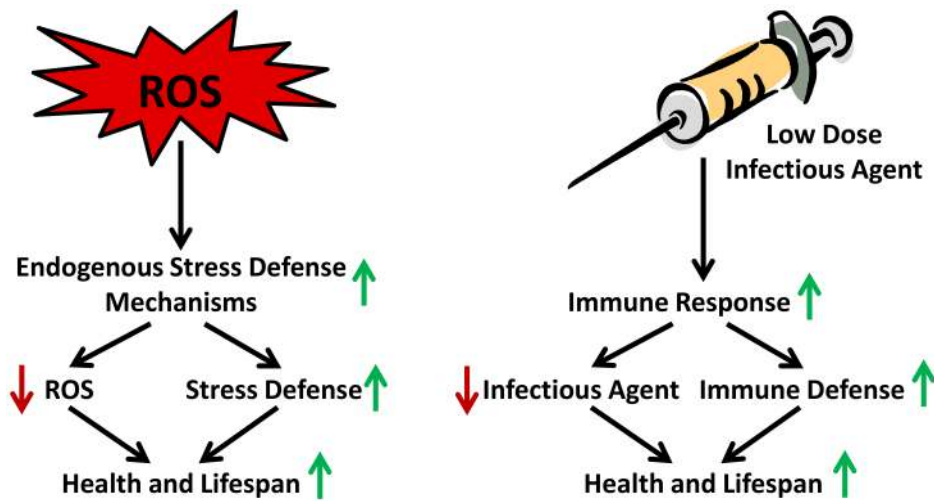
M. Ristow and K. Schmeisser

FIGURE 3. Transiently increased ROS levels cause a vaccination-like adaptive response that promotes endogenous ROS defense capacity. The figure exemplifies the organismal stress response to low-level and/or short-term ROS exposure in comparison to the long-standing vaccination process, where inactive or impaired microbes exert an organismal immune response leading to a long-lasting defense capacity against future infections.

life-threatening disorders that reduce longevity. However, additional effects of CR on molecular processes improve cellular functions and therefore improve health-span *per se* have been observed, for instance the below mentioned activation of NF-E2-Related Factor 2 (NRF2) (Koizumi *et al.* 1987, Semsei *et al.* 1989, Rao *et al.* 1990, Pieri *et al.* 1992, Youngman *et al.* 1992, Xia *et al.* 1995, Masoro 1998, Barros *et al.* 2004, Mahlke *et al.* 2011, Qiu *et al.* 2010, Rippe *et al.* 2010, Sreekumar *et al.* 2002, Bishop and Guarente 2007). Another crucial role in CR and aging is attributed to the sirtuins, a conserved family of NAD^+-dependent deacetylases as reviewed elsewhere (Baur and Sinclair 2006, Canto and Auwerx 2009) (see also chapter "Sirtuin signaling").

An important factor regarding the effects of CR could also be thiore-doxin, as it is shown to be essential for the lifespan extension in *C. elegans* under dietary deprivation and knockouts of *eat-2*, a genetic surrogate of nematodal CR (Fierro-Gonzalez *et al.* 2011). The oxidoreductase thiore-doxin is not only involved in antioxidant response and redox regulation, but also acts as electron donor for metabolic enzymes and prevents aggre-gation of cytosolic proteins in the cell (Lillig and Holmgren 2007, Berndt *et al.* 2008). Thioredoxin gene expression is increased through NRF2 binding at the antioxidants responsive elements (AREs) and NRF2 is shown to be activated by ROS (Kim *et al.* 2001, Papaiahgari *et al.* 2006).

The activation of the transcription factor NRF2 from the leucine zip-per family is indeed a crucial pathway to mediate mitohormesis. NRF2

binds to the DNA via AREs, which coordinate a stress response to ROS by boosting the expression of antioxidant proteins and phase I and II detoxification enzymes (Rushmore *et al.* 1991). Under unstressed conditions, NRF2 is sequestered in the cytoplasm by its specific repressor Kelch-like ECH-Associated Protein 1 (KEAP1), an actin-binding protein, which also targets NRF2 for proteasomal degradation (Itoh *et al.* 1999). KEAP-1 has redox-sensitive cysteine residues, with which it sensors oxidants and electrophiles, leading to abrogation of the NRF2/KEAP1 complex (Zhang 2006, Itoh *et al.* 2004). NRF2 then translocates into the nucleus, where it executes its transcriptional regulating functions (Jaiswal 2004) (Figure 4). While the putative functional orthologue of KEAP1 in *C. elegans*, XREB (Hasegawa and Miwa 2010), has not been examined further so far, the worm NRF2 orthologue SKN-1 similarly responds to oxidative stress by upregulating antioxidant and phase II genes which in the end promotes stress resistance and lifespan extension (An and Blackwell 2003, Bishop and Guarente 2007, Tullet *et al.* 2008), as it is shown for various other species (Sykiotis and Bohmann 2008, Motohashi and Yamamoto 2004, Leiser and Miller 2010, Lewis *et al.* 2010).

Other transcription factors which are essential for lifespan extension due to various interventions are members of the Forkhead transcription factors (FOX) as well as heat shock factor 1 (HSF-1). FOXOs for example activate a number of target genes involved in cellular stress response and it has been shown, that mitohormetic upregulation of superoxide dismutase and catalase following oxidative stress is FOXO dependent (Kops *et al.* 2002, Nemoto and Finkel 2002, Brunet *et al.* 2004), whereas FOXAs are important mediators of development and facilitate the response to CR (Friedman and Kaestner 2006, Panowski *et al.* 2007). HSF-1 regulates the transcription of heat shock genes that encode proteins (HSPs) in response to heat and other stress, which is linked to protection against diseases and increased lifespan in model organisms (Akerfelt *et al.* 2010, Anckar and Sistonen 2011). HSPs are also linked to hormetic responses (Cypser and Johnson 2002). Other mechanisms specifically related to the stressors described in the chapters below will be mentioned at the appropriate position within this review (Figure 4).

4. REDUCTION OF SPECIFIC MACRONUTRIENTS

Macronutrients are carbohydrates, protein and fat (triacylglycerides), which consist of a few different monosaccharides (importantly including glucose), amino acids, and fatty acids, respectively. Metabolism of these macronutrients provides the majority of energy in form of ATP required by an organism. ATP generation out of fatty acids and most amino acids depends on mitochondrial OxPhos and therefore presence and consumption of oxygen. However, only glucose can be metabolized to generate ATP independently of the mitochondria and oxygen, hence without
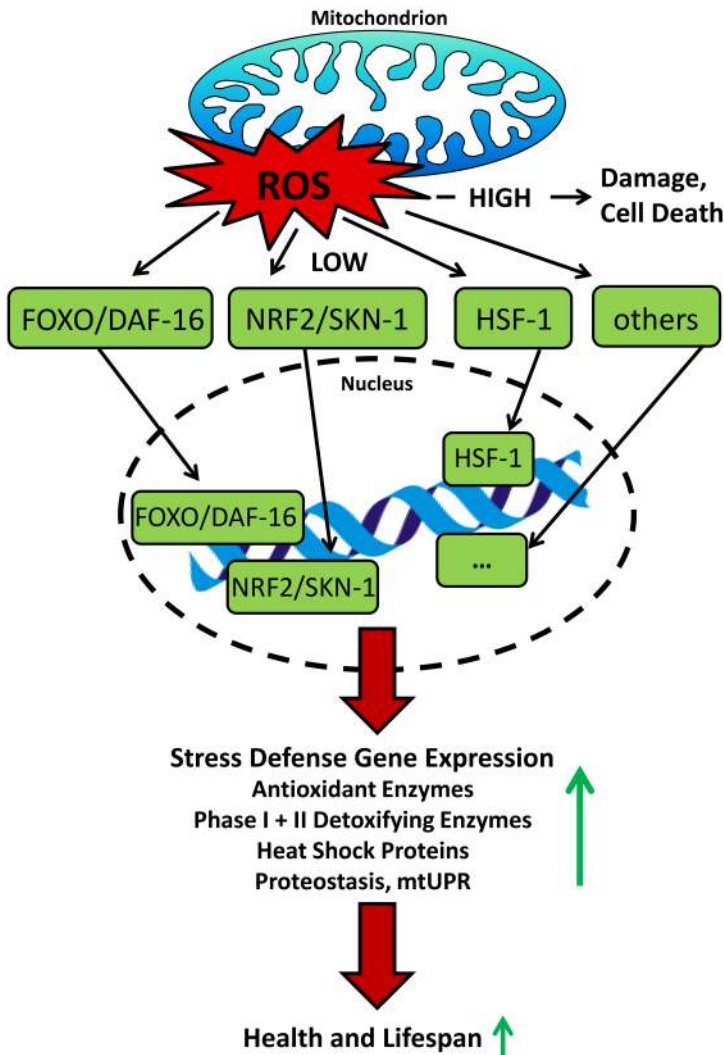
297

M. Ristow and K. Schmeisser

FIGURE 4. Overview on how ROS transcriptionally influence stress resistance and lifespan. High levels cause damage resulting in death of the cell and eventually the corresponding organism, whereas low levels are capable of activating transcription factors that mediate adaptive stress response culminating in increased lifespan.

increasing ROS production. Nevertheless, the generation of ATP via OxPhos is considerably more efficient than anaerobic ATP production from glucose or specific amino acids: One mole of glucose metabolized via mitochondrial OxPhos provides 30 moles of ATP, compared to 4 moles of ATP due to exclusively glycolytic breakdown. This implies that restricting glucose may induce OxPhos and mitochondrial metabolism more efficiently than globally restricting calorie uptake.

298

On one hand, only a few studies have investigated whether it is possible to mimic the CR mediated effect on lifespan by reducing only selected macronutrients, so the evidence available is limited. On the other hand, some studies point out that it might be not the amount of calories affecting health span, but rather the reduction of specific nutrients, as reviewed elsewhere (Fanson *et al.* 2009, Mair *et al.* 2005, Piper *et al.* 2005a).

Studies of fat restriction in invertebrates are lacking, while a restriction of lipids without overall CR in mice does not affect their lifespan (Iwasaki *et al.* 1988). Feeding a low-carbohydrate/high-fat diet to mice reduced lifespan slightly, at least in comparison to a high-carbohydrate/low-fat diet (Keipert *et al.* 2011). However, it is likely that fat restriction has less potential to delay the onset of metabolic disorders than carbohydrate restriction (Ryan *et al.* 2007, Volek *et al.* 2009).

In mice, it has been shown that a reduced nutritional protein content extent lifespan (Stoltzner 1977, Leto *et al.* 1976, Fernandes *et al.* 1976) as it was shown for casein restriction in *Drosophila* (Min and Tatar 2006). Studies examining the restriction of the essential amino acid and glutathione precursor methionine found it not only to be lifespan extending. Increasing mitochondrial biogenesis and function, energy expenditure, stress resistance, aerobic capacity, insulin sensitivity, glutathione (GSH) and expression of glutathione-S-transferase (GST) as well as a decrease of oxidative stress and cell damage due to adaptive changes in methionine and GSH metabolism were also observed (Zimmerman *et al.* 2003, Miller *et al.* 2005, Perrone *et al.* 2010, Richie *et al.* 1994, Malloy *et al.* 2006, Sanz *et al.* 2006, Perrone *et al.* 2012, Tsai *et al.* 2010, Caro *et al.* 2008). Interestingly, co-treatment with an antioxidant, N-acetylcysteine, blocks some of the health-promoting effects of methionine restriction, accentuating a critical role for ROS with mitohormetic adaption processes in this regard (Elshorbagy *et al.* 2012, Sanchez-Roman *et al.* 2012).

As mentioned above, glucose (besides a few amino acids) is the only macronutrient that can be metabolized and generate ATP without producing ROS. In support of the mitohormesis concept, it is documented that glucose restriction initiates health-promoting and lifespan extending effects in rodents and various lower organisms, for instance in *Drosophila* (Mair *et al.* 2005) and yeast (Lin *et al.* 2002). In the latter, studies showed that lifespan extension depends on enhanced respiration and sirtuin activation, which is still a matter of heated debate (Lin *et al.* 2000, Kaeberlein *et al.* 2004, Agarwal *et al.* 2005, Guarente and Picard 2005, Smith *et al.* 2007, Roux *et al.* 2009). However, also sirtuin-independent pathways have been discussed (Barros *et al.* 2004, Roux *et al.* 2009).

To achieve depletion specifically of glucose metabolism in eukaryotic model organisms such as rodents or *C. elegans* and hence, to mimic a ketogenic diet (i.e. a very low carbohydrate content) and recapitulate meta-

bolic hallmarks of CR in rodents, the glycolytic inhibitor 2-deoxy-glucose (DOG) is frequently used (Wick *et al.* 1957, Garriga-Canut *et al.* 2006, Lane *et al.* 1998, Ingram *et al.* 2004). DOG was found to be lifespan extending in *C. elegans* (Schulz *et al.* 2007), whereas and unexpectedly, increased mortality in rats was reported following chronic ingestion of DOG (Minor *et al.* 2010). It should be noted that shuttle mechanism for lactate and alanine may explain differential outcomes of glucose deprivation in metazoans and rodents, which however remains to be evaluated.

Similar as reported in yeast for media-based glucose restriction (Lin *et al.* 2002), DOG not only extends lifespan in *C. elegans*, but also increases respiration. However and unlike in *S. cerevisiae*, in *C. elegans* the effect seems to be independent of sirtuins. The authors suggested that the underlying mechanisms that lead to increased life expectancy are dependent on the AMP-dependent kinase (AMPK). AMPK acts as a highly conserved key regulator of energy metabolism within a cell, since functionally similar orthologues were found in lower species like flies and worms (Hardie *et al.* 2006, Apfeld *et al.* 2004, Greer *et al.* 2007a, Pan and Hardie 2002). AMPK is activated by metabolic stress like cellular lack of energy, resulting in upregulation of processes that produce energy, such as mitochondrial biogenesis. This leads to a compensation of the energy deficit and likely to additional health-promoting effects (Hardie *et al.* 2006).

Another approach to reduce glucose content within the cell is the impairment of GLUT-4 glucose transporters. Mice with disruption of GLUT-4 in both muscle and adipose tissue show fasting hyperglycemia, glucose intolerance, increased fatty acid turnover, and utilization. However, lifespan was not affected (Kotani *et al.* 2004). Strikingly, over-expression of GLUT-4 leading to an increase of cellular glucose does also not affect lifespan, whereas enhanced glucose abundance decreased lifespan significantly in *C. elegans* (McCarter *et al.* 2007, Lee *et al.* 2009b, Schlotterer *et al.* 2009, Schulz *et al.* 2007).

In humans, several approaches of varying macronutrients in the diet have been established, especially to lose weight in states of obesity. In this regard, low fat/high carbohydrate diets seem to be as efficient as low carbohydrate/high protein diets. Meta-analyses have shown that reducing carbohydrates may additionally reduce the risk of cardiovascular diseases (Nordmann *et al.* 2006, Hession *et al.* 2009, Volek *et al.* 2009, Wang *et al.* 2002). Furthermore, the reduction of several inflammation markers in overweight men and women with atherogenic dyslipidemia was reported (Forsythe *et al.* 2008). It was also shown that a ketogenic diet was capable to lower blood glucose levels in obese diabetic patients more effectively than overall CR (Hussain *et al.* 2012). In contrast, a Swedish study in over 43.000 middle-aged women found a significant increase in cardiovascular diseases following a ketogenic diet (Lagiou *et al.* 2012). The authors sug-

gested that the protein source might play an important role and could contribute to this unexpected outcome. Interestingly, it was shown that a short-term low-carbohydrate/high fat intake may increase postprandial plasma glucose, suggesting a decrease in first-phase insulin secretion after the diet has started. However, other studies detect decreased glucose plasma levels on the long run, which could be due to adaptive mechanisms (Nobels *et al.* 1989, Boden *et al.* 2005).

5. CALORIE RESTRICTION MIMETICS (CRM)

CRMs are defined as pharmaceutical or naturally occurring compounds that may mimic the metabolic state of CR. Ideally these compounds would allow the organisms to eat normally, i.e. *ad libitum*, while the metabolic state would reflect reduced caloric uptake. The best studied compound in this regards, DOG has been introduced above. However, due to increased mortality in rats following chronic ingestion of DOG (Minor *et al.* 2010) this compound meanwhile appears of questionable usefulness. While beyond the immediate scope of this review, it should be noted that DOG as well as CR have been repeatedly shown to exert remarkable neuro-protective effects as reviewed elsewhere (Arumugam *et al.* 2006).

The phytochemical resveratrol is found to be CR mimetic as it potentially slows aging and certainly delays age-related diseases by activating sirtuins and also mitohormetic responses (Wood *et al.* 2004, Baur *et al.* 2006, Rubiolo *et al.* 2008) also based on a concept named xenohormesis (Howitz and Sinclair 2008). This is possibly linked to the fact that resveratrol may induce mtROS formation (Zini *et al.* 1999). Interestingly, genetic disruption of cellular mechanisms that target degradation of xenobiotics has been shown to result in lifespan extension in multiple species, suggesting adaptive response processes (Curran and Ruvkun 2007, Smith *et al.* 2008, Melo and Ruvkun 2012).

More specifically and focusing exclusively on mtROS formation, a recent study in *C. elegans* found that chemical inhibition of complex I of the mitochondrial electron transport chain (ETC) also mimics CR including increased physical activity and stress resistance, as well as extended lifespan. Interestingly, it was further shown that these complex I inhibitors extend lifespan independent of sirtuins and AMPK, but solely need a transient ROS increase to activate p38 MAP kinase and neuronal NRF2, suggesting that CR extends lifespan by inducing ROS formation (Schmeisser *et al.* 2013b). Consistently, *C. elegans* with genetic impairment of complex I, III, and IV are also long-lived (Dillin *et al.* 2002, Zuryn *et al.* 2010, Rea *et al.* 2007). In mice, inhibition of complex IV leads also to lifespan extension as well as elevated fat utilization, increased insulin sensitivity, and increased mitochondrial biogenesis (Deepa *et al.* 2012). Also, juglone, a known ROS generator and herbicide, has been reported to

301

increase lifespan in low concentrations due to enhanced oxidative stress response (Heidler *et al.* 2010).

In this regard it is interesting to note that a significant number of pharmaceutically effective compounds, including phytochemicals like resveratrol (Zini *et al.* 1999), sulforaphane (Singh *et al.* 2005), niacin (Fukushima 2005), and berberine (Turner *et al.* 2008), as well as anti-diabetic drugs like metformin (El-Mir *et al.* 2000) and PPARγ-activating thiazolidinediones (Brunmair *et al.* 2004b, Nadanaciva *et al.* 2007), and lastly cholesterol-lowering HMG-CoA-synthase inhibitors ("statins") (Nadanaciva *et al.* 2007) and PPARα-activating fibrates (Brunmair *et al.* 2004a, Nadanaciva *et al.* 2007), have been found to inhibit mitochondri-al complex I of the ETC. Since inhibition of complex I generates a mito-chondrial ROS signal, these independent findings insinuate that this group of compounds exerts pleitropic effects, however sharing a com-mon denominator by acting as potential CRMs which however needs fur-ther investigation.

6. IMPAIRED INSULIN/IGF-1 SIGNALING (IIS)

Mammalian insulin and IGF-1 (insulin-like growth factor 1) are pep-tide hormones produced in beta-cells of the pancreas and the liver, respectively. Insulin is a key regulator of glucose metabolism, especially involved in the regulation of cellular glucose uptake, fat metabolism, and food uptake. IGF-1 is produced following growth hormone (GH, a.k.a. somatotropin) mediated stimulation in the liver, and mediates childhood growth and anabolic effects in adults. Furthermore, most of the direct receptor-mediated effects of GH, i.e. IGF-1-independent effects, counter-act insulin action. Insulin, IGF-1, and GH bind to different specific recep-tors to affect cellular functions. With a significantly lower affinity, insulin can activate the IFG-1 receptor, and *vice versa.*

Mice with impairment of GH or IGF-1 function and signaling show dwarfism and prolonged lifespan, somewhat resembling CR conditions (Quarrie and Riabowol 2004, Brown-Borg *et al.* 1996). Artificially increas-ing GH levels abrogates the lifespan extension and leads to elevated body size (Pendergrass *et al.* 1993, Steger *et al.* 1993). Furthermore, impair-ment of the neuronal IGF-1 receptor or heterozygous global disruption of this receptor increases murine lifespan and may be responsible for pre-vention of neurodegeneration and proteotoxicity (Holzenberger *et al.* 2003, Kappeler *et al.* 2008). Conversely, long-term IGF-1 exposure leads to decreased mitochrondrial function and cell viability in human fibroblasts (Bitto *et al.* 2010).

Impairment of the insulin receptor in humans is linked to insulin resistance, a state which is defined as an inadequate reduction of intra-cellular response to extracellular insulin stimulus (Kahn 1994). One main function of the insulin receptor activation due to extracellular

insulin is the translocation of glucose transporter GLUT-4 and hence, glucose uptake in the cell. Accordingly, the outcome of insulin resistance is reduced glucose availability within the cell, which is associated with DM type 2 (Biddinger and Kahn 2006). This disease is linked to decreased lifespan also due to a number of secondary complications, including cardiovascular disease and an increased incidence of cancers (Kannel and McGee 1979, Franco *et al.* 2007, Coughlin *et al.* 2004).

Since in mice a global disruption of the insulin receptor knockout leads to embryonic lethality, muscle-specific knock-out mice were established to study the role of insulin receptor signaling. Noteworthy, muscle-tissue is the most relevant tissue in regards to glucose metabolism. Interestingly, those mice showed elevated fat mass, serum triacylglycerides and free fatty acids, but they neither experienced hyperglycemia nor the development of diabetes (Brüning *et al.* 1998). Moreover, they displayed enhanced glucose uptake in muscle cells in response to exercise like wild type mice do (Wojtaszewski *et al.* 1999). Lifespan data on those mice are not available, but mice with an adipose tissue-specific knockout have an increased mean and maximum lifespan (Blüher *et al.* 2003). Furthermore, mice with a global knockout in the insulin receptor substrate 1 (IRS-1) demonstrate increased resistance to several age-related pathologies and are long-lived, as are mice with neuronal knockout of IRS-2 and heterozygous global IRS-2 knockouts (Selman *et al.* 2008, Page *et al.* 2013, Taguchi *et al.* 2007). In addition, there are hints that specific mutations in the insulin receptor might also be associated with longevity in humans (van Heemst *et al.* 2005, Pawlikowska *et al.* 2009).

Other than mammals, invertebrates like *C. elegans* and *Drosophila* do not have distinct receptors for IGF-1 and insulin, but rather share a common receptor. Impaired insulin/IGF-1 signaling (but not its complete disruption) in invertebrates strikingly extends lifespan (Kimura *et al.* 1997, Clancy *et al.* 2001, Tatar *et al.* 2001).

C. elegans that carry a mutation within *daf*-2, the worm orthologue of the insulin/IGF-1 receptor, have a lifespan that is twice as long as in wild type worms (Kenyon *et al.* 1993). Recent studies have shown that the mitochondrial energy production is altered by impairment of DAF-2. Such mutants did not display the typical age-dependent decrease in mitochondria protein and bioenergetics competence, but a higher membrane potential and an increase in ROS, which is interestingly not associated with more, but less damage to mitochondrial DNA and protein (Brys *et al.* 2010, Zarse *et al.* 2012). The inhibition of IIS leads to lifespan extension due to changes in gene expression mediated by the FOXO transcription factor DAF-16 (Kenyon 2010). Reduction of IIS followed by lifespan extension and promotion of stress resistance in the worm not only requires DAF-16, it activates also SKN-1 in parallel, which facilitates the above mentioned beneficial adaptive response (Tullet *et al.* 2008); the

303

same is true for HSF-1 (Kenyon 2005, Chiang *et al.* 2012). Also, mitochondrial L-proline catabolism plays an important role in that regard since it is upregulated by impaired DAF-2 signaling, which lead to a transient increase in ROS production mediating adaptive response processes to extend lifespan, proving the link between impaired IIS and mitohormesis (Zarse *et al.* 2012).

Assuming that impairment of the insulin/IGF-1 receptor reduces glucose uptake one could expect that the same lifespan extending mechanisms act here as they occur in regard to glucose restriction or overall CR (see above). In fact, there are several studies proposing shared processes and pathways involved in both interventions (Yechoor *et al.* 2004, Brooks *et al.* 2007, Katic *et al.* 2007, Russell and Kahn 2007, Westbrook *et al.* 2009, Zarse *et al.* 2012), while others propose independent mechanisms (Greer *et al.* 2007a, Lakowski and Hekimi 1998, Bartke *et al.* 2007, Houthoofd *et al.* 2003, Min *et al.* 2008, Bonkowski *et al.* 2009, Brown-Borg *et al.* 2002, Clancy *et al.* 2002).

7. AMP-DEPENDENT KINASE (AMPK) SIGNALING

AMPK acts as a sensor of available nutrients and hence energy that is regulated by the cellular AMP/ATP ratio and upstream kinases (Hardie *et al.* 2003). Whenever an energy deficit occurs and concurrently the AMP/ATP ratio rises, AMPK activates catabolic and represses anabolic processes. In other words, being activated by stress that inhibits ATP generation or increases ATP consumption, like glucose starvation or muscle contraction, AMPK inhibits energy consuming pathways and induces ATP-generating processes (Hardie *et al.* 2003, Salt *et al.* 1998, Winder and Hardie 1996).

AMPK exists as heterotrimeric complex consisting of a catalytic α-subunit and the regulatory β- and γ-subunits (Kemp *et al.* 2003). Activation of AMPK requires specific phosphorylation events by upstream kinases such as the serine/threonine protein kinase LKB1 within the catalytic domain of the α-subunit (Woods *et al.* 2003). Widely expressed, AMPK regulates food uptake in response to nutrient signals and hormones (Minokoshi *et al.* 2004) and is an important initiator of mitochondrial biogenesis (Zong *et al.* 2002, Winder *et al.* 2000), glucose and fatty acid uptake (Barnes *et al.* 2002, Habets *et al.* 2009), as well as β-oxidation (Merrill *et al.* 1997). In *C. elegans*, AMPK overexpression extends lifespan and is required for the lifespan extension due to impaired insulin/IGF-1 signaling (Apfeld *et al.* 2004). However, the role of AMPK in CR is less clearly established. The kinase appears to be necessary to mediate lifespan extension due to CR when food limitation starts in middle age employing a pathway that requires DAF-16/FOXO (Greer *et al.* 2007a). The direct activation of FOXO by AMPK has also been described in mammals (Greer *et al.*

2007b), linking it to oxidative stress response and therefore potentially mitohormesis.

Accordingly, AMPK is activated by DOG and involved in the induction of mitochondrial metabolism and hence the mitohormetic response (Schulz *et al.* 2007). Another example for an AMPK-activating substance is metformin, an antidiabetic drug and inhibitor of the mitochondrial complex I (El-Mir *et al.* 2000), which was found to be lifespan-extending due to AMPK-activation in *C. elegans* and mice (Onken and Driscoll 2010, Anisimov *et al.* 2008). Moreover, metformin was shown to promote adaptive processes, which are also involved in CR and oxidative stress response like activation of NRF2/SKN-1, culminating in increased life expectancy (Onken and Driscoll 2010). As described earlier, the CR mimetic resveratrol slows aging and delays age-related diseases by activating, besides sirtuins, also AMPK, again linking it to mitohormetic responses (Zini *et al.* 1999, Baur *et al.* 2006). It has been reported that many AMPK activators, including resveratrol and metformin, act by inhibiting mitochondrial function (Hawley *et al.* 2010). As a consequence of impaired mitochondrial function, the AMP/ATP ratio rises, leading to AMPK activation followed by increased mitochondrial biogenesis, respiration, β-oxidation, and finally increased ROS production (Schulz *et al.* 2007, Hardie 2011). It has moreover been proposed that ROS themselves are also capable of activating AMPK (Zmijewski *et al.* 2010, Alexander *et al.* 2010) and due to this, by acting up- and downstream of AMPK, the stress response may be further amplified. Interestingly, hypoxia has been shown to activate AMPK not by changing the AMP/ATP ratio, but rather by increased ROS production, since the activation is inhibited by antioxidants (Emerling *et al.* 2009).

However, recent findings suggest that mitochondrial ROS production may be more relevant than AMPK activation in regards to lifespan extension: consistent with the *nuo-6* mutation in *C. elegans* (Yang and Hekimi 2010), inhibiting complex I of the respiratory chain by rotenone and other chemicals generates a ROS signal that extends lifespan in the absence of AMPK, sirtuins, or both (Schmeisser *et al.* 2013b). This indicates that ROS formation alone, i.e. in the absence of energy sensors, is still capable of promoting longevity. Consistently, it was shown that nematodes lacking AMPK live shorter and die prematurely in the dauer stage since their triglyceride stores are exhausted (Narbonne and Roy 2009, Xie and Roy 2012). The study of Xie and colleagues pointed out an important role for ROS in replacing essential AMPK functions: An increase in hydrogen peroxide activated the transcription factor hypoxia-inducible factor 1 (HIF-1; see also chapter "Hypoxia"), which is capable of stimulating key enzymes involved in the biosynthesis of fatty acids, leading to an increased survival of the dauer larvae (Xie and Roy 2012).

M. Ristow and K. Schmeisser

Hence, AMPK not only acts as regulator of metabolism, but also may play an important role in ROS signaling and adaptive response processes, which highlights the universal character of mitohormesis within cellular metabolism, whereas ROS signals still promote longevity even in the absence of AMPK.

8. TOR SIGNALING

The so-called "target of rapamycin" (TOR) pathway is known to be another major regulator of life expectancy by sensing nutrient and environmental signals (Pan *et al.* 2012). The mammalian TOR (mTOR) is a serine/threonine protein kinase and a member of the phosphatidylinositol 3-kinase-related kinase protein family which consists of two functionally distinct multi-protein complexes known as TOR complex 1 (TORC1) and TORC2 (Brunn *et al.* 1997). Each complex has an accessory protein; for TORC1 it is named regulatory-associated protein of mTOR (RAPTOR), for TORC2 rapamycin-insensitive companion of mTOR (RICTOR) (Hara *et al.* 2002, Laplante and Sabatini 2012). The major sensor of cellular inputs like nutrients, hormones, energy, and oxidative stress is TORC1, while TORC2 executes regulatory functions concerning cell survival and cytoskeletal polarity (Laplante and Sabatini 2012). TOR signaling has been shown to be regulated by AMPK, suggesting that both nutrient-sensing pathways are key regulators of mitochondrial metabolism (Gwinn *et al.* 2008).

Impairment of the TOR pathway is shown to be lifespan-extending in various organisms (Kaeberlein *et al.* 2005, Powers *et al.* 2006, Jia *et al.* 2004, Kapahi *et al.* 2004). The immunosuppressive and antifungal drug rapamycin acts as inhibitor of the TOR pathway as it inhibits TORC1 and is known to extend median and maximum lifespan of *C. elegans* and mice (Harrison *et al.* 2009, Robida-Stubbs *et al.* 2012). Notably, rapamycin not only extends lifespan, but also induces insulin resistance and impaired glucose metabolism (Lamming *et al.* 2012), again consistent with cellular energy deprivation and subsequent induction of mitohormesis. Similarly, mTOR signaling has been linked to oxidative nutrient metabolism in rodents (Sengupta *et al.* 2010).

Consistent with this, lifespan extension in yeast due to impaired TOR signaling is promoted by inducing expression of proteins from the respiratory complexes, mitochondrial ETC activity and overall mitochondrial metabolism (Pan and Shadel 2009, Powers *et al.* 2006, Bonawitz *et al.* 2007, Pan *et al.* 2011). In agreement with this, the influence of TOR on mitochondrial biogenesis and turnover is also found in mammals in a strongly tissue-dependent manner. In murine skeleton muscle tissue and cells for instance, rapamycin decreases expression of mitochondrial genes resulting in decreased oxygen consumption (Cunningham *et al.* 2007), whereas in fatty tissue opposite effects have been observed.

306

Adipocyte-specific disruption of RAPTOR is linked to higher rates of mitochondrial uncoupling followed by enhanced energy expenditure, which protects the mice from gaining weight (Polak *et al.* 2008). Higher respiration rates and energy expenditure are also linked to increased expression of genes involved in OxPhos and beta-oxidation, especially in older mice (Katic *et al.* 2007).

There are several protein families like 4E-BP, ATG, and S6K, which modulate mitochondrial biogenesis downstream in the TOR signaling pathway. Consistently, the translational regulator 4E-BP is shown to have strong influence on the expression of OxPhos genes. In *Drosophila*, CR alters mRNA profiles via TORC1 in a 4E-BP dependent manner (Zid *et al.* 2009). Furthermore, TOR downstream acting proteins are not only involved in mitochondrial biogenesis, but also mitochondrial quality: ATG-5 mediates the degrading of dysfunctional mitochondria by autophagy (Twig *et al.* 2008), recently called "mitophagy" (Pua and He 2009). Notably, autophagy has also an important role in response to cellular stress, including starvation and pathogen infection, as well as in IIS mediated lifespan regulation (Kroemer *et al.* 2010, Levine *et al.* 2011, Toth *et al.* 2008, Hansen *et al.* 2008).

Due to the fact that TOR signaling plays a crucial role in mitochondrial biogenesis and turnover it is consequently involved in regulation of mtROS levels. For example, mouse mitochondria from skeletal muscle cells with impaired ATG-7 exhibit increased production of ROS (Wu *et al.* 2009b). This negative correlation between TOR signaling and ROS is also observed in yeast, where both *tor-1* knock-out and rapamycin treatment caused increased levels of superoxide due to enhanced mitochondrial biogenesis, strikingly coupled with less oxidative damage within the cell (Pan *et al.* 2011). This research manifests that ROS stimulation due to TOR acts also as mitohormetic stimulus and that mitohormesis is also in this regard the key mediator of lifespan extension (Pan 2011). Impaired TOR signaling through either genetically inhibited TORC1 or the usage of rapamycin is also known to activate SKN-1 and DAF-16 in *C. elegans*, mediating increased stress resistance and longevity (Robida-Stubbs *et al.* 2012).

It is assumed that TOR is another key mediator of CR since it has been shown that yeast and *Drosophila* carrying a deletion in the TOR gene do not benefit of CR in regards to lifespan extension (Kaeberlein *et al.* 2005, Kapahi *et al.* 2004). To evidence this hypothesis and point out whether the TOR pathway is involved in CR benefits, further research is strongly needed.

9. SIRTUIN SIGNALING

Sirtuins are NAD^+-dependent deacetylases that catalyze the removal of acetyl groups from lysine residues of specifically histones and other

proteins. They modulate cell-protective mechanisms such as oxidative stress defense, DNA repair, protein folding, energy utilization, and autophagy (Haigis and Sinclair 2010). The first identified member of this protein family was named *silent information regulator 2* (SIR2) (Sinclair *et al.* 1997, Kaeberlein *et al.* 1999), giving rise to the term "sirtuins". By today, seven mammalian orthologues have been found, named SIRT1 to SIRT7 (Blander and Guarente 2004), whereas SIRT1 and SIRT3 are the closest orthologues to SIR2 (Merksamer *et al.* 2013). Sirtuins are linked to longevity, since overexpression has been shown to extend lifespan in yeast (Kaeberlein *et al.* 1999) as well as in worms (Tissenbaum and Guarente 2001, Viswanathan and Guarente 2011, Mouchiroud *et al.* 2013, Ludewig *et al.* 2013, Schmeisser *et al.* 2013a) and flies (Rogina and Helfand 2004, Bauer *et al.* 2009). However, others could not confirm the results in *C. elegans* and *Drosophila* (Burnett *et al.* 2011), whereas one study found sirtuin overexpression only in the fat body of relevance for longevity (Banerjee *et al.* 2012). Sirtuins were found to be necessary to mediate lifespan extension due to CR (Lin *et al.* 2000, Guarente and Picard 2005, Boily *et al.* 2008), whereas others found no such connection (Kaeberlein *et al.* 2004, Smith *et al.* 2007, Schulz *et al.* 2007). In addition, a recent publication pointed out an important role for p53 modulating SIRT1 during CR, as reviewed elsewhere (Tucci 2012).

However, the role of sirtuins in oxidative stress and mitohormetic responses has been implicitly discussed also in this regard (Lin *et al.* 2000), supported by the observations, that *sir2* overexpression rescues the short lifespan phenotype due to hydrogen peroxide treatment in yeast (Oberdoerffer *et al.* 2008) and that SIRT3 is necessary to mitigate oxidative stress during CR (Someya *et al.* 2010, Qiu *et al.* 2010). There is evidence that the mammalian SIRT1 is involved in mediating oxidative stress response, as it directly deacetylates several FOX members (Brunet *et al.* 2004, Motta *et al.* 2004, van der Horst *et al.* 2004). In contracting muscle cells SIRT1 mediates the protection against oxidative stress via enhanced expression of SOD-2 (Pardo *et al.* 2011). Correspondingly, SIRT2 activates FOXO3a, which promotes resistance to hydrogen peroxide (Wang *et al.* 2007). Moreover, SIRT1 has been also shown to activate peroxisome-proliferator-activated receptor (PPAR) gamma co-activator-1 alpha (PGC-1α) (Rodgers *et al.* 2005), a transcriptional co-activator that promotes mitochondrial biogenesis and expression of antioxidant genes including calalase, SOD, and glutathione peroxidase (St. Pierre *et al.* 2006). Furthermore, SIRT1 suppresses the inducible nitric oxide synthase (iNOS) and thus may decrease cellular ROS levels (Lee *et al.* 2009a). The catalytic activity of SOD-2 is dependent of the mitochondrial SIRT3, which is also capable of enhancing SOD-2 activity (Qiu *et al.* 2010). Accordingly, genetic impairment of SIRT3 in mice leads to higher ROS levels, genomic instability, and susceptibility to cancer (Kim *et al.* 2010), establishing SIRT3 as anticarcinogenic protein by improving stress

response, which is supported also by more recent research (Bell *et al.* 2011, Finley *et al.* 2011). Consistently, SIRT6 has been shown to promote DNA repair in response to oxidative stress (Mao *et al.* 2011). Genetic impairment of SIRT6 results in genetic instability and premature aging (Mostoslavsky *et al.* 2006), whereas overexpression promotes lifespan extension, at least in male mice (Kanfi *et al.* 2012). Finally, SIRT7 mediates oxidative stress response as well, since cardiomyocytes of SIRT7 knockout mice are more sensitive to hydrogen peroxide treatment (Vakhrusheva *et al.* 2008, Calabrese *et al.* 2007).

From a traditional viewpoint, these findings support the notion that sirtuins promote health and lifespan, at least in parts, via increased resistance towards ROS (Webster *et al.* 2012) and particularly mitohormetic response processes (Merksamer *et al.* 2013). As outlined in more detail elsewhere (Merksamer *et al.* 2013), physiological stressors including CR may decrease the activity of antioxidant enzymes like SOD by acetylation processes resulting in hyperacetylation (Hirschey *et al.* 2010, Hirschey *et al.* 2011a, Hirschey *et al.* 2011b, Ozden *et al.* 2011). The following increase in ROS would activate defense mechanisms against oxidative stress, resulting in lower ROS levels in the steady state. Notably, such stresses have been also shown to increase SIRT3 expression, suggesting subsequently increased deacetylation of SOD and other mitochondrial proteins to counteract chronically increased ROS generation (Hirschey *et al.* 2010, Merksamer *et al.* 2013).

Very recently, an alternate mechanism linking sirtuin signaling to ROS-mediated lifespan extension has emerged (Schmeisser *et al.* 2013a): Sirtuins require NAD^+ as a cofactor, and accordingly produce nicotinamide. This product becomes methylated to 1-methylnicotinamide, which itself serves as a substrate for an aldehyde oxidase to produce hydrogen peroxide. The latter acts as a ROS signal to execute sirtuin effects, since disruption of either the methylase or the oxidase fully prevents sirtuin-mediated lifespan extension (Schmeisser *et al.* 2013a), also implying that sirtuin-mediated deacetylation processes may be of limited relevance regarding lifespan regulation.

10. HYPOXIA

Hypoxia is an environmental state that is characterized by decreased environmental availability of oxygen, which typically leads to reduced mitochondrial respiration rates and a variety of changes on the molecular level (Semenza 2012), notably including increased mtROS production (Kulisz *et al.* 2002). The master regulator of hypoxia-mediated transcriptional changes is HIF-1, a highly conserved transcription factor that promotes survival under hypoxic stress (Shen and Powell-Coffman 2003, Semenza 2012). Under normal oxygen conditions, the mammalian HIF-1α subunit is hydroxylated and targeted for proteasomal degradation by

309

the von Hippel-Lindau tumor suppressor protein (VHL) (Kim and Kaelin 2003). This signaling pathway seems to be highly conserved, since *C. elegans hif-1* and *vhl-1* genes encode homologs of HIF-1α subunit and VHL (Shen *et al.* 2005). However, it was shown that low oxygen atmosphere and decreased respiration is capable of increasing lifespan of *C. elegans* (Adachi *et al.* 1998), probably via stabilization of HIF-1 (Lee *et al.* 2010, Mehta *et al.* 2009, Zhang *et al.* 2009). This activation of the hypoxic signaling pathway was found to promote lifespan independently of CR or impaired IIS (Kaeberlein and Kapahi 2009, Mehta *et al.* 2009) as it is shown that CR due to deprivation of bacteria and genetically induced through mutation in *eat-2* increases lifespan in *hif-1* knockout nematodes, and impairment of DAF-2 is also able to promote longevity in those animals (Mehta *et al.* 2009). Notably, it was reported that loss of HIF-1 causes longevity as well (Zhang *et al.* 2009, Chen *et al.* 2009). In one study, DAF-16 seems to be essential for lifespan extension, indicating a mechanism similar to reduced IIS (Zhang *et al.* 2009), whereas others found no such connection, possibly insinuating that HIF-1 acts as a negative regulator of longevity in a pathway upstream of the endoplasmic reticulum (ER) stress response and downstream of CR and TOR signaling (Chen *et al.* 2009).

The unquestionable influences of HIF-1 on aging have initiated several competing hypotheses: One explanation could be that HIF-1 downregulates mitochondrial activity (Papandreou *et al.* 2006, Semenza 2011), as this is shown to be lifespan extending through RNAi-mediated knockdown of several mitochondrial proteins (Tormos and Chandel 2010, Rea *et al.* 2007, Dillin *et al.* 2002). Alternatively, HIF-1 could act in regards to stress response, like NRF2 or FOXO, especially since it is shown that HIF-1 and DAF-16 share various target genes (McElwee *et al.* 2004). In mammals, there are also links to TOR signaling and ER unfolded protein response (UPR) with mTOR signaling being reduced by hypoxia and HIF-1 translation being dependent on TOR (Stein *et al.* 1998, Wouters and Koritzinsky 2008), whereas both hypoxia and TOR are known to activate UPR (Romero-Ramirez *et al.* 2004).

Interestingly, mitochondrial-derived ROS during hypoxia lead to HIF-1 stabilization in cultured cells (Chandel *et al.* 1998), as well as activation of c-Jun N-terminal kinase 1 (JNK1), p53, and NF-κB (Chandel *et al.* 2000a, Chandel *et al.* 2000b). Moreover, in *C. elegans*, knockdown of genes encoding respiratory chain components and mutations in such, like *clk-1* and *isp-1*, lead not only to decreased respiration rates, but also to a mild increase in ROS formation, which is responsible for HIF-1 stabilization and longevity of the nematodes (Lee *et al.* 2010, Yang *et al.* 2009). Increased ROS levels under hypoxic conditions in *C. elegans* (Miller *et al.* 2011, Miller and Roth 2007) as well as in cultured cells (Guzy and Schumacker 2006) occur in a HIF-1 dependent manner. A recent study in

C. elegans found also an important role of DAF-16 in this regard, since it is delocalized to the nucleus and necessary to extend lifespan under hypoxic conditions (Leiser *et al.* 2013). However, in this study, lifespan extension did not require SIR-2.1, AAK-2, SKN-1, or CEP-1, the worms' orthologues of sirtuins, AMPK, NRF2 and p53, respectively. On the other hand, roles for the sirtuins in HIF-1 deacetylation, AAK-2 in adaption to anoxia, and CEP-1 acting downstream of HIF-1 have been described earlier (Dioum *et al.* 2009, Zhong *et al.* 2010, Lim *et al.* 2010, Leiser and Kaeberlein 2010, Larue and Padilla 2011, Sendoel *et al.* 2010). As mentioned above, a mild increase in oxidative stress leads to stabilization of HIF-1 followed by increased survival of *C. elegans* AAK-2/AMPK mutants due to HIF-1-dependent activation of genes involved in fatty acid biosynthesis (Xie and Roy 2012). This metabolic adjustment pointed out an important role for HIF-1 and ROS in compensating AMPK functions.

Nevertheless, studies that investigated the influence of hypoxia on mammalian aging are rare. This is not only because the mechanisms according to hypoxia in mammals are much more complex than in lower organisms like *C. elegans*, but also due to HIF-1α is involved in tumor growth and cancer development, notably also by altering glucose metabolism (Semenza 2012, Semenza *et al.* 1994). Discovered by its ability to increase erythropoetin production, HIF-1α was associated with the VHL hereditary cancer syndrome, a heterozygous disease characterized by development of various malign tumors in the kidneys, retina, and the central nervous system with an increase in HIF-1α being a negative predictor in metastatic tumors (Wang *et al.* 1995, Kaelin 2002, Semenza 2010).

However and to our best knowledge, the first evidence that links HIF-1 to longevity and aging *per se* only dates back to 2009 (Mehta *et al.* 2009), so future research will properly establish the role of oxygen availability in the aging process and bring hypoxic mechanisms and connections to other pathways to light.

11. TEMPERATURE STRESS

As early as in 1908 it was hypothesized that body temperature may be linked or even determine life expectancy (Loeb 1908). A few years later, the hypothesis was experimentally supported by showing that lowering temperature extends lifespan of poikilothermic *Drosophila* (Loeb and Northrop 1916). Subsequently, benefits from exposure to lowered temperature regarding lifespan have been shown in other organisms like *C. elegans* or fish (Klass 1977, Liu and Walford 1966) and notably also in homoeothermic (warm-blooded) animals like rats and mice (Holloszy and Smith 1986, Conti *et al.* 2006). On the other hand, increasing ambient temperature or mild heat stress are also linked to increased lifespan in various organisms (Shama *et al.* 1998, Wu *et al.* 2009a). As mentioned above, HSPs are major regulators of response to heat stress in almost all

organisms investigated ranging from bacteria to mammals (Lindquist and Craig 1988, Fargnoli *et al.* 1990, Udelsman *et al.* 1993, Lithgow *et al.* 1995, Rea *et al.* 2005). HSPs consist of a large number of proteins, often being classified according to their molecular weight: HSP40, HSP60, HSP70, HSP90, HSP110 (with 40, 60, 70, 90, and 110 kilo-daltons in size, respectively) and the small HSPs represent the majority of HSPs (Li and Srivastava 2004). Some HSPs are also known as chaperones, playing crucial roles in the UPR to prevent polypeptides from aggregating into nonfunctional structures (Calderwood *et al.* 2009, Jazwinski 2005, Parikh *et al.* 1987), which has also been reported to play a role in lifespan regulation (Calfon *et al.* 2002, Henis-Korenblit *et al.* 2010, Yoneda *et al.* 2004). Transcriptionally regulated by HSF-1, HSPs have been unquestionably linked to hormetic processes (Akerfelt *et al.* 2010, Cypser and Johnson 2002). For instance, increased expression of HSP-70 family members following activation of HSF-1 due to a variety of stressors leads to protection against the latter, notably including ROS (Westerheide and Morimoto 2005, Raynes *et al.* 2012). Conversely, HSF-1 depletion shortens lifespan in *C. elegans*, as overexpression increases longevity and is required for the lifespan extension due to impaired insulin signaling (Hsu *et al.* 2003). The same study found that DAF-16 is necessary for extending lifespan in *hsf-1* overexpressing worms, suggesting that both transcription factors might synergistically act to exert their beneficial effects (Hsu *et al.* 2003) (Figure 4). Hormetic heat stress is linked to improved mitochondrial function (Shama *et al.* 1998), which is required for ROS defense (Grant *et al.* 1997). Notably, long-lived *C. elegans daf-2* mutants are resistant to thermal and oxidative stress and display increased expression of various HSPs and antioxidant and drug-metabolizing enzymes (McElwee *et al.* 2007, Lithgow and Walker 2002).

A mechanism for the observed increased lifespan at low temperatures was recently suggested in a study using *C. elegans*, pointing out an important role for a member of the transient receptor potential (TRP) family of cationic channels, TRPA-1 (Xiao *et al.* 2013). TRPA-1 alters its permeability to Ca^{2+}, Na^+, and K^+ when activated by temperatures around 17°C or lower (Clapham 2003, Story *et al.* 2003). Worms that lack TRPA-1 have a shorter lifespan when exposed to cold in comparison to wild type animals, whereas overexpression of *trpa-1* leads to increased lifespan at 15°C and 20°C, but not under warm (25°C) conditions. These effects were dependent on a calcium influx, which activates the calcium-sensitive protein kinase C (PKC) and the serine/threonine-protein kinase 1 (SGK-1). Interestingly, DAF-16/FOXO has been shown to be necessary to promote longevity in this regard. The TRPA-1 pathway induces nuclear activity of DAF-16, surprisingly without stimulating its nuclear translocation. The well-known fact that calcium influx increases ROS generation in mitochondria, as reviewed elsewhere (Brookes *et al.* 2004, Csordas and

312

Hajnoczky 2009), insinuates that these ROS act as signal molecules to activate DAF-16 and promote longevity in this regard. Another study reported that hypothermia causes not only calcium influx into mitochondria, but also leads to a redox imbalance caused by an increase in ROS concentration (Brinkkoetter *et al.* 2008). Thus, mitohormetic processes could be also responsible for the lifespan extension following exposure to cold temperatures.

12. PHYSICAL ACTIVITY

Physical inactivity promotes the onset of a variety of diseases like obesity, cardiovascular disease, DM type 2, and cancer. Consistently, regular physical activity unquestionably exerts beneficial or preventive effects on the above mentioned diseases, and additionally delays depressive symptoms, neurodegeneration (including Alzheimer's disease), and general aging (Warburton *et al.* 2006, James *et al.* 1984, Hu *et al.* 2001, Brown *et al.* 2012, Lanza *et al.* 2008, Manini *et al.* 2006, Powers *et al.* 2011). Exercise is not only linked to enhanced mitochondrial biogenesis and oxidative metabolism, but also to increased generation of mtROS (Powers and Jackson 2008, Chevion *et al.* 2003, Davies *et al.* 1982, Alessio and Goldfarb 1988, Alessio *et al.* 1988). Thus, and because of its obvious beneficial effects in regards to health and aging, make it a paradigm of adaptive response processes and finally mitohormesis (Radak *et al.* 2008, Radak *et al.* 2005, Ji *et al.* 2006, Watson 2013). However, similar to physical inactivity, overtraining or excessive exercise represents the other end of the hormesis curve as the adaption process is inhibited, leading to incomplete recovery (Chevion *et al.* 2003) and resulting in maladaptation and possibly increased risk of diseases (Alessio *et al.* 1988).

To our knowledge, the first direct evidence that increased ROS production following exercise may act as stimulus to activate mitochondria biogenesis and mediates potential health-beneficial effects dates back to 1982 (Davies *et al.* 1982). An indirect clue was already given in 1971 with an antioxidant, namely vitamin E, causing unfavorable effects on the endurance performance of swimmers (Sharman *et al.* 1971). Since then, a bulk of studies (in most cases inadvertently) proved the hypothesis that ROS are required for the health-promoting effects of physical activity, causing an increase in antioxidant defense mechanisms and with this, prolong health span and mean lifespan (Crawford and Davies 1994, Davies 1986, Kim *et al.* 1996, Marzatico *et al.* 1997, Balakrishnan and Anuradha 1998, Ji *et al.* 2006, Powers and Lennon 1999, Niess *et al.* 1999, Hollander *et al.* 2001, Higuchi *et al.* 1985, Gomez-Cabrera *et al.* 2008b, Quintanilha 1984, Vincent *et al.* 1999, Boveris and Navarro 2008).

One of the main changes due to regular physical activity is the increase in mitochondria energy metabolism. Exercise activates PGC-1α, which is capable of controlling mitochondrial gene expression via NRF1

313

and the mitochondrial transcription factor A (TFAM). This mediates enhanced replication of mitochondrial DNA, leading to increased mitochondrial biogenesis and efficient muscle contraction (Nikolaidis and Jamurtas 2009, Akimoto *et al.* 2005, Baar 2004, Arbogast and Reid 2004). Furthermore, PGC-1 promotes the response to oxidative stress through activation of NRF2 and induction of antioxidant enzyme expression (St. Pierre *et al.* 2006). Another important point is the massive consumption of ATP followed by an increase in AMP, which activates AMPK, leading again to induction of PGC-1 and enhanced mitochondrial biogenesis (Bergeron *et al.* 2001, Atherton *et al.* 2005). This increase in mitochondrial metabolism leads to enhanced oxygen consumption in muscle fibers followed by lower intracellular oxygen tension during exercise, promoting ROS generation (Franco *et al.* 1999, Puntschart *et al.* 1996). There are also other so-called contraction-induced changes that stimulate ROS production in muscle, for instance increased CO_2 tension, decreased cellular pH, and rise in muscle temperature (Arbogast and Reid 2004). The main source of ROS during exercise is probably skeletal muscle (Davies *et al.* 1982, Powers and Jackson 2008), but other tissues such as heart, lungs, and blood are also likely to be important contributors (Powers and Jackson 2008, Nikolaidis and Jamurtas 2009). On cellular level, mtROS were considered to be the predominant fraction of ROS produced during physical activity over decades (Koren *et al.* 1983, Davies *et al.* 1982), whereas recent research pointed out also important roles for nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, phospholipase A2, and xanthine oxidase (Powers *et al.* 2011).

ROS signals caused by a single bout of exercise only already activate antioxidant defense enzymes like mitochondrial SOD and inducible nitric oxide synthase (iNOS) (Hemmrich *et al.* 2003, Hollander *et al.* 2001). Regular exercise leads to proper adaptation to oxidative stress due to upregulation of diverse SODs, catalase, HSPs, and glutathione peroxidase (Powers and Lennon 1999, Leeuwenburgh and Heinecke 2001, Franco *et al.* 1999, Puntschart *et al.* 1996). The second line of antioxidant response which includes repair systems is important to minimize the damaging effects of ROS and is also activated through regular physical activity (Crawford and Davies 1994, Davies 1986), assigning important roles for proteasomal degradation and DNA repair enzymes (Radak *et al.* 2000, Radak *et al.* 1999, Radak *et al.* 2003).

Correspondingly, there is convincing evidence that supplementation of antioxidants is useless (Gey *et al.* 1970, Keren and Epstein 1980, Maughan 1999, Theodorou *et al.* 2011, Yfanti *et al.* 2010) or even harmful for athletes, potentially abolishing the beneficial effects on endurance performance, immune status, muscle development, and prevention of diseases (Gomez-Cabrera *et al.* 2008a, Strobel *et al.* 2011, Ristow *et al.* 2009, Marshall *et al.* 2002, Khassaf *et al.* 2003). For instance, athletes sup-

plementing vitamin C and E did not display an induction of insulin sensitivity and endogenous antioxidant defense regulators due to exercise as seen in the control group (Ristow *et al.* 2009). It was shown that enhanced mitochondrial biogenesis and with this, increased respiration and ROS generation according to physical activity is prevented by co-treatment with antioxidants, leading to the inhibition of the beneficial mitohormetic response (Gomez-Cabrera *et al.* 2008a, Strobel *et al.* 2011, Kang *et al.* 2009, Fischer *et al.* 2006, Ristow *et al.* 2009). Furthermore, studies proved the harmful effect of antioxidants in regards to performance as it has shown to delay the recovery process (Close *et al.* 2006, Jackson 2008). Hence, supplementation of antioxidants should not be recommended to healthy athletes due to evidence that antioxidants have counter-productive effects on performance, health, and the onset of diseases.

13. OUTLOOK

All the above mentioned interventions are able to promote health- and lifespan in a variety of model organisms via mitohormetic processes (Figure 5). Future research will have to show whether these interventions will be capable of slowing aging and prolonging health span also in humans, in case it is not been shown yet. However, it seems unquestionable that the hypothesis of mitohormesis is, at least in parts, suitable to explain how the aging process could be beneficially influenced. Of course, mitohormesis cannot be considered in isolation to understand aging, which is to describe unfortunately beyond the topic and space limitations of this review. Notably, recent evidence suggests that stem cell aging is linked to impaired ROS signaling, i.e. that low levels of ROS production may prevent stem cell decline (Owusu-Ansah and Banerjee 2009, Owusu-Ansah *et al.* 2008, Morimoto *et al.* 2013). Given the eminent role of stem cell maintenance in the prevention of aging, it will be interesting to see whether the emerging link to increased ROS levels can be expanded. Secondly, ROS-mediated nitric oxide-signaling appears to be an increasingly expanding field of mitochondrial biology and disease control (D'Antona *et al.* 2010, Nisoli *et al.* 2005). Moreover, processes like proteostasis and mitochondrial UPR exert, while beyond the scope of this review, significant links to ROS-dependent signaling events, suggesting an overarching ROS-triggered mechanism in cellular and systemic quality control (Taylor and Dillin 2013, Balch *et al.* 2008). Furthermore, it should be emphasized that ROS signaling is a rather established mechanism in plant biology research (Mittler *et al.* 2011), which could not possibly be covered in the current review.

Related to the theory of mitohormesis is the *Epigenetic oxidative redox shift* (EORS) theory of aging, proposing a metabolic shift away from the use of mitochondrial energy towards reliance on glycolysis as a cause of aging. This is due to epigenetic mediators influencing histone deacety-
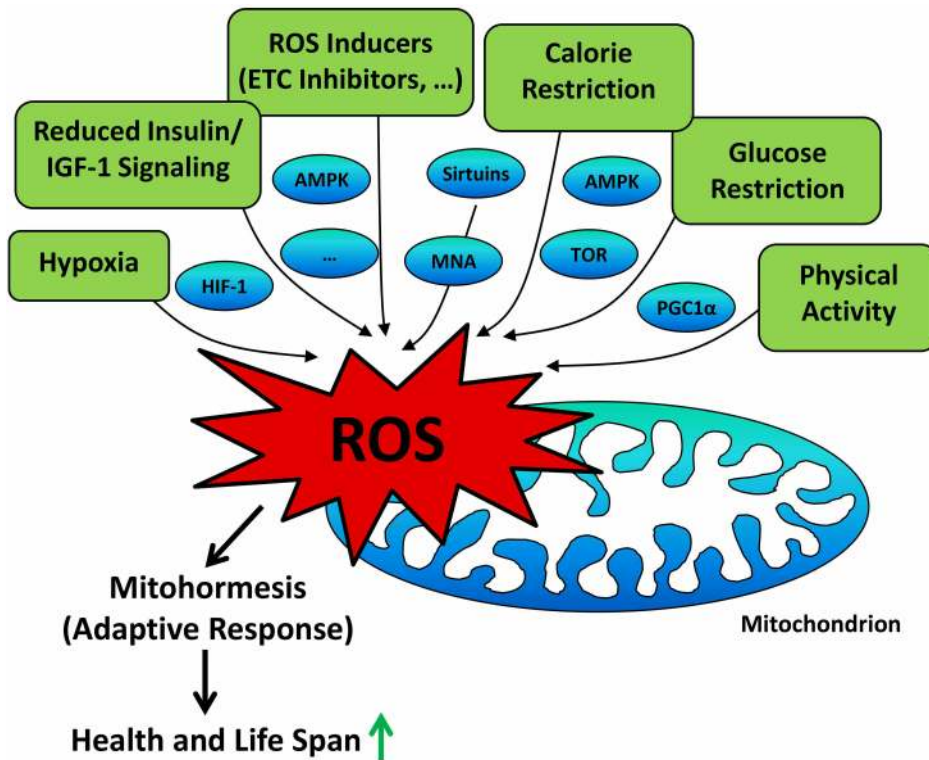
M. Ristow and K. Schmeisser

FIGURE 5. A non-exhaustive overview on lifespan-extending interventions linked to mitohormetic ROS signaling. As outlined in the text of the current review, a number of apparently diverse interventions lead to a mitohormetic response mechanism, insinuating that distinct molecular pathways culminate in a common mechanistic denominator by promoting a ROS-dependent stress response.

lases as well as histone acetylases and DNA methyltransferases (Brewer 2010, Ghosh *et al.* 2012). The shift in the oxidized direction of relevant oxidants and reductants, such as cysteine/cystine or GSH/GSSG occurs with aging and is initiated by low demands of mitochondrial produced energy. The low energy demand is caused by low physical or mental activity, initiating a vicious cycle of oxidized signaling molecules, transcription factors, membrane receptors, and epigenetic transcriptional regulators. This results in the inability to respond to energy demands and stress, leading to typical age accompaniments like cell death and organ failure. Notably, this EORS occurs upstream of the commonly observed increase in ROS damage to macromolecules (Brewer 2010, Ghosh *et al.* 2012).

Another interesting approach which further extends the mitohormesis concept is the *Redox stress hypothesis of aging* (Sohal and Orr 2012), according to which ROS have essential functions in regulating protein activity. The theory distinguishes between young and old organisms, proposing that in the first part of life thiol redox potential is high, whereas ROS generation is relatively low. In older organisms, ROS formation

316

Mitochondrial Hormesis and Lifespan

increases, which would lead to a pro-oxidized shift in redox state and overoxidation of thiols, resulting in loss of sensitivity and coordination among the regulatory processes, a progressive decline of function and finally death. Notably and like mitohormesis, the hypothesis relegates cumulative damages through ROS and antioxidant defense to an auxiliary status, with little impact on altering redox-sensitive signaling (Sohal and Orr 2012).

Taken together, mitohormesis unifies a significant number of lifespan-regulating molecular pathways, and may, dependent on additional scientific evidence, become a common denominator in aging research.

ACKNOWLEDGMENTS

REFERENCES

Abner, E. L., Schmitt, F. A., Mendiondo, M. S., Marcum, J. L. and Kryscio, R. J. 2011. Vitamin E and all-cause mortality: a meta-analysis. *Curr Aging Sci,* 4, 158-70.
Adachi, H., Fujiwara, Y. and Ishii, N. 1998. Effects of oxygen on protein carbonyl and aging in Caenorhabditis elegans mutants with long (age-1) and short (mev-1) life spans. *J Gerontol A Biol Sci Med Sci,* 53, B240-4.
Agarwal, S., Sharma, S., Agrawal, V. and Roy, N. 2005. Caloric restriction augments ROS defense in S. cerevisiae by a Sir2p independent mechanism. *Free Radic Res,* 39, 55-62.
Akerfelt, M., Morimoto, R. I. and Sistonen, L. 2010. Heat shock factors: integrators of cell stress, development and lifespan. *Nat Rev Mol Cell Biol,* 11, 545-55.
Akimoto, T., Pohnert, S. C., Li, P., Zhang, M., Gumbs, C., Rosenberg, P. B., Williams, R. S. and Yan, Z. 2005. Exercise stimulates Pgc-1alpha transcription in skeletal muscle through activation of the p38 MAPK pathway. *J Biol Chem,* 280, 19587-93.
Albanes, D., Heinonen, O. P., Taylor, P. R., Virtamo, J., Edwards, B. K., Rautalahti, M., Hartman, A. M., Palmgren, J., Freedman, L. S., Haapakoski, J., Barrett, M. J., Pietinen, P., Malila, N., Tala, E., Liippo, K., Salomaa, E. R., Tangrea, J. A., Teppo, L., Askin, F. B., Taskinen, E., Erozan, Y., Greenwald, P. and Huttunen, J. K. 1996. Alpha-Tocopherol and beta-carotene supplements and lung cancer incidence in the alpha-tocopherol, beta-carotene cancer prevention study: effects of base-line characteristics and study compliance. *J Natl Cancer Inst,* 88, 1560-70.
Alessio, H. M. and Goldfarb, A. H. 1988. Lipid peroxidation and scavenger enzymes during exercise: adaptive response to training. *J Appl Physiol,* 64, 1333-6.
Alessio, H. M., Goldfarb, A. H. and Cutler, R. G. 1988. MDA content increases in fast- and slow-twitch skeletal muscle with intensity of exercise in a rat. *Am J Physiol,* 255, C874-7.
Alexander, A., Cai, S. L., Kim, J., Nanez, A., Sahin, M., MacLean, K. H., Inoki, K., Guan, K. L., Shen, J., Person, M. D., Kusewitt, D., Mills, G. B., Kastan, M. B. and Walker, C. L. 2010. ATM signals to TSC2 in the cytoplasm to regulate mTORC1 in response to ROS. *Proc Natl Acad Sci U S A,* 107, 4153-8.

317

M. Ristow and K. Schmeisser

An, J. H. and Blackwell, T. K. 2003. SKN-1 links C. elegans mesendodermal specification to a conserved oxidative stress response. *Genes Dev,* 17, 1882-93.

Anckar, J. and Sistonen, L. 2011. Regulation of HSF1 function in the heat stress response: implications in aging and disease. *Annu Rev Biochem,* 80, 1089-115.

Anisimov, V. N., Berstein, L. M., Egormin, P. A., Piskunova, T. S., Popovich, I. G., Zabezhinski, M. A., Tyndyk, M. L., Yurova, M. V., Kovalenko, I. G., Poroshina, T. E. and Semenchenko, A. V. 2008. Metformin slows down aging and extends life span of female SHR mice. *Cell Cycle,* 7, 2769-73.

Apfeld, J., O'Connor, G., McDonagh, T., DiStefano, P. S. and Curtis, R. 2004. The AMP-activated protein kinase aak-2 links energy levels and insulin-like signals to lifespan in C. elegans. *Genes Dev,* 18, 3004-9.

Arbogast, S. and Reid, M. B. 2004. Oxidant activity in skeletal muscle fibers is influenced by temperature, CO2 level, and muscle-derived nitric oxide. *Am J Physiol Regul Integr Comp Physiol,* 287, R698-705.

Arumugam, T. V., Gleichmann, M., Tang, S. C. and Mattson, M. P. 2006. Hormesis/preconditioning mechanisms, the nervous system and aging. *Ageing Res Rev,* 5, 165-78.

Atherton, P. J., Babraj, J., Smith, K., Singh, J., Rennie, M. J. and Wackerhage, H. 2005. Selective activation of AMPK-PGC-1alpha or PKB-TSC2-mTOR signaling can explain specific adaptive responses to endurance or resistance training-like electrical muscle stimulation. *FASEB J,* 19, 786-8.

Baar, K. 2004. Involvement of PPAR gamma co-activator-1, nuclear respiratory factors 1 and 2, and PPAR alpha in the adaptive response to endurance exercise. *Proc Nutr Soc,* 63, 269-73.

Bakaev, V. V. and Lyudmila, M. B. 2002. Effect of ascorbic acid on longevity in the nematoda Caenorhabditis elegans. *Biogerontology 3 (suppl.1),* 12-16.

Balakrishnan, S. D. and Anuradha, C. V. 1998. Exercise, depletion of antioxidants and antioxidant manipulation. *Cell Biochem Funct,* 16, 269-75.

Balch, W. E., Morimoto, R. I., Dillin, A. and Kelly, J. W. 2008. Adapting proteostasis for disease intervention. *Science,* 319, 916-9.

Banerjee, K. K., Ayyub, C., Ali, S. Z., Mandot, V., Prasad, N. G. and Kolthur-Seetharam, U. 2012. dSir2 in the adult fat body, but not in muscles, regulates life span in a diet-dependent manner. *Cell Rep,* 2, 1485-91.

Barnes, K., Ingram, J. C., Porras, O. H., Barros, L. F., Hudson, E. R., Fryer, L. G., Foufelle, F., Carling, D., Hardie, D. G. and Baldwin, S. A. 2002. Activation of GLUT1 by metabolic and osmotic stress: potential involvement of AMP-activated protein kinase (AMPK). *J Cell Sci,* 115, 2433-42.

Barja G. 1993. Oxygen radicals, a failure or a success of evolution? Free Radic Res Commun 18, 63-70.

Barros, M. H., Bandy, B., Tahara, E. B. and Kowaltowski, A. J. 2004. Higher respiratory activity decreases mitochondrial reactive oxygen release and increases life span in Saccharomyces cerevisiae. *J Biol Chem,* 279, 49883-8.

Bartke, A., Masternak, M. M., Al-Regaiey, K. A. and Bonkowski, M. S. 2007. Effects of dietary restriction on the expression of insulin-signaling-related genes in long-lived mutant mice. *Interdiscip Top Gerontol,* 35, 69-82.

Bauer, J. H., Morris, S. N., Chang, C., Flatt, T., Wood, J. G. and Helfand, S. L. 2009. dSir2 and Dmp53 interact to mediate aspects of CR-dependent lifespan extension in D. melanogaster. *Aging (Albany NY),* 1, 38-48.

Baur, J. A., Pearson, K. J., Price, N. L., Jamieson, H. A., Lerin, C., Kalra, A., Prabhu, V. V., Allard, J. S., Lopez-Lluch, G., Lewis, K., Pistell, P. J., Poosala, S., Becker, K. G., Boss, O., Gwinn, D., Wang, M., Ramaswamy, S., Fishbein, K. W., Spencer, R. G., Lakatta, E. G., Le Couteur, D., Shaw, R. J., Navas, P., Puigserver, P., Ingram, D. K., de Cabo, R. and Sinclair, D. A. 2006. Resveratrol improves health and survival of mice on a high-calorie diet. *Nature,* 444, 337-342.

Baur, J. A. and Sinclair, D. A. 2006. Therapeutic potential of resveratrol: the in vivo evidence. *Nat Rev Drug Discov,* 5, 493-506.

Bell, E. L., Emerling, B. M., Ricoult, S. J. and Guarente, L. 2011. SirT3 suppresses hypoxia inducible factor 1alpha and tumor growth by inhibiting mitochondrial ROS production. *Oncogene,* 30, 2986-96.

Bergeron, R., Ren, J. M., Cadman, K. S., Moore, I. K., Perret, P., Pypaert, M., Young, L. H., Semenkovich, C. F. and Shulman, G. I. 2001. Chronic activation of AMP kinase results in NRF-1 activation and mitochondrial biogenesis. *Am J Physiol Endocrinol Metab,* 281, E1340-6.

318

Berndt, C., Lillig, C. H. and Holmgren, A. 2008. Thioredoxins and glutaredoxins as facilitators of protein folding. *Biochim Biophys Acta,* 1783, 641-50.

Berrington de Gonzalez, A., Hartge, P., Cerhan, J. R., Flint, A. J., Hannan, L., MacInnis, R. J., Moore, S. C., Tobias, G. S., Anton-Culver, H., Freeman, L. B., Beeson, W. L., Clipp, S. L., English, D. R., Folsom, A. R., Freedman, D. M., Giles, G., Hakansson, N., Henderson, K. D., Hoffman-Bolton, J., Hoppin, J. A., Koenig, K. L., Lee, I. M., Linet, M. S., Park, Y., Pocobelli, G., Schatzkin, A., Sesso, H. D., Weiderpass, E., Willcox, B. J., Wolk, A., Zeleniuch-Jacquotte, A., Willett, W. C. and Thun, M. J. 2010. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med,* 363, 2211-9.

Biddinger, S. B. and Kahn, C. R. 2006. From mice to men: insights into the insulin resistance syndromes. *Annu Rev Physiol,* 68, 123-58.

Bishop, N. A. and Guarente, L. 2007. Two neurons mediate diet-restriction-induced longevity in C. elegans. *Nature,* 447, 545-9.

Bitto, A., Lerner, C., Torres, C., Roell, M., Malaguti, M., Perez, V., Lorenzini, A., Hrelia, S., Ikeno, Y., Matzko, M. E., McCarter, R. and Sell, C. 2010. Long-term igf-I exposure decreases autophagy and cell viability. *PLoS ONE,* 5, e12592.

Bjelakovic, G., Nikolova, D., Gluud, L. L., Simonetti, R. G. and Gluud, C. 2007. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. *JAMA,* 297, 842-57.

Blander, G. and Guarente, L. 2004. The sir2 family of protein deacetylases. *Annu Rev Biochem,* 73, 417-35.

Blüher, M., Kahn, B. B. and Kahn, C. R. 2003. Extended longevity in mice lacking the insulin receptor in adipose tissue. *Science,* 299, 572-4.

Boden, G., Sargrad, K., Homko, C., Mozzoli, M. and Stein, T. P. 2005. Effect of a low-carbohydrate diet on appetite, blood glucose levels, and insulin resistance in obese patients with type 2 diabetes. *Ann Intern Med,* 142, 403-11.

Boily, G., Seifert, E. L., Bevilacqua, L., He, X. H., Sabourin, G., Estey, C., Moffat, C., Crawford, S., Saliba, S., Jardine, K., Xuan, J., Evans, M., Harper, M. E. and McBurney, M. W. 2008. SirT1 regulates energy metabolism and response to caloric restriction in mice. *PLoS ONE,* 3, e1759.

Bonawitz, N. D., Chatenay-Lapointe, M., Pan, Y. and Shadel, G. S. 2007. Reduced TOR signaling extends chronological life span via increased respiration and upregulation of mitochondrial gene expression. *Cell Metab,* 5, 265-77.

Bonkowski, M. S., Dominici, F. P., Arum, O., Rocha, J. S., Al Regaiey, K. A., Westbrook, R., Spong, A., Panici, J., Masternak, M. M., Kopchick, J. J. and Bartke, A. 2009. Disruption of growth hormone receptor prevents calorie restriction from improving insulin action and longevity. *PLoS ONE,* 4, e4567.

Boveris, A. and Chance, B. 1973. The mitochondrial generation of hydrogen peroxide. General properties and effect of hyperbaric oxygen. *Biochem J,* 134, 707-16.

Boveris, A. and Navarro, A. 2008. Systemic and mitochondrial adaptive responses to moderate exercise in rodents. *Free Radic Biol Med,* 44, 224-9.

Bratic, A. and Larsson, N. G. 2013. The role of mitochondria in aging. *J Clin Invest,* 123, 951-7.

Brewer, G. J. 2010. Epigenetic oxidative redox shift (EORS) theory of aging unifies the free radical and insulin signaling theories. *Exp Gerontol,* 45, 173-9.

Brinkkoetter, P. T., Song, H., Losel, R., Schnetzke, U., Gottmann, U., Feng, Y., Hanusch, C., Beck, G. C., Schnuelle, P., Wehling, M., van der Woude, F. J. and Yard, B. A. 2008. Hypothermic injury: the mitochondrial calcium, ATP and ROS love-hate triangle out of balance. *Cell Physiol Biochem,* 22, 195-204.

Brookes, P. S., Yoon, Y., Robotham, J. L., Anders, M. W. and Sheu, S. S. 2004. Calcium, ATP, and ROS: a mitochondrial love-hate triangle. *Am J Physiol Cell Physiol,* 287, C817-33.

Brooks, N. L., Trent, C. M., Raetzsch, C. F., Flurkey, K., Boysen, G., Perfetti, M. T., Jeong, Y. C., Klebanov, S., Patel, K. B., Khodush, V. R., Kupper, L. L., Carling, D., Swenberg, J. A., Harrison, D. E. and Combs, T. P. 2007. Low utilization of circulating glucose after food withdrawal in Snell dwarf mice. *J Biol Chem,* 282, 35069-77.

Brown-Borg, H. M., Borg, K. E., Meliska, C. J. and Bartke, A. 1996. Dwarf mice and the ageing process. *Nature,* 384, 33.

Brown-Borg, H. M., Rakoczy, S. G., Romanick, M. A. and Kennedy, M. A. 2002. Effects of growth hormone and insulin-like growth factor-1 on hepatocyte antioxidative enzymes. *Exp Biol Med (Maywood),* 227, 94-104.

319

M. Ristow and K. Schmeisser

Brown, B. M., Peiffer, J. J. and Martins, R. N. 2013. Multiple effects of physical activity on molecular and cognitive signs of brain aging: can exercise slow neurodegeneration and delay Alzheimer's disease? *Mol Psychiatry*, 8, 864-74.

Brown, M. F. and Stuart, J. A. 2007. Correlation of mitochondrial superoxide dismutase and DNA polymerase beta in mammalian dermal fibroblasts with species maximal lifespan. *Mech Ageing Dev*, 128, 696-705.

Brunet, A., Sweeney, L. B., Sturgill, J. F., Chua, K. F., Greer, P. L., Lin, Y., Tran, H., Ross, S. E., Mostoslavsky, R., Cohen, H. Y., Hu, L. S., Cheng, H. L., Jedrychowski, M. P., Gygi, S. P., Sinclair, D. A., Alt, F. W. and Greenberg, M. E. 2004. Stress-dependent regulation of FOXO transcription factors by the SIRT1 deacetylase. *Science,* 303, 2011-5.

Brüning, J. C., Michael, M. D., Winnay, J. N., Hayashi, T., Hörsch, D., Accili, D., Goodyear, L. J. and Kahn, C. R. 1998. A muscle-specific insulin receptor knockout exhibits features of the metabolic syndrome of NIDDM without altering glucose tolerance. *Mol Cell*, 2, 559-69.

Brunmair, B., Lest, A., Staniek, K., Gras, F., Scharf, N., Roden, M., Nohl, H., Waldhausl, W. and Furnsinn, C. 2004a. Fenofibrate impairs rat mitochondrial function by inhibition of respiratory complex I. *J Pharmacol Exp Ther,* 311, 109-14.

Brunmair, B., Staniek, K., Gras, F., Scharf, N., Althaym, A., Clara, R., Roden, M., Gnaiger, E., Nohl, H., Waldhausl, W. and Furnsinn, C. 2004b. Thiazolidinediones, like metformin, inhibit respiratory complex I: a common mechanism contributing to their antidiabetic actions? *Diabetes,* 53, 1052-9.

Brunn, G. J., Hudson, C. C., Sekulic, A., Williams, J. M., Hosoi, H., Houghton, P. J., Lawrence, J. C. and Abraham, R. T. 1997. Phosphorylation of the translational repressor PHAS-I by the mammalian target of rapamycin. *Science,* 277, 99-101.

Brys, K., Castelein, N., Matthijssens, F., Vanfleteren, J. R. and Braeckman, B. P. 2010. Disruption of insulin signalling preserves bioenergetic competence of mitochondria in ageing Caenorhabditis elegans. *BMC Biol,* 8, 91.

Buchowski, M. S., Hongu, N., Acra, S., Wang, L., Warolin, J. and Roberts, L. J., 2nd 2012. Effect of modest caloric restriction on oxidative stress in women, a randomized trial. *PLoS ONE,* 7, e47079.

Burnett, C., Valentini, S., Cabreiro, F., Goss, M., Somogyvari, M., Piper, M. D., Hoddinott, M., Sutphin, G. L., Leko, V., McElwee, J. J., Vazquez-Manrique, R. P., Orfila, A. M., Ackerman, D., Au, C., Vinti, G., Riesen, M., Howard, K., Neri, C., Bedalov, A., Kaeberlein, M., Soti, C., Partridge, L. and Gems, D. 2011. Absence of effects of Sir2 overexpression on lifespan in C. elegans and Drosophila. *Nature,* 477, 482-5.

Calabrese, E. J., Bachmann, K. A., Bailer, A. J., Bolger, P. M., Borak, J., Cai, L., Cedergreen, N., Cherian, M. G., Chiueh, C. C., Clarkson, T. W., Cook, R. R., Diamond, D. M., Doolittle, D. J., Dorato, M. A., Duke, S. O., Feinendegen, L., Gardner, D. E., Hart, R. W., Hastings, K. L., Hayes, A. W., Hoffmann, G. R., Ives, J. A., Jaworowski, Z., Johnson, T. E., Jonas, W. B., Kaminski, N. E., Keller, J. G., Klaunig, J. E., Knudsen, T. B., Kozumbo, W. J., Lettieri, T., Liu, S. Z., Maisseu, A., Maynard, K. I., Masoro, E. J., McClellan, R. O., Mehendale, H. M., Mothersill, C., Newlin, D. B., Nigg, H. N., Oehme, F. W., Phalen, R. F., Philbert, M. A., Rattan, S. I., Riviere, J. E., Rodricks, J., Sapolsky, R. M., Scott, B. R., Seymour, C., Sinclair, D. A., Smith-Sonneborn, J., Snow, E. T., Spear, L., Stevenson, D. E., Thomas, Y., Tubiana, M., Williams, G. M. and Mattson, M. P. 2007. Biological stress response terminology: Integrating the concepts of adaptive response and preconditioning stress within a hormetic dose-response framework. *Toxicol Appl Pharmacol,* 222, 122-8.

Calabrese, E. J. and Baldwin, L. A. 2002. Defining hormesis. *Hum Exp Toxicol,* 21, 91-7.

Calderwood, S. K., Murshid, A. and Prince, T. 2009. The shock of aging: molecular chaperones and the heat shock response in longevity and aging—a mini-review. *Gerontology,* 55, 550-8.

Calfon, M., Zeng, H., Urano, F., Till, J. H., Hubbard, S. R., Harding, H. P., Clark, S. G. and Ron, D. 2002. IRE1 couples endoplasmic reticulum load to secretory capacity by processing the XBP-1 mRNA. *Nature,* 415, 92-6.

Canto, C. and Auwerx, J. 2009. Caloric restriction, SIRT1 and longevity. *Trends Endocrinol Metab,* 20, 325-31.

Caro, P., Gomez, J., Lopez-Torres, M., Sanchez, I., Naudi, A., Jove, M., Pamplona, R. and Barja, G. 2008. Forty percent and eighty percent methionine restriction decrease mitochondrial ROS generation and oxidative stress in rat liver. *Biogerontology,* 9, 183-96.

Chance, B., Sies, H. and Boveris, A. 1979. Hydroperoxide metabolism in mammalian organs. *Physiol Rev,* 59, 527-605.

Chandel, N. S., Maltepe, E., Goldwasser, E., Mathieu, C. E., Simon, M. C. and Schumacker, P. T. 1998. Mitochondrial reactive oxygen species trigger hypoxia-induced transcription. *Proc Natl Acad Sci U S A,* 95, 11715-20.

Chandel, N. S., McClintock, D. S., Feliciano, C. E., Wood, T. M., Melendez, J. A., Rodriguez, A. M. and Schumacker, P. T. 2000a. Reactive oxygen species generated at mitochondrial complex III stabilize hypoxia-inducible factor-1alpha during hypoxia: a mechanism of O2 sensing. *J Biol Chem,* 275, 25130-8.

Chandel, N. S., Trzyna, W. C., McClintock, D. S. and Schumacker, P. T. 2000b. Role of oxidants in NF-kappa B activation and TNF-alpha gene transcription induced by hypoxia and endotoxin. *J Immunol,* 165, 1013-21.

Chen, D., Thomas, E. L. and Kapahi, P. 2009. HIF-1 modulates dietary restriction-mediated lifespan extension via IRE-1 in Caenorhabditis elegans. *PLoS Genet,* 5, e1000486.

Chevion, S., Moran, D. S., Heled, Y., Shani, Y., Regev, G., Abbou, B., Berenshtein, E., Stadtman, E. R. and Epstein, Y. 2003. Plasma antioxidant status and cell injury after severe physical exercise. *Proc Natl Acad Sci U S A,* 100, 5119-23.

Chiang, W. C., Ching, T. T., Lee, H. C., Mousigian, C. and Hsu, A. L. 2012. HSF-1 Regulators DDL-1/2 Link Insulin-like Signaling to Heat-Shock Responses and Modulation of Longevity. *Cell,* 148, 322-34.

Clancy, D. J., Gems, D., Hafen, E., Leevers, S. J. and Partridge, L. 2002. Dietary restriction in long-lived dwarf flies. *Science,* 296, 319.

Clancy, D. J., Gems, D., Harshman, L. G., Oldham, S., Stocker, H., Hafen, E., Leevers, S. J. and Partridge, L. 2001. Extension of life-span by loss of CHICO, a Drosophila insulin receptor substrate protein. *Science,* 292, 104-6.

Clapham, D. E. 2003. TRP channels as cellular sensors. *Nature,* 426, 517-24.

Close, G. L., Ashton, T., Cable, T., Doran, D., Holloway, C., McArdle, F. and MacLaren, D. P. 2006. Ascorbic acid supplementation does not attenuate post-exercise muscle soreness following muscle-damaging exercise but may delay the recovery process. *Br J Nutr,* 95, 976-81.

Cocheme, H. M., Quin, C., McQuaker, S. J., Cabreiro, F., Logan, A., Prime, T. A., Abakumova, I., Patel, J. V., Fearnley, I. M., James, A. M., Porteous, C. M., Smith, R. A., Saeed, S., Carre, J. E., Singer, M., Gems, D., Hartley, R. C., Partridge, L. and Murphy, M. P. 2011. Measurement of H2O2 within living Drosophila during aging using a ratiometric mass spectrometry probe targeted to the mitochondrial matrix. *Cell Metab,* 13, 340-50.

Colman, R. J., Anderson, R. M., Johnson, S. C., Kastman, E. K., Kosmatka, K. J., Beasley, T. M., Allison, D. B., Cruzen, C., Simmons, H. A., Kemnitz, J. W. and Weindruch, R. 2009. Caloric restriction delays disease onset and mortality in rhesus monkeys. *Science,* 325, 201-4.

Conti, B., Sanchez-Alavez, M., Winsky-Sommerer, R., Morale, M. C., Lucero, J., Brownell, S., Fabre, V., Huitron-Resendiz, S., Henriksen, S., Zorrilla, E. P., de Lecea, L. and Bartfai, T. 2006. Transgenic mice with a reduced core body temperature have an increased life span. *Science,* 314, 825-8.

Cook, N. R., Albert, C. M., Gaziano, J. M., Zaharris, E., MacFadyen, J., Danielson, E., Buring, J. E. and Manson, J. E. 2007. A randomized factorial trial of vitamins C and E and beta carotene in the secondary prevention of cardiovascular events in women: results from the Women's Antioxidant Cardiovascular Study. *Arch Intern Med,* 167, 1610-8.

Coughlin, S. S., Calle, E. E., Teras, L. R., Petrelli, J. and Thun, M. J. 2004. Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. *Am J Epidemiol,* 159, 1160-7.

Crawford, D. R. and Davies, K. J. 1994. Adaptive response and oxidative stress. *Environ Health Perspect,* 102 Suppl 10, 25-8.

Csordas, G. and Hajnoczky, G. 2009. SR/ER-mitochondrial local communication: calcium and ROS. *Biochim Biophys Acta,* 1787, 1352-62.

Cunningham, J. T., Rodgers, J. T., Arlow, D. H., Vazquez, F., Mootha, V. K. and Puigserver, P. 2007. mTOR controls mitochondrial oxidative function through a YY1-PGC-1alpha transcriptional complex. *Nature,* 450, 736-40.

Curran, S. P. and Ruvkun, G. 2007. Lifespan regulation by evolutionarily conserved genes essential for viability. *PLoS Genet,* 3, e56.

Cypser, J. R. and Johnson, T. E. 2002. Multiple stressors in Caenorhabditis elegans induce stress hormesis and extended longevity. *J Gerontol A Biol Sci Med Sci,* 57, B109-14.

321

M. Ristow and K. Schmeisser

Czernichow, S., Bertrais, S., Blacher, J., Galan, P., Briancon, S., Favier, A., Safar, M. and Hercberg, S. 2005. Effect of supplementation with antioxidants upon long-term risk of hypertension in the SU.VI.MAX study: association with plasma antioxidant levels. *J Hypertens,* 23, 2013-8.

Czernichow, S., Couthouis, A., Bertrais, S., Vergnaud, A. C., Dauchet, L., Galan, P. and Hercberg, S. 2006. Antioxidant supplementation does not affect fasting plasma glucose in the Supplementation with Antioxidant Vitamins and Minerals (SU.VI.MAX) study in France: association with dietary intake and plasma concentrations. *Am J Clin Nutr,* 84, 395-9.

D'Antona, G., Ragni, M., Cardile, A., Tedesco, L., Dossena, M., Bruttini, F., Caliaro, F., Corsetti, G., Bottinelli, R., Carruba, M. O., Valerio, A. and Nisoli, E. 2010. Branched-chain amino acid supplementation promotes survival and supports cardiac and skeletal muscle mitochondrial biogenesis in middle-aged mice. *Cell Metab,* 12, 362-72.

Dai, D. F., Santana, L. F., Vermulst, M., Tomazela, D. M., Emond, M. J., MacCoss, M. J., Gollahon, K., Martin, G. M., Loeb, L. A., Ladiges, W. C. and Rabinovitch, P. S. 2009. Overexpression of catalase targeted to mitochondria attenuates murine cardiac aging. *Circulation,* 119, 2789-97.

Davies, K. J. 1986. Intracellular proteolytic systems may function as secondary antioxidant defenses: an hypothesis. *J Free Radic Biol Med,* 2, 155-73.

Davies, K. J., Quintanilha, A. T., Brooks, G. A. and Packer, L. 1982. Free radicals and tissue damage produced by exercise. *Biochem Biophys Res Commun,* 107, 1198-205.

de Castro, E., Hegi de Castro, S. and Johnson, T. E. 2004. Isolation of long-lived mutants in Caenorhabditis elegans using selection for resistance to juglone. *Free Radic Biol Med,* 37, 139-45.

Deepa, S. S., Pulliam, D., Hill, S., Shi, Y., Walsh, M. E., Salmon, A., Sloane, L., Zhang, N., Zeviani, M., Viscomi, C., Musi, N. and Van Remmen, H. 2013. Improved insulin sensitivity associated with reduced mitochondrial complex IV assembly and activity. *FASEB J,* 27, 1371-80.

Delaney, J. R., Ahmed, U., Chou, A., Sim, S., Carr, D., Murakami, C. J., Schleit, J., Sutphin, G. L., An, E. H., Castanza, A., Fletcher, M., Higgins, S., Jelic, M., Klum, S., Muller, B., Peng, Z. J., Rai, D., Ros, V., Singh, M., Wende, H. V., Kennedy, B. K. and Kaeberlein, M. 2013. Stress profiling of longevity mutants identifies Afg3 as a mitochondrial determinant of cytoplasmic mRNA translation and aging. *Aging Cell,* 12, 156-66.

DeNicola, G. M., Karreth, F. A., Humpton, T. J., Gopinathan, A., Wei, C., Frese, K., Mangal, D., Yu, K. H., Yeo, C. J., Calhoun, E. S., Scrimieri, F., Winter, J. M., Hruban, R. H., Iacobuzio-Donahue, C., Kern, S. E., Blair, I. A. and Tuveson, D. A. 2011. Oncogene-induced Nrf2 transcription promotes ROS detoxification and tumorigenesis. *Nature,* 475, 106-9.

Dillin, A., Hsu, A. L., Arantes-Oliveira, N., Lehrer-Graiwer, J., Hsin, H., Fraser, A. G., Kamath, R. S., Ahringer, J. and Kenyon, C. 2002. Rates of behavior and aging specified by mitochondrial function during development. *Science,* 298, 2398-401.

Dioum, E. M., Chen, R., Alexander, M. S., Zhang, Q., Hogg, R. T., Gerard, R. D. and Garcia, J. A. 2009. Regulation of hypoxia-inducible factor 2alpha signaling by the stress-responsive deacetylase sirtuin 1. *Science,* 324, 1289-93.

Dong, M. Q., Venable, J. D., Au, N., Xu, T., Park, S. K., Cociorva, D., Johnson, J. R., Dillin, A. and Yates, J. R., 3rd 2007. Quantitative mass spectrometry identifies insulin signaling targets in C. elegans. *Science,* 317, 660-3.

Dubey, A., Forster, M. J., Lal, H. and Sohal, R. S. 1996. Effect of age and caloric intake on protein oxidation in different brain regions and on behavioral functions of the mouse. *Arch Biochem Biophys,* 333, 189-97.

El-Mir, M. Y., Nogueira, V., Fontaine, E., Averet, N., Rigoulet, M. and Leverve, X. 2000. Dimethylbiguanide inhibits cell respiration via an indirect effect targeted on the respiratory chain complex I. *J Biol Chem,* 275, 223-8.

Elshorbagy, A. K., Valdivia-Garcia, M., Mattocks, D. A., Plummer, J. D., Orentreich, D. S., Orentreich, N., Refsum, H. and Perrone, C. E. 2013. Effect of taurine and N-acetylcysteine on methionine restriction-mediated adiposity resistance. *Metabolism,* 62, 509-17.

Emerling, B. M., Weinberg, F., Snyder, C., Burgess, Z., Mutlu, G. M., Viollet, B., Budinger, G. R. and Chandel, N. S. 2009. Hypoxic activation of AMPK is dependent on mitochondrial ROS but independent of an increase in AMP/ATP ratio. *Free Radic Biol Med,* 46, 1386-91.

Fanson, B. G., Weldon, C. W., Perez-Staples, D., Simpson, S. J. and Taylor, P. W. 2009. Nutrients, not caloric restriction, extend lifespan in Queensland fruit flies (Bactrocera tryoni). *Aging Cell* 8, 514-23.

322

Mitochondrial Hormesis and Lifespan

Fargnoli, J., Kunisada, T., Fornace, A. J., Jr., Schneider, E. L. and Holbrook, N. J. 1990. Decreased expression of heat shock protein 70 mRNA and protein after heat treatment in cells of aged rats. *Proc Natl Acad Sci U S A,* 87, 846-50.

Fernandes, G., Yunis, E. J. and Good, R. A. 1976. Influence of diet on survival of mice. *Proc Natl Acad Sci U S A,* 73, 1279-83.

Fierro-Gonzalez, J. C., Gonzalez-Barrios, M., Miranda-Vizuete, A. and Swoboda, P. 2011. The thioredoxin TRX-1 regulates adult lifespan extension induced by dietary restriction in Caenorhabditis elegans. *Biochem Biophys Res Commun,* 406, 478-82.

Finkel, T. 1998. Oxygen radicals and signaling. *Curr Opin Cell Biol,* 10, 248-53.

Finkel, T. 2012. From sulfenylation to sulfhydration: what a thiolate needs to tolerate. *Sci Signal,* 5, pe10.

Finley, L. W., Carracedo, A., Lee, J., Souza, A., Egia, A., Zhang, J., Teruya-Feldstein, J., Moreira, P. I., Cardoso, S. M., Clish, C. B., Pandolfi, P. P. and Haigis, M. C. 2011. SIRT3 opposes reprogramming of cancer cell metabolism through HIF1alpha destabilization. *Cancer Cell,* 19, 416-28.

Fischer, C. P., Hiscock, N. J., Basu, S., Vessby, B., Kallner, A., Sjoberg, L. B., Febbraio, M. A. and Pedersen, B. K. 2006. Vitamin E isoform-specific inhibition of the exercise-induced heat shock protein 72 expression in humans. *J Appl Physiol,* 100, 1679-87.

Fishbein, L. E. 1991. Biological effects of dietary restriction. New York: Springer-Verlag.

Fontana, L. and Klein, S. 2007. Aging, adiposity, and calorie restriction. *JAMA,* 297, 986-94.

Fontana, L., Meyer, T. E., Klein, S. and Holloszy, J. O. 2004. Long-term calorie restriction is highly effective in reducing the risk for atherosclerosis in humans. *Proc Natl Acad Sci U S A,* 101, 6659-63.

Fontana, L., Partridge, L. and Longo, V. D. 2010. Extending healthy life span—from yeast to humans. *Science,* 328, 321-6.

Forsythe, C. E., Phinney, S. D., Fernandez, M. L., Quann, E. E., Wood, R. J., Bibus, D. M., Kraemer, W. J., Feinman, R. D. and Volek, J. S. 2008. Comparison of low fat and low carbohydrate diets on circulating fatty acid composition and markers of inflammation. *Lipids,* 43, 65-77.

Franco, A. A., Odom, R. S. and Rando, T. A. 1999. Regulation of antioxidant enzyme gene expression in response to oxidative stress and during differentiation of mouse skeletal muscle. *Free Radical Biology and Medicine,* 27, 1122-1132.

Franco, O. H., Steyerberg, E. W., Hu, F. B., Mackenbach, J. and Nusselder, W. 2007. Associations of diabetes mellitus with total life expectancy and life expectancy with and without cardiovascular disease. *Arch Intern Med,* 167, 1145-51.

Friedman, J. R. and Kaestner, K. H. 2006. The Foxa family of transcription factors in development and metabolism. *Cell Mol Life Sci,* 63, 2317-28.

Fukui, H. and Moraes, C. T. 2008. The mitochondrial impairment, oxidative stress and neurodegeneration connection: reality or just an attractive hypothesis? *Trends Neurosci,* 31, 251-6.

Fukushima, T. 2005. Niacin Metabolism and Parkinson's Disease. *Environ Health Prev Med,* 10, 3-8.

Garriga-Canut, M., Schoenike, B., Qazi, R., Bergendahl, K., Daley, T. J., Pfender, R. M., Morrison, J. F., Ockuly, J., Stafstrom, C., Sutula, T. and Roopra, A. 2006. 2-Deoxy-D-glucose reduces epilepsy progression by NRSF-CtBP-dependent metabolic regulation of chromatin structure. *Nat Neurosci,* 9, 1382-7.

Gey, G. O., Cooper, K. H. and Bottenberg, R. A. 1970. Effect of ascorbic acid on endurance performance and athletic injury. *JAMA,* 211, 105.

Ghosh, D., LeVault, K. R., Barnett, A. J. and Brewer, G. J. 2012. A reversible early oxidized redox state that precedes macromolecular ROS damage in aging nontransgenic and 3xTg-AD mouse neurons. *J Neurosci,* 32, 5821-32.

Gomez-Cabrera, M. C., Domenech, E., Romagnoli, M., Arduini, A., Borras, C., Pallardo, F. V., Sastre, J. and Vina, J. 2008a. Oral administration of vitamin C decreases muscle mitochondrial biogenesis and hampers training-induced adaptations in endurance performance. *Am J Clin Nutr,* 87, 142-9.

Gomez-Cabrera, M. C., Domenech, E. and Vina, J. 2008b. Moderate exercise is an antioxidant: Upregulation of antioxidant genes by training. *Free Radic Biol Med,* 44, 126-31.

Grant, C. M., MacIver, F. H. and Dawes, I. W. 1997. Mitochondrial function is required for resistance to oxidative stress in the yeast Saccharomyces cerevisiae. *FEBS Lett,* 410, 219-22.

Gredilla, R., Sanz, A., Lopez-Torres, M. and Barja, G. 2001. Caloric restriction decreases mitochondrial free radical generation at complex I and lowers oxidative damage to mitochondrial DNA in the rat heart. *FASEB J,* 15, 1589-91.

323

M. Ristow and K. Schmeisser

Greenberg, E. R., Baron, J. A., Tosteson, T. D., Freeman, D. H., Jr., Beck, G. J., Bond, J. H., Colacchio, T. A., Coller, J. A., Frankl, H. D., Haile, R. W. and et al. 1994. A clinical trial of antioxidant vitamins to prevent colorectal adenoma. Polyp Prevention Study Group. *N Engl J Med,* 331, 141-7.

Greer, E. L., Dowlatshahi, D., Banko, M. R., Villen, J., Hoang, K., Blanchard, D., Gygi, S. P. and Brunet, A. 2007a. An AMPK-FOXO pathway mediates longevity induced by a novel method of dietary restriction in C. elegans. *Curr Biol,* 17, 1646-56.

Greer, E. L., Oskoui, P. R., Banko, M. R., Maniar, J. M., Gygi, M. P., Gygi, S. P. and Brunet, A. 2007b. The energy sensor AMP-activated protein kinase directly regulates the mammalian FOXO3 transcription factor. *J Biol Chem,* 282, 30107-19.

Gruber, J., Schaffer, S. and Halliwell, B. 2008. The mitochondrial free radical theory of ageing—where do we stand? *Front Biosci,* 13, 6554-79.

Guarente, L. and Picard, F. 2005. Calorie restriction—the SIR2 connection. *Cell,* 120, 473-82.

Guzy, R. D. and Schumacker, P. T. 2006. Oxygen sensing by mitochondria at complex III: the paradox of increased reactive oxygen species during hypoxia. *Exp Physiol,* 91, 807-19.

Gwinn, D. M., Shackelford, D. B., Egan, D. F., Mihaylova, M. M., Mery, A., Vasquez, D. S., Turk, B. E. and Shaw, R. J. 2008. AMPK phosphorylation of raptor mediates a metabolic checkpoint. *Mol Cell,* 30, 214-26.

Habets, D. D., Coumans, W. A., El Hasnaoui, M., Zarrinpashneh, E., Bertrand, L., Viollet, B., Kiens, B., Jensen, T. E., Richter, E. A., Bonen, A., Glatz, J. F. and Luiken, J. J. 2009. Crucial role for LKB1 to AMPKalpha2 axis in the regulation of CD36-mediated long-chain fatty acid uptake into cardiomyocytes. *Biochim Biophys Acta,* 1791, 212-9.

Haigis, M. C. and Sinclair, D. A. 2010. Sirtuins in Aging and Age-Related Diseases. In: Handbook of the Biology of Aging (edited by Masoro, E. J. and Austad, S. N.). AbeBooks, Academic Press.

Halliwell, B. and Gutteridge, J. M. 2007. Free Radicals in Biology and Medicine (fourth ed.). *Oxford University Press.*

Hansen, M., Chandra, A., Mitic, L. L., Onken, B., Driscoll, M. and Kenyon, C. 2008. A Role for Autophagy in the Extension of Lifespan by Dietary Restriction in C. elegans. *PLoS Genet,* 4, e24.

Hara, K., Maruki, Y., Long, X., Yoshino, K., Oshiro, N., Hidayat, S., Tokunaga, C., Avruch, J. and Yonezawa, K. 2002. Raptor, a binding partner of target of rapamycin (TOR), mediates TOR action. *Cell,* 110, 177-89.

Hardie, D. G. 2011. Sensing of energy and nutrients by AMP-activated protein kinase. *Am J Clin Nutr,* 93, 891S-6.

Hardie, D. G., Hawley, S. A. and Scott, J. W. 2006. AMP-activated protein kinase: development of the energy sensor concept. *J Physiol,* 574, 7-15.

Hardie, D. G., Scott, J. W., Pan, D. A. and Hudson, E. R. 2003. Management of cellular energy by the AMP-activated protein kinase system. *FEBS Lett,* 546, 113-20.

Harman, D. 1956. Aging: a theory based on free radical and radiation chemistry. *J Gerontol,* 11, 298-300.

Harman, D. 1972. The biologic clock: the mitochondria? *J Am Geriatr Soc,* 20, 145-7.

Harrington, L. A. and Harley, C. B. 1988. Effect of vitamin E on lifespan and reproduction in Caenorhabditis elegans. *Mech Ageing Dev,* 43, 71-8.

Harrison, D. E., Strong, R., Sharp, Z. D., Nelson, J. F., Astle, C. M., Flurkey, K., Nadon, N. L., Wilkinson, J. E., Frenkel, K., Carter, C. S., Pahor, M., Javors, M. A., Fernandez, E. and Miller, R. A. 2009. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. *Nature,* 460, 392-5.

Harvey, A. E., Lashinger, L. M., Otto, G., Nunez, N. P. and Hursting, S. D. 2013. Decreased systemic IGF-1 in response to calorie restriction modulates murine tumor cell growth, nuclear factor-kappaB activation, and inflammation-related gene expression. *Mol Carcinog,* 52, 997-1006.

Hasegawa, K. and Miwa, J. 2010. Genetic and cellular characterization of Caenorhabditis elegans mutants abnormal in the regulation of many phase II enzymes. *PLoS ONE,* 5, e11194.

Hawley, S. A., Ross, F. A., Chevtzoff, C., Green, K. A., Evans, A., Fogarty, S., Towler, M. C., Brown, L. J., Ogunbayo, O. A., Evans, A. M. and Hardie, D. G. 2010. Use of cells expressing gamma subunit variants to identify diverse mechanisms of AMPK activation. *Cell Metab,* 11, 554-65.

He, X. Y., Zhao, X. L., Gu, Q., Shen, J. P., Hu, Y. and Hu, R. M. 2012. Calorie restriction from a young age preserves the functions of pancreatic beta cells in aging rats. *Tohoku J Exp Med,* 227, 245-52.

Heidler, T., Hartwig, K., Daniel, H. and Wenzel, U. 2010. Caenorhabditis elegans lifespan extension caused by treatment with an orally active ROS-generator is dependent on DAF-16 and SIR-2.1. *Biogerontology* 11, 183-95.

Heilbronn, L. K., de Jonge, L., Frisard, M. I., DeLany, J. P., Larson-Meyer, D. E., Rood, J., Nguyen, T., Martin, C. K., Volaufova, J., Most, M. M., Greenway, F. L., Smith, S. R., Deutsch, W. A., Williamson, D. A. and Ravussin, E. 2006. Effect of 6-month calorie restriction on biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals: a randomized controlled trial. *JAMA,* 295, 1539-48.

Hemmrich, K., Suschek, C. V., Lerzynski, G. and Kolb-Bachofen, V. 2003. iNOS activity is essential for endothelial stress gene expression protecting against oxidative damage. *J Appl Physiol,* 95, 1937-46.

Henis-Korenblit, S., Zhang, P., Hansen, M., McCormick, M., Lee, S. J., Cary, M. and Kenyon, C. 2010. Insulin/IGF-1 signaling mutants reprogram ER stress response regulators to promote longevity. *Proc Natl Acad Sci U S A,* 107, 9730-5.

Hession, M., Rolland, C., Kulkarni, U., Wise, A. and Broom, J. 2009. Systematic review of randomized controlled trials of low-carbohydrate vs. low-fat/low-calorie diets in the management of obesity and its comorbidities. *Obes Rev,* 10, 36-50.

Higuchi, M., Cartier, L. J., Chen, M. and Holloszy, J. O. 1985. Superoxide dismutase and catalase in skeletal muscle: adaptive response to exercise. *J Gerontol,* 40, 281-6.

Hirschey, M. D., Shimazu, T., Goetzman, E., Jing, E., Schwer, B., Lombard, D. B., Grueter, C. A., Harris, C., Biddinger, S., Ilkayeva, O. R., Stevens, R. D., Li, Y., Saha, A. K., Ruderman, N. B., Bain, J. R., Newgard, C. B., Farese, R. V., Jr., Alt, F. W., Kahn, C. R. and Verdin, E. 2010. SIRT3 regulates mitochondrial fatty-acid oxidation by reversible enzyme deacetylation. *Nature,* 464, 121-5.

Hirschey, M. D., Shimazu, T., Huang, J. Y., Schwer, B. and Verdin, E. 2011a. SIRT3 Regulates Mitochondrial Protein Acetylation and Intermediary Metabolism. *Cold Spring Harb Symp Quant Biol,* 76, 267-77.

Hirschey, M. D., Shimazu, T., Jing, E., Grueter, C. A., Collins, A. M., Aouizerat, B., Stancakova, A., Goetzman, E., Lam, M. M., Schwer, B., Stevens, R. D., Muehlbauer, M. J., Kakar, S., Bass, N. M., Kuusisto, J., Laakso, M., Alt, F. W., Newgard, C. B., Farese, R. V., Jr., Kahn, C. R. and Verdin, E. 2011b. SIRT3 Deficiency and Mitochondrial Protein Hyperacetylation Accelerate the Development of the Metabolic Syndrome. *Mol Cell,* 44, 177-90.

Hollander, J., Fiebig, R., Gore, M., Ookawara, T., Ohno, H. and Ji, L. L. 2001. Superoxide dismutase gene expression is activated by a single bout of exercise in rat skeletal muscle. *Pflugers Arch,* 442, 426-34.

Holloszy, J. O. and Fontana, L. 2007. Caloric restriction in humans. *Exp Gerontol,* 42, 709-12.

Holloszy, J. O. and Smith, E. K. 1986. Longevity of cold-exposed rats: a reevaluation of the "rate-of-living theory". *J Appl Physiol,* 61, 1656-60.

Holzenberger, M., Dupont, J., Ducos, B., Leneuve, P., Geloen, A., Even, P. C., Cervera, P. and Le Bouc, Y. 2003. IGF-1 receptor regulates lifespan and resistance to oxidative stress in mice. *Nature,* 421, 182-7.

Honda, Y. and Honda, S. 1999. The daf-2 gene network for longevity regulates oxidative stress resistance and Mn-superoxide dismutase gene expression in Caenorhabditis elegans. *FASEB J,* 13, 1385-93.

Houthoofd, K., Braeckman, B. P., Johnson, T. E. and Vanfleteren, J. R. 2003. Life extension via dietary restriction is independent of the Ins/IGF-1 signalling pathway in Caenorhabditis elegans. *Exp Gerontol,* 38, 947-54.

Houthoofd, K., Fidalgo, M. A., Hoogewijs, D., Braeckman, B. P., Lenaerts, I., Brys, K., Matthijssens, F., De Vreese, A., Van Eygen, S., Munoz, M. J. and Vanfleteren, J. R. 2005. Metabolism, physiology and stress defense in three aging Ins/IGF-1 mutants of the nematode Caenorhabditis elegans. *Aging Cell,* 4, 87-95.

Howitz, K. T. and Sinclair, D. A. 2008. Xenohormesis: sensing the chemical cues of other species. *Cell,* 133, 387-91.

Hsu, A. L., Murphy, C. T. and Kenyon, C. 2003. Regulation of aging and age-related disease by DAF-16 and heat-shock factor. *Science,* 300, 1142-5.

Hu, F. B., Manson, J. E., Stampfer, M. J., Colditz, G., Liu, S., Solomon, C. G. and Willett, W. C. 2001. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med,* 345, 790-7.

Huang, T. T., Naeemuddin, M., Elchuri, S., Yamaguchi, M., Kozy, H. M., Carlson, E. J. and Epstein, C. J. 2006. Genetic modifiers of the phenotype of mice deficient in mitochondrial superoxide dismutase. *Hum Mol Genet,* 15, 1187-94.

M. Ristow and K. Schmeisser

Hulbert, A. J., Clancy, D. J., Mair, W., Braeckman, B. P., Gems, D. and Partridge, L. 2004. Metabolic rate is not reduced by dietary-restriction or by lowered insulin/IGF-1 signalling and is not correlated with individual lifespan in Drosophila melanogaster. *Exp Gerontol,* 39, 1137-43.

Hussain, T. A., Mathew, T. C., Dashti, A. A., Asfar, S., Al-Zaid, N. and Dashti, H. M. 2012. Effect of low-calorie versus low-carbohydrate ketogenic diet in type 2 diabetes. *Nutrition,* 28, 1016-21.

Ingram, D. K., Anson, R. M., de Cabo, R., Mamczarz, J., Zhu, M., Mattison, J., Lane, M. A. and Roth, G. S. 2004. Development of calorie restriction mimetics as a prolongevity strategy. *Ann N Y Acad Sci,* 1019, 412-23.

Ingram, D. K., Roth, G. S., Lane, M. A., Ottinger, M. A., Zou, S., de Cabo, R. and Mattison, J. A. 2006. The potential for dietary restriction to increase longevity in humans: extrapolation from monkey studies. *Biogerontology,* 7, 143-8.

Ishii, N., Senoo-Matsuda, N., Miyake, K., Yasuda, K., Ishii, T., Hartman, P. S. and Furukawa, S. 2004. Coenzyme Q10 can prolong C. elegans lifespan by lowering oxidative stress. *Mech Ageing Dev,* 125, 41-6.

Itoh, K., Tong, K. I. and Yamamoto, M. 2004. Molecular mechanism activating Nrf2-Keap1 pathway in regulation of adaptive response to electrophiles. *Free Radic Biol Med,* 36, 1208-13.

Itoh, K., Wakabayashi, N., Katoh, Y., Ishii, T., Igarashi, K., Engel, J. D. and Yamamoto, M. 1999. Keap1 represses nuclear activation of antioxidant responsive elements by Nrf2 through binding to the amino-terminal Neh2 domain. *Genes Dev,* 13, 76-86.

Iwasaki, K., Gleiser, C. A., Masoro, E. J., McMahan, C. A., Seo, E. J. and Yu, B. P. 1988. Influence of the restriction of individual dietary components on longevity and age-related disease of Fischer rats: the fat component and the mineral component. *J Gerontol,* 43, B13-21.

Jackson, M. J. 2008. Free radicals generated by contracting muscle: By-products of metabolism or key regulators of muscle function? *Free Radic Biol Med,* 44, 132-41.

Jaiswal, A. K. 2004. Nrf2 signaling in coordinated activation of antioxidant gene expression. *Free Radic Biol Med,* 36, 1199-207.

James, D. E., Kraegen, E. W. and Chisholm, D. J. 1984. Effect of exercise training on whole-body insulin sensitivity and responsiveness. *J Appl Physiol,* 56, 1217-22.

Jang, Y. C., Perez, V. I., Song, W., Lustgarten, M. S., Salmon, A. B., Mele, J., Qi, W., Liu, Y., Liang, H., Chaudhuri, A., Ikeno, Y., Epstein, C. J., Van Remmen, H. and Richardson, A. 2009. Overexpression of Mn superoxide dismutase does not increase life span in mice. *J Gerontol A Biol Sci Med Sci,* 64, 1114-25.

Jazwinski, S. M. 2005. The retrograde response links metabolism with stress responses, chromatin-dependent gene activation, and genome stability in yeast aging. *Gene,* 354, 22-7.

Ji, L. L., Gomez-Cabrera, M. C. and Vina, J. 2006. Exercise and hormesis: activation of cellular antioxidant signaling pathway. *Ann N Y Acad Sci,* 1067, 425-35.

Jia, K., Chen, D. and Riddle, D. L. 2004. The TOR pathway interacts with the insulin signaling pathway to regulate C. elegans larval development, metabolism and life span. *Development,* 131, 3897-906.

Johnson, T. E., de Castro, E., Hegi de Castro, S., Cypser, J., Henderson, S. and Tedesco, P. 2001. Relationship between increased longevity and stress resistance as assessed through gerontogene mutations in Caenorhabditis elegans. *Exp Gerontol,* 36, 1609-17.

Kaeberlein, M. and Kapahi, P. 2009. The hypoxic response and aging. *Cell Cycle,* 8, 2324.

Kaeberlein, M., Kirkland, K. T., Fields, S. and Kennedy, B. K. 2004. Sir2-independent life span extension by calorie restriction in yeast. *PLoS Biol,* 2, E296.

Kaeberlein, M., McVey, M. and Guarente, L. 1999. The SIR2/3/4 complex and SIR2 alone promote longevity in Saccharomyces cerevisiae by two different mechanisms. *Genes Dev,* 13, 2570-80.

Kaeberlein, M., Powers, R. W., 3rd, Steffen, K. K., Westman, E. A., Hu, D., Dang, N., Kerr, E. O., Kirkland, K. T., Fields, S. and Kennedy, B. K. 2005. Regulation of yeast replicative life span by TOR and Sch9 in response to nutrients. *Science,* 310, 1193-6.

Kaelin, W. G., Jr. 2002. Molecular basis of the VHL hereditary cancer syndrome. *Nat Rev Cancer,* 2, 673-82.

Kahn, C. R. 1994. Banting Lecture: Insulin action, diabetogenes, and the cause of type II diabetes. *Diabetes,* 43, 1066-84.

Kanfi, Y., Naiman, S., Amir, G., Peshti, V., Zinman, G., Nahum, L., Bar-Joseph, Z. and Cohen, H. Y. 2012. The sirtuin SIRT6 regulates lifespan in male mice. *Nature,* 483, 218-21.

326

Mitochondrial Hormesis and Lifespan

Kang, C., O'Moore, K. M., Dickman, J. R. and Ji, L. L. 2009. Exercise activation of muscle peroxisome proliferator-activated receptor-gamma coactivator-1alpha signaling is redox sensitive. *Free Radic Biol Med,* 47, 1394-400.

Kannel, W. B. and McGee, D. L. 1979. Diabetes and cardiovascular risk factors: the Framingham study. *Circulation,* 59, 8-13.

Kapahi, P., Zid, B. M., Harper, T., Koslover, D., Sapin, V. and Benzer, S. 2004. Regulation of lifespan in Drosophila by modulation of genes in the TOR signaling pathway. *Curr Biol,* 14, 885-90.

Kappeler, L., De Magalhaes Filho, C. M., Dupont, J., Leneuve, P., Cervera, P., Perin, L., Loudes, C., Blaise, A., Klein, R., Epelbaum, J., Le Bouc, Y. and Holzenberger, M. 2008. Brain IGF-1 receptors control mammalian growth and lifespan through a neuroendocrine mechanism. *PLoS Biol,* 6, e254.

Kataja-Tuomola, M., Sundell, J. R., Mannisto, S., Virtanen, M. J., Kontto, J., Albanes, D. and Virtamo, J. 2008. Effect of alpha-tocopherol and beta-carotene supplementation on the incidence of type 2 diabetes. *Diabetologia,* 51, 47-53.

Katic, M., Kennedy, A. R., Leykin, I., Norris, A., McGettrick, A., Gesta, S., Russell, S. J., Bluher, M., Maratos-Flier, E. and Kahn, C. R. 2007. Mitochondrial gene expression and increased oxidative metabolism: role in increased lifespan of fat-specific insulin receptor knock-out mice. *Aging Cell,* 6, 827-39.

Katsiki, N. and Manes, C. 2009. Is there a role for supplemented antioxidants in the prevention of atherosclerosis? *Clin Nutr,* 28, 3-9.

Keipert, S., Voigt, A. and Klaus, S. 2011. Dietary effects on body composition, glucose metabolism, and longevity are modulated by skeletal muscle mitochondrial uncoupling in mice. *Aging Cell,* 10, 122-36.

Kemp, B. E., Stapleton, D., Campbell, D. J., Chen, Z. P., Murthy, S., Walter, M., Gupta, A., Adams, J. J., Katsis, F., van Denderen, B., Jennings, I. G., Iseli, T., Michell, B. J. and Witters, L. A. 2003. AMP-activated protein kinase, super metabolic regulator. *Biochem Soc Trans,* 31, 162-8.

Kenyon, C. 2005. The plasticity of aging: insights from long-lived mutants. *Cell,* 120, 449-60.

Kenyon, C., Chang, J., Gensch, E., Rudner, A. and Tabtiang, R. 1993. A C. elegans mutant that lives twice as long as wild type. *Nature,* 366, 461-4.

Kenyon, C. J. 2010. The genetics of aging. *Nature,* 464, 504-512.

Keren, G. and Epstein, Y. 1980. The effect of high dosage vitamin C intake on aerobic and anaerobic capacity. *J Sports Med Phys Fitness,* 20, 145-8.

Kharade, S. V., Mittal, N., Das, S. P., Sinha, P. and Roy, N. 2005. Mrg19 depletion increases S. cerevisiae lifespan by augmenting ROS defence. *FEBS Lett,* 579, 6809-13.

Khassaf, M., McArdle, A., Esanu, C., Vasilaki, A., McArdle, F., Griffiths, R. D., Brodie, D. A. and Jackson, M. J. 2003. Effect of vitamin C supplements on antioxidant defence and stress proteins in human lymphocytes and skeletal muscle. *J Physiol,* 549, 645-52.

Kim, H. S., Patel, K., Muldoon-Jacobs, K., Bisht, K. S., Aykin-Burns, N., Pennington, J. D., van der Meer, R., Nguyen, P., Savage, J., Owens, K. M., Vassilopoulos, A., Ozden, O., Park, S. H., Singh, K. K., Abdulkadir, S. A., Spitz, D. R., Deng, C. X. and Gius, D. 2010. SIRT3 is a mitochondria-localized tumor suppressor required for maintenance of mitochondrial integrity and metabolism during stress. *Cancer Cell,* 17, 41-52.

Kim, J., Takahashi, M., Shimizu, T., Shirasawa, T., Kajita, M., Kanayama, A. and Miyamoto, Y. 2008. Effects of a potent antioxidant, platinum nanoparticle, on the lifespan of Caenorhabditis elegans. *Mech Ageing Dev,* 129, 322-31.

Kim, J. D., McCarter, R. J. and Yu, B. P. 1996. Influence of age, exercise, and dietary restriction on oxidative stress in rats. *Aging (Milano),* 8, 123-9.

Kim, W. and Kaelin, W. G., Jr. 2003. The von Hippel-Lindau tumor suppressor protein: new insights into oxygen sensing and cancer. *Curr Opin Genet Dev,* 13, 55-60.

Kim, Y. and Sun, H. 2007. Functional genomic approach to identify novel genes involved in the regulation of oxidative stress resistance and animal lifespan. *Aging Cell,* 6, 489-503.

Kim, Y. C., Masutani, H., Yamaguchi, Y., Itoh, K., Yamamoto, M. and Yodoi, J. 2001. Hemin-induced activation of the thioredoxin gene by Nrf2. A differential regulation of the antioxidant responsive element by a switch of its binding factors. *J Biol Chem,* 276, 18399-406.

Kimura, K. D., Tissenbaum, H. A., Liu, Y. and Ruvkun, G. 1997. daf-2, an insulin receptor-like gene that regulates longevity and diapause in Caenorhabditis elegans. *Science,* 277, 942-6.

Klass, M. R. 1977. Aging in the nematode Caenorhabditis elegans: major biological and environmental factors influencing life span. *Mech Ageing Dev,* 6, 413-29.

327

M. Ristow and K. Schmeisser

Koizumi, A., Weindruch, R. and Walford, R. L. 1987. Influences of dietary restriction and age on liver enzyme activities and lipid peroxidation in mice. *J Nutr,* 117, 361-7.

Kops, G. J., Dansen, T. B., Polderman, P. E., Saarloos, I., Wirtz, K. W., Coffer, P. J., Huang, T. T., Bos, J. L., Medema, R. H. and Burgering, B. M. 2002. Forkhead transcription factor FOXO3a protects quiescent cells from oxidative stress. *Nature,* 419, 316-21.

Koren, A., Sauber, C., Sentjurc, M. and Schara, M. 1983. Free radicals in tetanic activity of isolated skeletal muscle. *Comp Biochem Physiol B,* 74, 633-5.

Kotani, K., Peroni, O. D., Minokoshi, Y., Boss, O. and Kahn, B. B. 2004. GLUT4 glucose transporter deficiency increases hepatic lipid production and peripheral lipid utilization. *J Clin Invest,* 114, 1666-75.

Kroemer, G., Marino, G. and Levine, B. 2010. Autophagy and the integrated stress response. *Mol Cell,* 40, 280-93.

Kulisz, A., Chen, N., Chandel, N. S., Shao, Z. and Schumacker, P. T. 2002. Mitochondrial ROS initiate phosphorylation of p38 MAP kinase during hypoxia in cardiomyocytes. *Am J Physiol Lung Cell Mol Physiol,* 282, L1324-9.

Lagiou, P., Sandin, S., Lof, M., Trichopoulos, D., Adami, H. O. and Weiderpass, E. 2012. Low carbohydrate-high protein diet and incidence of cardiovascular diseases in Swedish women: prospective cohort study. *Bmj,* 344, e4026.

Lakowski, B. and Hekimi, S. 1998. The genetics of caloric restriction in Caenorhabditis elegans. *Proc Natl Acad Sci U S A,* 95, 13091-6.

Lamming, D. W., Wood, J. G. and Sinclair, D. A. 2004. Small molecules that regulate lifespan: evidence for xenohormesis. *Mol Microbiol,* 53, 1003-9.

Lamming, D. W., Ye, L., Katajisto, P., Goncalves, M. D., Saitoh, M., Stevens, D. M., Davis, J. G., Salmon, A. B., Richardson, A., Ahima, R. S., Guertin, D. A., Sabatini, D. M. and Baur, J. A. 2012. Rapamycin-induced insulin resistance is mediated by mTORC2 loss and uncoupled from longevity. *Science,* 335, 1638-43.

Lane, M. A., Ingram, D. K. and Roth, G. S. 1998. 2-Deoxy-D-glucose feeding in rats mimics physiologic effects of calorie restriction. *J Anti-Aging Medicine,* 1, 327-336.

Lanza, I. R., Short, D. K., Short, K. R., Raghavakaimal, S., Basu, R., Joyner, M. J., McConnell, J. P. and Nair, K. S. 2008. Endurance exercise as a countermeasure for aging. *Diabetes,* 57, 2933-42.

Lapointe, J. and Hekimi, S. 2010. When a theory of aging ages badly. *Cell Mol Life Sci,* 67, 1-8.

Larson-Meyer, D. E., Heilbronn, L. K., Redman, L. M., Newcomer, B. R., Frisard, M. I., Anton, S., Smith, S. R., Alfonso, A. and Ravussin, E. 2006. Effect of calorie restriction with or without exercise on insulin sensitivity, beta-cell function, fat cell size, and ectopic lipid in overweight subjects. *Diabetes Care,* 29, 1337-44.

Larue, B. L. and Padilla, P. A. 2011. Environmental and Genetic Preconditioning for Long-Term Anoxia Responses Requires AMPK in Caenorhabditis elegans. *PLoS ONE,* 6, e16790.

Lee, J. H., Song, M. Y., Song, E. K., Kim, E. K., Moon, W. S., Han, M. K., Park, J. W., Kwon, K. B. and Park, B. H. 2009a. Overexpression of SIRT1 protects pancreatic beta-cells against cytokine toxicity by suppressing the nuclear factor-kappaB signaling pathway. *Diabetes,* 58, 344-51.

Lee, S. J., Hwang, A. B. and Kenyon, C. 2010. Inhibition of respiration extends C. elegans lifespan via reactive oxygen species that increase HIF-1 activity. *Curr Biol,* 20, 2131-6.

Lee, S. J., Murphy, C. T. and Kenyon, C. 2009b. Glucose shortens the life span of C. elegans by down-regulating DAF-16/FOXO activity and aquaporin gene expression. *Cell Metab,* 10, 379-91.

Lee, S. S., Lee, R. Y., Fraser, A. G., Kamath, R. S., Ahringer, J. and Ruvkun, G. 2003. A systematic RNAi screen identifies a critical role for mitochondria in C. elegans longevity. *Nat Genet,* 33, 40-8.

Leeuwenburgh, C. and Heinecke, J. W. 2001. Oxidative stress and antioxidants in exercise. *Curr Med Chem,* 8, 829-38.

Lefevre, M., Redman, L. M., Heilbronn, L. K., Smith, J. V., Martin, C. K., Rood, J. C., Greenway, F. L., Williamson, D. A., Smith, S. R. and Ravussin, E. 2009. Caloric restriction alone and with exercise improves CVD risk in healthy non-obese individuals. *Atherosclerosis,* 203, 206-13.

Leiser, S. F., Fletcher, M., Begun, A. and Kaeberlein, M. 2013. Life-Span Extension From Hypoxia in Caenorhabditis elegans Requires Both HIF-1 and DAF-16 and Is Antagonized by SKN-1. *J Gerontol A Biol Sci Med Sci.*

Leiser, S. F. and Kaeberlein, M. 2010. A role for SIRT1 in the hypoxic response. *Mol Cell,* 38, 779-80.

Leiser, S. F. and Miller, R. A. 2010. Nrf2 Signaling: a Mechanism for Cellular Stress Resistance in Long-lived Mice. *Mol Cell Biol,* 30, 871-84.

Mitochondrial Hormesis and Lifespan

Leto, S., Kokkonen, G. C. and Barrows, C. H., Jr. 1976. Dietary protein, life-span, and biochemical variables in female mice. *J Gerontol*, 31, 144-8.

Levine, B., Mizushima, N. and Virgin, H. W. 2011. Autophagy in immunity and inflammation. *Nature,* 469, 323-35.

Lewis, K. N., Mele, J., Hayes, J. D. and Buffenstein, R. 2010. Nrf2, a Guardian of Healthspan and Gatekeeper of Species Longevity. *Integr Comp Biol,* 50, 829-843.

Li, Z. and Srivastava, P. 2004. Heat-shock proteins. *Curr Protoc Immunol,* Appendix 1, Appendix 1T.

Lillig, C. H. and Holmgren, A. 2007. Thioredoxin and related molecules—from biology to health and disease. *Antioxid Redox Signal,* 9, 25-47.

Lim, J. H., Lee, Y. M., Chun, Y. S., Chen, J., Kim, J. E. and Park, J. W. 2010. Sirtuin 1 modulates cellular responses to hypoxia by deacetylating hypoxia-inducible factor 1alpha. *Mol Cell,* 38, 864-78.

Lin, J., Cook, N. R., Albert, C., Zaharris, E., Gaziano, J. M., Van Denburgh, M., Buring, J. E. and Manson, J. E. 2009. Vitamins C and E and beta-carotene supplementation and cancer risk: A randomized controlled trial. *J Natl Cancer Inst,* 101, 14-23.

Lin, S. J., Defossez, P. A. and Guarente, L. 2000. Requirement of NAD and SIR2 for life-span extension by calorie restriction in Saccharomyces cerevisiae. *Science,* 289, 2126-8.

Lin, S. J., Ford, E., Haigis, M., Liszt, G. and Guarente, L. 2004. Calorie restriction extends yeast life span by lowering the level of NADH. *Genes Dev,* 18, 12-6.

Lin, S. J., Kaeberlein, M., Andalis, A. A., Sturtz, L. A., Defossez, P. A., Culotta, V. C., Fink, G. R. and Guarente, L. 2002. Calorie restriction extends Saccharomyces cerevisiae lifespan by increasing respiration. *Nature,* 418, 344-8.

Lindquist, S. and Craig, E. A. 1988. The heat-shock proteins. *Annu Rev Genet,* 22, 631-77.

Lippman, S. M., Klein, E. A., Goodman, P. J., Lucia, M. S., Thompson, I. M., Ford, L. G., Parnes, H. L., Minasian, L. M., Gaziano, J. M., Hartline, J. A., Parsons, J. K., Bearden, J. D., 3rd, Crawford, E. D., Goodman, G. E., Claudio, J., Winquist, E., Cook, E. D., Karp, D. D., Walther, P., Lieber, M. M., Kristal, A. R., Darke, A. K., Arnold, K. B., Ganz, P. A., Santella, R. M., Albanes, D., Taylor, P. R., Probstfield, J. L., Jagpal, T. J., Crowley, J. J., Meyskens, F. L., Jr., Baker, L. H. and Coltman, C. A., Jr. 2009. Effect of Selenium and Vitamin E on Risk of Prostate Cancer and Other Cancers: The Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA,* 301, 39-51.

Lithgow, G. J. and Walker, G. A. 2002. Stress resistance as a determinate of C. elegans lifespan. *Mech Ageing Dev,* 123, 765-71.

Lithgow, G. J., White, T. M., Melov, S. and Johnson, T. E. 1995. Thermotolerance and extended lifespan conferred by single-gene mutations and induced by thermal stress. *Proc Natl Acad Sci U S A,* 92, 7540-4.

Liu, R. K. and Walford, R. L. 1966. Increased growth and lifespan with lowered ambient temperature in the annual fish, Cynolebis Adloffi. *Nature,* 212, 1277-1278.

Liu, S., Ajani, U., Chae, C., Hennekens, C., Buring, J. E. and Manson, J. E. 1999. Long-term beta-carotene supplementation and risk of type 2 diabetes mellitus: a randomized controlled trial. *JAMA,* 282, 1073-5.

Liu, X., Jiang, N., Hughes, B., Bigras, E., Shoubridge, E. and Hekimi, S. 2005. Evolutionary conservation of the clk-1-dependent mechanism of longevity: loss of mclk1 increases cellular fitness and lifespan in mice. *Genes Dev,* 19, 2424-34.

Loeb, J. 1908. Über den Temperaturkoeffizienten für die Lebensdauer kaltblütiger Tiere und über die Ursache des natürlichen Todes. *Arch. Ges. Physiol.,* 124, 411-426.

Loeb, J. and Northrop, J. H. 1916. Is There a Temperature Coefficient for the Duration of Life? *Proc Natl Acad Sci U S A,* 2, 456-7.

Lonn, E., Bosch, J., Yusuf, S., Sheridan, P., Pogue, J., Arnold, J. M., Ross, C., Arnold, A., Sleight, P., Probstfield, J. and Dagenais, G. R. 2005. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. *JAMA,* 293, 1338-47.

Lopez-Torres, M., Perez-Campo, R., Rojas, C., Cadenas, S. and Barja, G. 1993. Maximum life span in vertebrates: relationship with liver antioxidant enzymes, glutathione system, ascorbate, urate, sensitivity to peroxidation, true malondialdehyde, in vivo H2O2, and basal and maximum aerobic capacity. *Mech Ageing Dev,* 70, 177-99.

Laplante, M., Sabatini, D. M. 2012. mTOR Signaling in Growth Control and Disease. Cell, 149, 2; 274-93

M. Ristow and K. Schmeisser

Ludewig A.H., Izrayelit Y., Park D., Malik R. U., Zimmermann A., Mahanti P., Fox B. W., Bethke A., Doering F., Riddle D. L. and Schroeder F. C. 2013. Pheromone sensing regulates *Caenorhabditis elegans* lifespan and stress resistance via the deacetylase SIR-2.1. *Proc Natl Acad Sci U S A*, 110, 5522-5527.

Magwere, T., Goodall, S., Skepper, J., Mair, W., Brand, M. D. and Partridge, L. 2006. The effect of dietary restriction on mitochondrial protein density and flight muscle mitochondrial morphology in Drosophila. *J Gerontol A Biol Sci Med Sci*, 61, 36-47.

Mahlke, M. A., Cortez, L. A., Ortiz, M. A., Rodriguez, M., Uchida, K., Shigenaga, M. K., Lee, S., Zhang, Y., Tominaga, K., Hubbard, G. B. and Ikeno, Y. 2011. The anti-tumor effects of calorie restriction are correlated with reduced oxidative stress in ENU-induced gliomas. *Pathobiol Aging Age Relat Dis*, 1.

Mair, W. and Dillin, A. 2008. Aging and survival: the genetics of life span extension by dietary restriction. *Annu Rev Biochem*, 77, 727-54.

Mair, W., Piper, M. D. and Partridge, L. 2005. Calories do not explain extension of life span by dietary restriction in Drosophila. *PLoS Biol*, 3, e223.

Malloy, V. L., Krajcik, R. A., Bailey, S. J., Hristopoulos, G., Plummer, J. D. and Orentreich, N. 2006. Methionine restriction decreases visceral fat mass and preserves insulin action in aging male Fischer 344 rats independent of energy restriction. *Aging Cell*, 5, 305-14.

Manini, T. M., Everhart, J. E., Patel, K. V., Schoeller, D. A., Colbert, L. H., Visser, M., Tylavsky, F., Bauer, D. C., Goodpaster, B. H. and Harris, T. B. 2006. Daily activity energy expenditure and mortality among older adults. *JAMA*, 296, 171-9.

Mao, Z., Hine, C., Tian, X., Van Meter, M., Au, M., Vaidya, A., Seluanov, A. and Gorbunova, V. 2011. SIRT6 promotes DNA repair under stress by activating PARP1. *Science*, 332, 1443-6.

Marshall, R. J., Scott, K. C., Hill, R. C., Lewis, D. D., Sundstrom, D., Jones, G. L. and Harper, J. 2002. Supplemental vitamin C appears to slow racing greyhounds. *J Nutr*, 132, 1616S-21S.

Marzatico, F., Pansarasa, O., Bertorelli, L., Somenzini, L. and Della Valle, G. 1997. Blood free radical antioxidant enzymes and lipid peroxides following long-distance and lactacidemic performances in highly trained aerobic and sprint athletes. *J Sports Med Phys Fitness*, 37, 235-9.

Masoro, E. J. 1998. Hormesis and the antiaging action of dietary restriction. *Exp Gerontol*, 33, 61-6.

Masoro, E. J., Yu, B. P. and Bertrand, H. A. 1982. Action of food restriction in delaying the aging process. *Proc Natl Acad Sci U S A*, 79, 4239-41.

Mattison, J. A., Roth, G. S., Beasley, T. M., Tilmont, E. M., Handy, A. M., Herbert, R. L., Longo, D. L., Allison, D. B., Young, J. E., Bryant, M., Barnard, D., Ward, W. F., Qi, W., Ingram, D. K. and de Cabo, R. 2012. Impact of caloric restriction on health and survival in rhesus monkeys from the NIA study. *Nature*, 489, 318-21.

Mattson, M. P. 2008. Hormesis defined. *Ageing Res Rev*, 7, 1-7.

Maughan, R. J. 1999. Nutritional ergogenic aids and exercise performance. *Nutrition Research Reviews*, 12, 255-80.

McCarter, R., Mejia, W., Ikeno, Y., Monnier, V., Kewitt, K., Gibbs, M., McMahan, A. and Strong, R. 2007. Plasma glucose and the action of calorie restriction on aging. *J Gerontol A Biol Sci Med Sci*, 62, 1059-70.

McCay, C. M., Crowel, M. F. and Maynard, L. A. 1935. The effect of retarded growth upon the length of the life span and upon ultimate body size. *J Nutr*, 10, 63-79.

McElwee, J. J., Schuster, E., Blanc, E., Piper, M. D., Thomas, J. H., Patel, D. S., Selman, C., Withers, D. J., Thornton, J. M., Partridge, L. and Gems, D. 2007. Evolutionary conservation of regulated longevity assurance mechanisms. *Genome Biol*, 8, R132.

McElwee, J. J., Schuster, E., Blanc, E., Thomas, J. H. and Gems, D. 2004. Shared transcriptional signature in Caenorhabditis elegans Dauer larvae and long-lived daf-2 mutants implicates detoxification system in longevity assurance. *J Biol Chem*, 279, 44533-43.

Mehta, R., Steinkraus, K. A., Sutphin, G. L., Ramos, F. J., Shamieh, L. S., Huh, A., Davis, C., Chandler-Brown, D. and Kaeberlein, M. 2009. Proteasomal regulation of the hypoxic response modulates aging in C. elegans. *Science*, 324, 1196-8.

Melo, J. A. and Ruvkun, G. 2012. Inactivation of Conserved C. elegans Genes Engages Pathogen- and Xenobiotic-Associated Defenses. *Cell*, 149, 452-66.

Melov, S., Ravenscroft, J., Malik, S., Gill, M. S., Walker, D. W., Clayton, P. E., Wallace, D. C., Malfroy, B., Doctrow, S. R. and Lithgow, G. J. 2000. Extension of life-span with superoxide dismutase/catalase mimetics. *Science*, 289, 1567-9.

Mitochondrial Hormesis and Lifespan

Merksamer, P. I., Liu, Y., He, W., Hirschey, M. D., Chen, D. and Verdin, E. 2013. The sirtuins, oxidative stress and aging: an emerging link. *Aging (Albany NY)*, 5, 144-50.

Merrill, G. F., Kurth, E. J., Hardie, D. G. and Winder, W. W. 1997. AICA riboside increases AMP-activated protein kinase, fatty acid oxidation, and glucose uptake in rat muscle. *Am J Physiol*, 273, E1107-12.

Mesquita, A., Weinberger, M., Silva, A., Sampaio-Marques, B., Almeida, B., Leao, C., Costa, V., Rodrigues, F., Burhans, W. C. and Ludovico, P. 2010. Caloric restriction or catalase inactivation extends yeast chronological lifespan by inducing H2O2 and superoxide dismutase activity. *Proc Natl Acad Sci U S A*, 107, 15123-8.

Miller, D. L., Budde, M. W. and Roth, M. B. 2011. HIF-1 and SKN-1 Coordinate the Transcriptional Response to Hydrogen Sulfide in Caenorhabditis elegans. *PLoS ONE*, 6, e25476.

Miller, D. L. and Roth, M. B. 2007. Hydrogen sulfide increases thermotolerance and lifespan in Caenorhabditis elegans. *Proc Natl Acad Sci U S A*, 104, 20618-22.

Miller, R. A., Buehner, G., Chang, Y., Harper, J. M., Sigler, R. and Smith-Wheelock, M. 2005. Methionine-deficient diet extends mouse lifespan, slows immune and lens aging, alters glucose, T4, IGF-I and insulin levels, and increases hepatocyte MIF levels and stress resistance. *Aging Cell*, 4, 119-25.

Min, K. J. and Tatar, M. 2006. Restriction of amino acids extends lifespan in Drosophila melanogaster. *Mech Ageing Dev*, 127, 643-6.

Min, K. J., Yamamoto, R., Buch, S., Pankratz, M. and Tatar, M. 2008. Drosophila lifespan control by dietary restriction independent of insulin-like signaling. *Aging Cell*, 7, 199-206.

Minokoshi, Y., Alquier, T., Furukawa, N., Kim, Y. B., Lee, A., Xue, B., Mu, J., Foufelle, F., Ferre, P., Birnbaum, M. J., Stuck, B. J. and Kahn, B. B. 2004. AMP-kinase regulates food intake by responding to hormonal and nutrient signals in the hypothalamus. *Nature*, 428, 569-74.

Minor, R. K., Smith, D. L., Jr., Sossong, A. M., Kaushik, S., Poosala, S., Spangler, E. L., Roth, G. S., Lane, M., Allison, D. B., de Cabo, R., Ingram, D. K. and Mattison, J. A. 2010. Chronic ingestion of 2-deoxy-D-glucose induces cardiac vacuolization and increases mortality in rats. *Toxicol Appl Pharmacol*, 243, 332-9.

Mittler, R., Vanderauwera, S., Suzuki, N., Miller, G., Tognetti, V. B., Vandepoele, K., Gollery, M., Shulaev, V. and Van Breusegem, F. 2011. ROS signaling: the new wave? *Trends Plant Sci*, 16, 300-9.

Morimoto, H., Iwata, K., Ogonuki, N., Inoue, K., Atsuo, O., Kanatsu-Shinohara, M., Morimoto, T., Yabe-Nishimura, C. and Shinohara, T. 2013. ROS are required for mouse spermatogonial stem cell self-renewal. *Cell Stem Cell*, 12, 774-86.

Moskovitz, J., Bar-Noy, S., Williams, W. M., Requena, J., Berlett, B. S. and Stadtman, E. R. 2001. Methionine sulfoxide reductase (MsrA) is a regulator of antioxidant defense and lifespan in mammals. *Proc Natl Acad Sci U S A*, 98, 12920-5.

Mostoslavsky, R., Chua, K. F., Lombard, D. B., Pang, W. W., Fischer, M. R., Gellon, L., Liu, P., Mostoslavsky, G., Franco, S., Murphy, M. M., Mills, K. D., Patel, P., Hsu, J. T., Hong, A. L., Ford, E., Cheng, H. L., Kennedy, C., Nunez, N., Bronson, R., Frendewey, D., Auerbach, W., Valenzuela, D., Karow, M., Hottiger, M. O., Hursting, S., Barrett, J. C., Guarente, L., Mulligan, R., Demple, B., Yancopoulos, G. D. and Alt, F. W. 2006. Genomic instability and aging-like phenotype in the absence of mammalian SIRT6. *Cell*, 124, 315-29.

Motohashi, H. and Yamamoto, M. 2004. Nrf2-Keap1 defines a physiologically important stress response mechanism. *Trends Mol Med*, 10, 549-57.

Motta, M. C., Divecha, N., Lemieux, M., Kamel, C., Chen, D., Gu, W., Bultsma, Y., McBurney, M. and Guarente, L. 2004. Mammalian SIRT1 represses forkhead transcription factors. *Cell*, 116, 551-63.

Mouchiroud L., Houtkooper R. H., Moullan N., Katsyuba E., Ryu D., Canto C., Mottis A., Jo Y. S., Viswanathan M., Schoonjans K., Guarente L. and Auwerx J. 2013. The NAD(+)/Sirtuin Pathway Modulates Longevity through Activation of Mitochondrial UPR and FOXO Signaling. Cell, 154, 430-441.

Muller, F. L., Lustgarten, M. S., Jang, Y., Richardson, A. and Van Remmen, H. 2007. Trends in oxidative aging theories. *Free Radic Biol Med*, 43, 477-503.

Murphy, C. T., McCarroll, S. A., Bargmann, C. I., Fraser, A., Kamath, R. S., Ahringer, J., Li, H. and Kenyon, C. 2003. Genes that act downstream of DAF-16 to influence the lifespan of Caenorhabditis elegans. *Nature*, 424, 277-83.

331

M. Ristow and K. Schmeisser

Nadanaciva, S., Dykens, J. A., Bernal, A., Capaldi, R. A. and Will, Y. 2007. Mitochondrial impairment by PPAR agonists and statins identified via immunocaptured OXPHOS complex activities and respiration. *Toxicol Appl Pharmacol,* 223, 277-87.

Narbonne, P. and Roy, R. 2009. Caenorhabditis elegans dauers need LKB1/AMPK to ration lipid reserves and ensure long-term survival. *Nature,* 457, 210-4.

Nemoto, S. and Finkel, T. 2002. Redox regulation of forkhead proteins through a p66shc-dependent signaling pathway. *Science,* 295, 2450-2.

Niess, A. M., Dickhuth, H. H., Northoff, H. and Fehrenbach, E. 1999. Free radicals and oxidative stress in exercise—immunological aspects. *Exerc Immunol Rev,* 5, 22-56.

Nikolaidis, M. G. and Jamurtas, A. Z. 2009. Blood as a reactive species generator and redox status regulator during exercise. *Arch Biochem Biophys,* 490, 77-84.

Nisoli, E., Tonello, C., Cardile, A., Cozzi, V., Bracale, R., Tedesco, L., Falcone, S., Valerio, A., Cantoni, O., Clementi, E., Moncada, S. and Carruba, M. O. 2005. Calorie restriction promotes mitochondrial biogenesis by inducing the expression of eNOS. *Science,* 310, 314-7.

Nobels, F., van Gaal, L. and de Leeuw, I. 1989. Weight reduction with a high protein, low carbohydrate, calorie-restricted diet: effects on blood pressure, glucose and insulin levels. *Neth J Med,* 35, 295-302.

Nordmann, A. J., Nordmann, A., Briel, M., Keller, U., Yancy, W. S., Jr., Brehm, B. J. and Bucher, H. C. 2006. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. *Arch Intern Med,* 166, 285-93.

Oberdoerffer, P., Michan, S., McVay, M., Mostoslavsky, R., Vann, J., Park, S. K., Hartlerode, A., Stegmuller, J., Hafner, A., Loerch, P., Wright, S. M., Mills, K. D., Bonni, A., Yankner, B. A., Scully, R., Prolla, T. A., Alt, F. W. and Sinclair, D. A. 2008. SIRT1 redistribution on chromatin promotes genomic stability but alters gene expression during aging. *Cell,* 135, 907-18.

Omenn, G. S., Goodman, G. E., Thornquist, M. D., Balmes, J., Cullen, M. R., Glass, A., Keogh, J. P., Meyskens, F. L., Valanis, B., Williams, J. H., Barnhart, S. and Hammar, S. 1996. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med,* 334, 1150-5.

Onken, B. and Driscoll, M. 2010. Metformin induces a dietary restriction-like state and the oxidative stress response to extend C. elegans Healthspan via AMPK, LKB1, and SKN-1. *PLoS ONE,* 5, e8758.

Orr, W. C. and Sohal, R. S. 1994. Extension of life-span by overexpression of superoxide dismutase and catalase in Drosophila melanogaster. *Science,* 263, 1128-30.

Owusu-Ansah, E. and Banerjee, U. 2009. Reactive oxygen species prime Drosophila haematopoietic progenitors for differentiation. *Nature,* 461, 537-41.

Owusu-Ansah, E., Yavari, A., Mandal, S. and Banerjee, U. 2008. Distinct mitochondrial retrograde signals control the G1-S cell cycle checkpoint. *Nat Genet,* 40, 356-61.

Ozden, O., Park, S. H., Kim, H. S., Jiang, H., Coleman, M. C., Spitz, D. R. and Gius, D. 2011. Acetylation of MnSOD directs enzymatic activity responding to cellular nutrient status or oxidative stress. *Aging (Albany NY),* 3, 102-7.

Page, M. M., Richardson, J., Wiens, B. E., Tiedtke, E., Peters, C. W., Faure, P. A., Burness, G. and Stuart, J. A. 2010. Antioxidant enzyme activities are not broadly correlated with longevity in 14 vertebrate endotherm species. *Age (Dordr),* 32, 255-70.

Page, M. M. and Stuart, J. A. 2012. Activities of DNA base excision repair enzymes in liver and brain correlate with body mass, but not lifespan. *Age (Dordr),* 34, 1195-209.

Page, M. M., Withers, D. J. and Selman, C. 2013. Longevity of insulin receptor substrate1 null mice is not associated with increased basal antioxidant protection or reduced oxidative damage. *Age (Dordr),* 35, 647-58.

Pan, D. A. and Hardie, D. G. 2002. A homologue of AMP-activated protein kinase in Drosophila melanogaster is sensitive to AMP and is activated by ATP depletion. *Biochem J,* 367, 179-86.

Pan, Y. 2011. Mitochondria, reactive oxygen species, and chronological aging: A message from yeast. *Exp Gerontol,* 46, 847-52.

Pan, Y., Nishida, Y., Wang, M. and Verdin, E. 2012. Metabolic Regulation, Mitochondria and the Life-Prolonging Effect of Rapamycin: A Mini-Review. *Gerontology,* 58, 524-30.

Pan, Y., Schroeder, E. A., Ocampo, A., Barrientos, A. and Shadel, G. S. 2011. Regulation of yeast chronological life span by TORC1 via adaptive mitochondrial ROS signaling. *Cell Metab,* 13, 668-78.

Mitochondrial Hormesis and Lifespan

Pan, Y. and Shadel, G. S. 2009. Extension of chronological life span by reduced TOR signaling requires down-regulation of Sch9p and involves increased mitochondrial OXPHOS complex density. *Aging (Albany NY),* 1, 131-45.

Panowski, S. H., Wolff, S., Aguilaniu, H., Durieux, J. and Dillin, A. 2007. PHA-4/Foxa mediates diet-restriction-induced longevity of C. elegans. *Nature,* 447, 550-5.

Papaiahgari, S., Zhang, Q., Kleeberger, S. R., Cho, H. Y. and Reddy, S. P. 2006. Hyperoxia stimulates an Nrf2-ARE transcriptional response via ROS-EGFR-PI3K-Akt/ERK MAP kinase signaling in pulmonary epithelial cells. *Antioxid Redox Signal,* 8, 43-52.

Papandreou, I., Cairns, R. A., Fontana, L., Lim, A. L. and Denko, N. C. 2006. HIF-1 mediates adaptation to hypoxia by actively downregulating mitochondrial oxygen consumption. *Cell Metab,* 3, 187-97.

Pardo, P. S., Mohamed, J. S., Lopez, M. A. and Boriek, A. M. 2011. Induction of Sirt1 by mechanical stretch of skeletal muscle through the early response factor EGR1 triggers an antioxidative response. *J Biol Chem,* 286, 2559-66.

Parikh, V. S., Morgan, M. M., Scott, R., Clements, L. S. and Butow, R. A. 1987. The mitochondrial genotype can influence nuclear gene expression in yeast. *Science,* 235, 576-80.

Park, S., Park, N. Y., Valacchi, G. and Lim, Y. 2012. Calorie restriction with a high-fat diet effectively attenuated inflammatory response and oxidative stress-related markers in obese tissues of the high diet fed rats. *Mediators Inflamm,* 2012, 984643.

Parkes, T. L., Elia, A. J., Dickinson, D., Hilliker, A. J., Phillips, J. P. and Boulianne, G. L. 1998. Extension of Drosophila lifespan by overexpression of human SOD1 in motorneurons. *Nat Genet,* 19, 171-4.

Pawlikowska, L., Hu, D., Huntsman, S., Sung, A., Chu, C., Chen, J., Joyner, A., Schork, N. J., Hsueh, W. C., Reiner, A. P., Psaty, B. M., Atzmon, G., Barzilai, N., Cummings, S. R., Browner, W. S., Kwok, P. Y. and Ziv, E. 2009. Association of common genetic variation in the insulin/IGF1 signaling pathway with human longevity. *Aging Cell,* 8, 460-72.

Pearl, R. 1928. The rate of living. Being an account of some experimental studies on the biology of life duration. Pp. 183-185. New York, Alfred Knopf.

Pendergrass, W. R., Li, Y., Jiang, D. and Wolf, N. S. 1993. Decrease in cellular replicative potential in "giant" mice transfected with the bovine growth hormone gene correlates to shortened life span. *J Cell Physiol,* 156, 96-103.

Perez, V. I., Bokov, A., Van Remmen, H., Mele, J., Ran, Q., Ikeno, Y. and Richardson, A. 2009. Is the oxidative stress theory of aging dead? *Biochim Biophys Acta,* 1790, 1005-14.

Perez, V. I., Cortez, L. A., Lew, C. M., Rodriguez, M., Webb, C. R., Van Remmen, H., Chaudhuri, A., Qi, W., Lee, S., Bokov, A., Fok, W., Jones, D., Richardson, A., Yodoi, J., Zhang, Y., Tominaga, K., Hubbard, G. B. and Ikeno, Y. 2011. Thioredoxin 1 Overexpression Extends Mainly the Earlier Part of Life Span in Mice. *J Gerontol A Biol Sci Med Sci,* 66, 1286-99.

Perrone, C. E., Malloy, V. L., Orentreich, D. S. and Orentreich, N. 2013. Metabolic adaptations to methionine restriction that benefit health and lifespan in rodents. *Exp Gerontol,* 48, 654-60.

Perrone, C. E., Mattocks, D. A., Jarvis-Morar, M., Plummer, J. D. and Orentreich, N. 2010. Methionine restriction effects on mitochondrial biogenesis and aerobic capacity in white adipose tissue, liver, and skeletal muscle of F344 rats. *Metabolism,* 59, 1000-11.

Phillips, J. P., Campbell, S. D., Michaud, D., Charbonneau, M. and Hilliker, A. J. 1989. Null mutation of copper/zinc superoxide dismutase in Drosophila confers hypersensitivity to paraquat and reduced longevity. *Proc Natl Acad Sci U S A,* 86, 2761-5.

Pieri, C., Falasca, M., Marcheselli, F., Moroni, F., Recchioni, R., Marmocchi, F. and Lupidi, G. 1992. Food restriction in female Wistar rats: V. Lipid peroxidation and antioxidant enzymes in the liver. *Arch Gerontol Geriatr,* 14, 93-9.

Piper, M. D., Mair, W. and Partridge, L. 2005a. Counting the calories: the role of specific nutrients in extension of life span by food restriction. *J Gerontol A Biol Sci Med Sci,* 60, 549-55.

Piper, M. D., Skorupa, D. and Partridge, L. 2005b. Diet, metabolism and lifespan in Drosophila. *Exp Gerontol,* 40, 857-62.

Piper, P. W., Harris, N. L. and MacLean, M. 2006. Preadaptation to efficient respiratory maintenance is essential both for maximal longevity and the retention of replicative potential in chronologically ageing yeast. *Mech Ageing Dev,* 127, 733-40.

Polak, P., Cybulski, N., Feige, J. N., Auwerx, J., Ruegg, M. A. and Hall, M. N. 2008. Adipose-specific knockout of raptor results in lean mice with enhanced mitochondrial respiration. *Cell Metab,* 8, 399-410.

M. Ristow and K. Schmeisser

Powers, R. W., 3rd, Kaeberlein, M., Caldwell, S. D., Kennedy, B. K. and Fields, S. 2006. Extension of chronological life span in yeast by decreased TOR pathway signaling. *Genes Dev,* 20, 174-84.

Powers, S. K. and Jackson, M. J. 2008. Exercise-induced oxidative stress: cellular mechanisms and impact on muscle force production. *Physiol Rev,* 88, 1243-76.

Powers, S. K. and Lennon, S. L. 1999. Analysis of cellular responses to free radicals: focus on exercise and skeletal muscle. *Proc Nutr Soc,* 58, 1025-33.

Powers, S. K., Nelson, W. B. and Hudson, M. B. 2011. Exercise-induced oxidative stress in humans: cause and consequences. *Free Radic Biol Med,* 51, 942-50.

Pua, H. H. and He, Y. W. 2009. Mitophagy in the little lymphocytes: an essential role for autophagy in mitochondrial clearance in T lymphocytes. *Autophagy,* 5, 745-6.

Puntschart, A., Vogt, M., Widmer, H. R., Hoppeler, H. and Billeter, R. 1996. Hsp70 expression in human skeletal muscle after exercise. *Acta Physiol Scand,* 157, 411-7.

Qiu, X., Brown, K., Hirschey, M. D., Verdin, E. and Chen, D. 2010. Calorie restriction reduces oxidative stress by SIRT3-mediated SOD2 activation. *Cell Metab,* 12, 662-7.

Quarrie, J. K. and Riabowol, K. T. 2004. Murine models of life span extension. *Sci Aging Knowledge Environ,* 2004, re5.

Quick, K. L., Ali, S. S., Arch, R., Xiong, C., Wozniak, D. and Dugan, L. L. 2008. A carboxyfullerene SOD mimetic improves cognition and extends the lifespan of mice. *Neurobiol Aging,* 29, 117-28.

Quintanilha, A. T. 1984. Effects of physical exercise and/or vitamin E on tissue oxidative metabolism. *Biochem Soc Trans,* 12, 403-4.

Radak, Z., Apor, P., Pucsok, J., Berkes, I., Ogonovszky, H., Pavlik, G., Nakamoto, H. and Goto, S. 2003. Marathon running alters the DNA base excision repair in human skeletal muscle. *Life Sci,* 72, 1627-33.

Radak, Z., Chung, H. Y. and Goto, S. 2005. Exercise and hormesis: oxidative stress-related adaptation for successful aging. *Biogerontology,* 6, 71-5.

Radak, Z., Chung, H. Y., Koltai, E., Taylor, A. W. and Goto, S. 2008. Exercise, oxidative stress and hormesis. *Ageing Res Rev,* 7, 34-42.

Radak, Z., Kaneko, T., Tahara, S., Nakamoto, H., Ohno, H., Sasvari, M., Nyakas, C. and Goto, S. 1999. The effect of exercise training on oxidative damage of lipids, proteins, and DNA in rat skeletal muscle: evidence for beneficial outcomes. *Free Radic Biol Med,* 27, 69-74.

Radak, Z., Sasvari, M., Nyakas, C., Pucsok, J., Nakamoto, H. and Goto, S. 2000. Exercise preconditioning against hydrogen peroxide-induced oxidative damage in proteins of rat myocardium. *Arch Biochem Biophys,* 376, 248-51.

Rao, G., Xia, E., Nadakavukaren, M. J. and Richardson, A. 1990. Effect of dietary restriction on the age-dependent changes in the expression of antioxidant enzymes in rat liver. *J Nutr,* 120, 602-9.

Rattan, S. I. 2008. Hormesis in aging. *Ageing Res Rev,* 7, 63-78.

Rattan, S. I. and Demirovic, D. 2010. Hormesis as a Mechanism for the Anti-Aging Effects of Calorie Restriction. In: Calorie Restriction, Aging and Longevity (edited by Everitt, A. V., Rattan, S. I. S., Couteur, D. G. and Cabo, R. D.). Pp. 233-245. Springer Netherlands.

Rautalahti, M. T., Virtamo, J. R., Taylor, P. R., Heinonen, O. P., Albanes, D., Haukka, J. K., Edwards, B. K., Karkkainen, P. A., Stolzenberg-Solomon, R. Z. and Huttunen, J. 1999. The effects of supplementation with alpha-tocopherol and beta-carotene on the incidence and mortality of carcinoma of the pancreas in a randomized, controlled trial. *Cancer,* 86, 37-42.

Raynes, R., Leckey, B. D., Jr., Nguyen, K. and Westerheide, S. D. 2012. Heat shock and caloric restriction have a synergistic effect on the heat shock response in a sir2.1-dependent manner in Caenorhabditis elegans. *J Biol Chem,* 287, 29045-53.

Rea, S. L., Ventura, N. and Johnson, T. E. 2007. Relationship between mitochondrial electron transport chain dysfunction, development, and life extension in caenorhabditis elegans. *PLoS Biol,* 5, e259.

Rea, S. L., Wu, D., Cypser, J. R., Vaupel, J. W. and Johnson, T. E. 2005. A stress-sensitive reporter predicts longevity in isogenic populations of Caenorhabditis elegans. *Nat Genet,* 37, 894-8.

Rhee, S. G., Bae, Y. S., Lee, S. R. and Kwon, J. 2000. Hydrogen peroxide: a key messenger that modulates protein phosphorylation through cysteine oxidation. *Sci STKE,* 2000, pe1.

Richie, J. P., Jr., Leutzinger, Y., Parthasarathy, S., Malloy, V., Orentreich, N. and Zimmerman, J. A. 1994. Methionine restriction increases blood glutathione and longevity in F344 rats. *FASEB J,* 8, 1302-7.

Rippe, C., Lesniewski, L., Connell, M., LaRocca, T., Donato, A. and Seals, D. 2010. Short-term calorie restriction reverses vascular endothelial dysfunction in old mice by increasing nitric oxide and reducing oxidative stress. *Aging Cell,* 9, 304-12.

Ristow, M. 2006. Oxidative metabolism in cancer growth. *Curr Opin Clin Nutr Metabol,* 9, 339-345.

Ristow, M., Zarse, K., Oberbach, A., Klöting, N., Birringer, M., Kiehntopf, M., Stumvoll, M., Kahn, C. R. and Blüher, M. 2009. Antioxidants prevent health-promoting effects of physical exercise in humans. *Proc Nat Acad Sci,* 106, 8665-70.

Robida-Stubbs, S., Glover-Cutter, K., Lamming, D. W., Mizunuma, M., Narasimhan, S. D., Neumann-Haefelin, E., Sabatini, D. M. and Blackwell, T. K. 2012. TOR Signaling and Rapamycin Influence Longevity by Regulating SKN-1/Nrf and DAF-16/FoxO. *Cell Metab,* 15, 713-24.

Rodgers, J. T., Lerin, C., Haas, W., Gygi, S. P., Spiegelman, B. M. and Puigserver, P. 2005. Nutrient control of glucose homeostasis through a complex of PGC-1alpha and SIRT1. *Nature,* 434, 113-8.

Rogina, B. and Helfand, S. L. 2004. Sir2 mediates longevity in the fly through a pathway related to calorie restriction. *Proc Natl Acad Sci U S A,* 101, 15998-16003. .

Romero-Ramirez, L., Cao, H., Nelson, D., Hammond, E., Lee, A. H., Yoshida, H., Mori, K., Glimcher, L. H., Denko, N. C., Giaccia, A. J., Le, Q. T. and Koong, A. C. 2004. XBP1 is essential for survival under hypoxic conditions and is required for tumor growth. *Cancer Res,* 64, 5943-7.

Roux, A. E., Leroux, A., Alaamery, M. A., Hoffman, C. S., Chartrand, P., Ferbeyre, G. and Rokeach, L. A. 2009. Pro-aging effects of glucose signaling through a G protein-coupled glucose receptor in fission yeast. *PLoS Genet,* 5, e1000408.

Ruan, H., Tang, X. D., Chen, M. L., Joiner, M. L., Sun, G., Brot, N., Weissbach, H., Heinemann, S. H., Iverson, L., Wu, C. F. and Hoshi, T. 2002. High-quality life extension by the enzyme peptide methionine sulfoxide reductase. *Proc Natl Acad Sci U S A,* 99, 2748-53.

Rubiolo, J. A., Mithieux, G. and Vega, F. V. 2008. Resveratrol protects primary rat hepatocytes against oxidative stress damage: activation of the Nrf2 transcription factor and augmented activities of antioxidant enzymes. *Eur J Pharmacol,* 591, 66-72.

Rubner, M. 1908. III. Das Wachstumsproblem und die Lebensdauer des Menschen und einiger Säugetiere vom energetischen Standpunkt aus betrachtet. In: Das Problem der Lebensdauer und seine Beziehungen zum Wachstum und der Ernährung (edited by Rubner, M.). Pp. 127-208. Munich and Berlin: R. Oldenbourg.

Rushmore, T. H., Morton, M. R. and Pickett, C. B. 1991. The antioxidant responsive element. Activation by oxidative stress and identification of the DNA consensus sequence required for functional activity. *J Biol Chem,* 266, 11632-9.

Russell, S. J. and Kahn, C. R. 2007. Endocrine regulation of ageing. *Nat Rev Mol Cell Biol,* 8, 681-91.

Ryan, A. S., Ortmeyer, H. K. and Sorkin, J. D. 2012. Exercise with calorie restriction improves insulin sensitivity and glycogen synthase activity in obese postmenopausal women with impaired glucose tolerance. *Am J Physiol Endocrinol Metab,* 302, E145-52.

Ryan, M. C., Abbasi, F., Lamendola, C., Carter, S. and McLaughlin, T. L. 2007. Serum alanine aminotransferase levels decrease further with carbohydrate than fat restriction in insulin-resistant adults. *Diabetes Care,* 30, 1075-80.

Sacco, M., Pellegrini, F., Roncaglioni, M. C., Avanzini, F., Tognoni, G. and Nicolucci, A. 2003. Primary prevention of cardiovascular events with low-dose aspirin and vitamin E in type 2 diabetic patients: results of the Primary Prevention Project (PPP) trial. *Diabetes Care,* 26, 3264-72.

Salt, I. P., Johnson, G., Ashcroft, S. J. and Hardie, D. G. 1998. AMP-activated protein kinase is activated by low glucose in cell lines derived from pancreatic beta cells, and may regulate insulin release. *Biochem J,* 335 (Pt 3), 533-9.

Salway, K. D., Page, M. M., Faure, P. A., Burness, G. and Stuart, J. A. 2011. Enhanced protein repair and recycling are not correlated with longevity in 15 vertebrate endotherm species. *Age (Dordr),* 33, 33-47.

Sanchez-Roman, I., Gomez, A., Perez, I., Sanchez, C., Suarez, H., Naudi, A., Jove, M., Lopez-Torres, M., Pamplona, R. and Barja, G. 2012. Effects of aging and methionine restriction applied at old age on ROS generation and oxidative damage in rat liver mitochondria. *Biogerontology,* 13, 399-411.

Sanz, A., Caro, P., Ayala, V., Portero-Otin, M., Pamplona, R. and Barja, G. 2006. Methionine restriction decreases mitochondrial oxygen radical generation and leak as well as oxidative damage to mitochondrial DNA and proteins. *FASEB J,* 20, 1064-73.

M. Ristow and K. Schmeisser

Sanz, A., Fernandez-Ayala, D. J., Stefanatos, R. K. and Jacobs, H. T. 2010. Mitochondrial ROS production correlates with, but does not directly regulate lifespan in drosophila. *Aging (Albany NY),* 2, 200-3.

Sanz, A. and Stefanatos, R. K. 2008. The mitochondrial free radical theory of aging: a critical view. *Curr Aging Sci,* 1, 10-21.

Schipper, H. M. 2004. Brain iron deposition and the free radical-mitochondrial theory of ageing. *Ageing Res Rev,* 3, 265-301.

Schlotterer, A., Kukudov, G., Bozorgmehr, F., Hutter, H., Du, X., Oikonomou, D., Ibrahim, Y., Pfisterer, F., Rabbani, N., Thornalley, P., Sayed, A., Fleming, T., Humpert, P., Schwenger, V., Zeier, M., Hamann, A., Stern, D., Brownlee, M., Bierhaus, A., Nawroth, P. and Morcos, M. 2009. C. elegans as model for the study of high glucose mediated lifespan reduction. *Diabetes,* 58, 2450-6.

Schmeisser, K., Mansfeld, J., Kuhlow, D., Weimer, S., Priebe, S., Heiland, I., Birringer, M., Groth, M., Segref, A., Kanfi, Y., Price, N. L., Schmeisser, S., Schuster, S., Pfeiffer, A. F., Guthke, R., Platzer, M., Hoppe, T., Cohen, H. Y., Zarse, K., Sinclair, D. A. and Ristow, M. 2013a. Role of sirtuins in lifespan regulation is linked to methylation of nicotinamide. *Nat Chem Biol,* 9, 693-700.

Schmeisser, S., Priebe, S., Groth, M., Monajembashi, S., Hemmerich, P., Guthke, R., Platzer, M. and Ristow, M. 2013b. Neuronal ROS Signaling Rather Than AMPK/Sirtuin-Mediated Energy Sensing Links Dietary Restriction to Lifespan Extension. *Mol Metab,* 2, 92-102.

Schulz, T. J., Zarse, K., Voigt, A., Urban, N., Birringer, M. and Ristow, M. 2007. Glucose restriction extends Caenorhabditis elegans life span by inducing mitochondrial respiration and increasing oxidative stress. *Cell Metab,* 6, 280-293.

Selman, C., Lingard, S., Choudhury, A. I., Batterham, R. L., Claret, M., Clements, M., Ramadani, F., Okkenhaug, K., Schuster, E., Blanc, E., Piper, M. D., Al-Qassab, H., Speakman, J. R., Carmignac, D., Robinson, I. C., Thornton, J. M., Gems, D., Partridge, L. and Withers, D. J. 2008. Evidence for lifespan extension and delayed age-related biomarkers in insulin receptor substrate 1 null mice. *FASEB J,* 22, 807-18.

Semenza, G. L. 2010. Defining the role of hypoxia-inducible factor 1 in cancer biology and therapeutics. *Oncogene,* 29, 625-34.

Semenza, G. L. 2011. Hypoxia-inducible factor 1: Regulator of mitochondrial metabolism and mediator of ischemic preconditioning. *Biochim Biophys Acta,* 1813, 1263-8.

Semenza, G. L. 2012. Hypoxia-inducible factors in physiology and medicine. *Cell,* 148, 399-408.

Semenza, G. L., Roth, P. H., Fang, H. M. and Wang, G. L. 1994. Transcriptional regulation of genes encoding glycolytic enzymes by hypoxia-inducible factor 1. *J Biol Chem,* 269, 23757-63.

Semsei, I., Rao, G. and Richardson, A. 1989. Changes in the expression of superoxide dismutase and catalase as a function of age and dietary restriction. *Biochem Biophys Res Commun,* 164, 620-5.

Sena, L. A. and Chandel, N. S. 2012. Physiological roles of mitochondrial reactive oxygen species. *Mol Cell,* 48, 158-67.

Sendoel, A., Kohler, I., Fellmann, C., Lowe, S. W. and Hengartner, M. O. 2010. HIF-1 antagonizes p53-mediated apoptosis through a secreted neuronal tyrosinase. *Nature,* 465, 577-83.

Sengupta, S., Peterson, T. R., Laplante, M., Oh, S. and Sabatini, D. M. 2010. mTORC1 controls fasting-induced ketogenesis and its modulation by ageing. *Nature,* 468, 1100-4.

Sesso, H. D., Buring, J. E., Christen, W. G., Kurth, T., Belanger, C., MacFadyen, J., Bubes, V., Manson, J. E., Glynn, R. J. and Gaziano, J. M. 2008. Vitamins E and C in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. *JAMA,* 300, 2123-33.

Shama, S., Lai, C. Y., Antoniazzi, J. M., Jiang, J. C. and Jazwinski, S. M. 1998. Heat stress-induced life span extension in yeast. *Exp Cell Res,* 245, 379-88.

Sharma, P. K., Agrawal, V. and Roy, N. 2011. Mitochondria-mediated hormetic response in life span extension of calorie-restricted Saccharomyces cerevisiae. *Age (Dordr),* 33, 143-54.

Sharman, I. M., Down, M. G. and Sen, R. N. 1971. The effects of vitamin E and training on physiological function and athletic performance in adolescent swimmers. *Br J Nutr,* 26, 265-76.

Shen, C., Nettleton, D., Jiang, M., Kim, S. K. and Powell-Coffman, J. A. 2005. Roles of the HIF-1 hypoxia-inducible factor during hypoxia response in Caenorhabditis elegans. *J Biol Chem,* 280, 20580-20588.

Shen, C. and Powell-Coffman, J. A. 2003. Genetic analysis of hypoxia signaling and response in C elegans. *Ann N Y Acad Sci,* 995, 191-9.

Shibamura, A., Ikeda, T. and Nishikawa, Y. 2009. A method for oral administration of hydrophilic substances to Caenorhabditis elegans: effects of oral supplementation with antioxidants on the nematode lifespan. *Mech Ageing Dev,* 130, 652-5.

Sies, H. 1985. Oxidative Stress: Introductory Remarks. In: Oxidative Stress. London: Academic Press.

Sinclair, D. A., Mills, K. and Guarente, L. 1997. Accelerated aging and nucleolar fragmentation in yeast sgs1 mutants. *Science,* 277, 1313-6.

Singh, S. V., Srivastava, S. K., Choi, S., Lew, K. L., Antosiewicz, J., Xiao, D., Zeng, Y., Watkins, S. C., Johnson, C. S., Trump, D. L., Lee, Y. J., Xiao, H. and Herman-Antosiewicz, A. 2005. Sulforaphane-induced cell death in human prostate cancer cells is initiated by reactive oxygen species. *J Biol Chem,* 280, 19911-24.

Smith, D. L., Jr., McClure, J. M., Matecic, M. and Smith, J. S. 2007. Calorie restriction extends the chronological lifespan of Saccharomyces cerevisiae independently of the Sirtuins. *Aging Cell,* 6, 649-62.

Smith, E. D., Tsuchiya, M., Fox, L. A., Dang, N., Hu, D., Kerr, E. O., Johnston, E. D., Tchao, B. N., Pak, D. N., Welton, K. L., Promislow, D. E., Thomas, J. H., Kaeberlein, M. and Kennedy, B. K. 2008. Quantitative evidence for conserved longevity pathways between divergent eukaryotic species. *Genome Res,* 18, 564-70.

Sohal, R. S. and Orr, W. C. 2012. The redox stress hypothesis of aging. *Free Radic Biol Med,* 52, 539-55.

Sohal, R. S. and Weindruch, R. 1996. Oxidative stress, caloric restriction, and aging. *Science,* 273, 59-63.

Someya, S., Yu, W., Hallows, W. C., Xu, J., Vann, J. M., Leeuwenburgh, C., Tanokura, M., Denu, J. M. and Prolla, T. A. 2010. Sirt3 Mediates Reduction of Oxidative Damage and Prevention of Age-Related Hearing Loss under Caloric Restriction. *Cell,* 143, 802-12.

Song, Y., Cook, N. R., Albert, C. M., Van Denburgh, M. and Manson, J. E. 2009. Effects of vitamins C and E and beta-carotene on the risk of type 2 diabetes in women at high risk of cardiovascular disease: a randomized controlled trial. *Am J Clin Nutr,* 90, 429-37.

Southam, C. M. and Ehrlich, J. 1943. Effects of extract of western red-cedar heartwood on certain wood-decaying fungi in culture. *Phytopathology,* 33, 517-24.

Speakman, J. R., Selman, C., McLaren, J. S. and Harper, E. J. 2002. Living fast, dying when? The link between aging and energetics. *J Nutr,* 132, 1583S-97S.

Sreekumar, R., Unnikrishnan, J., Fu, A., Nygren, J., Short, K. R., Schimke, J., Barazzoni, R. and Nair, K. S. 2002. Effects of caloric restriction on mitochondrial function and gene transcripts in rat muscle. *Am J Physiol Endocrinol Metab,* 283, E38-43.

St. Pierre, J., Buckingham, J. A., Roebuck, S. J. and Brand, M. D. 2002. Topology of superoxide production from different sites in the mitochondrial electron transport chain. *J Biol Chem,* 277, 44784-90.

St. Pierre, J., Drori, S., Uldry, M., Silvaggi, J. M., Rhee, J., Jager, S., Handschin, C., Zheng, K., Lin, J., Yang, W., Simon, D. K., Bachoo, R. and Spiegelman, B. M. 2006. Suppression of reactive oxygen species and neurodegeneration by the PGC-1 transcriptional coactivators. *Cell,* 127, 397-408.

Steger, R. W., Bartke, A. and Cecim, M. 1993. Premature ageing in transgenic mice expressing different growth hormone genes. *J Reprod Fertil Suppl,* 46, 61-75.

Stein, I., Itin, A., Einat, P., Skaliter, R., Grossman, Z. and Keshet, E. 1998. Translation of vascular endothelial growth factor mRNA by internal ribosome entry: implications for translation under hypoxia. *Mol Cell Biol,* 18, 3112-9.

Stoltzner, G. 1977. Effects of life-long dietary protein restriction on mortality, growth, organ weights, blood counts, liver aldolase and kidney catalase in Balb/C mice. *Growth,* 41, 337-48.

Story, G. M., Peier, A. M., Reeve, A. J., Eid, S. R., Mosbacher, J., Hricik, T. R., Earley, T. J., Hergarden, A. C., Andersson, D. A., Hwang, S. W., McIntyre, P., Jegla, T., Bevan, S. and Patapoutian, A. 2003. ANKTM1, a TRP-like channel expressed in nociceptive neurons, is activated by cold temperatures. *Cell,* 112, 819-29.

Strobel, N. A., Peake, J. M., Matsumoto, A., Marsh, S. A., Coombes, J. S. and Wadley, G. D. 2011. Antioxidant Supplementation Reduces Skeletal Muscle Mitochondrial Biogenesis. *Med Sci Sports Exerc,* 43, 1017-24.

Sykiotis, G. P. and Bohmann, D. 2008. Keap1/Nrf2 signaling regulates oxidative stress tolerance and lifespan in Drosophila. *Dev Cell,* 14, 76-85.

Taguchi, A., Wartschow, L. M. and White, M. F. 2007. Brain IRS2 signaling coordinates life span and nutrient homeostasis. *Science,* 317, 369-72.

M. Ristow and K. Schmeisser

Takemori, K., Kimura, T., Shirasaka, N., Inoue, T., Masuno, K. and Ito, H. 2011. Food restriction improves glucose and lipid metabolism through Sirt1 expression: a study using a new rat model with obesity and severe hypertension. *Life Sci,* 88, 1088-94.

Tapia, P. C. 2006. Sublethal mitochondrial stress with an attendant stoichiometric augmentation of reactive oxygen species may precipitate many of the beneficial alterations in cellular physiology produced by caloric restriction, intermittent fasting, exercise and dietary phytonutrients: 'Mitohormesis' for health and vitality. *Med Hypotheses,* 66, 832-43.

Tatar, M., Kopelman, A., Epstein, D., Tu, M. P., Yin, C. M. and Garofalo, R. S. 2001. A mutant Drosophila insulin receptor homolog that extends life-span and impairs neuroendocrine function. *Science,* 292, 107-10.

Tatsuta, T. and Langer, T. 2008. Quality control of mitochondria: protection against neurodegeneration and ageing. *EMBO J,* 27, 306-14.

Taylor, R. C. and Dillin, A. 2013. XBP-1 is a cell-nonautonomous regulator of stress resistance and longevity. *Cell,* 153, 1435-47.

Theodorou, A. A., Nikolaidis, M. G., Paschalis, V., Koutsias, S., Panayiotou, G., Fatouros, I. G., Koutedakis, Y. and Jamurtas, A. Z. 2011. No effect of antioxidant supplementation on muscle performance and blood redox status adaptations to eccentric training. *Am J Clin Nutr,* 93, 1373-83.

Tissenbaum, H. A. and Guarente, L. 2001. Increased dosage of a sir-2 gene extends lifespan in Caenorhabditis elegans. *Nature,* 410, 227-30.

Tonks, N. K. 2005. Redox redux: revisiting PTPs and the control of cell signaling. *Cell,* 121, 667-70.

Tormos, K. V. and Chandel, N. S. 2010. Inter-connection between mitochondria and HIFs. *J Cell Mol Med,* 14, 795-804.

Toth, M. L., Sigmond, T., Borsos, E., Barna, J., Erdelyi, P., Takacs-Vellai, K., Orosz, L., Kovacs, A. L., Csikos, G., Sass, M. and Vellai, T. 2008. Longevity pathways converge on autophagy genes to regulate life span in Caenorhabditis elegans. *Autophagy,* 4, 330-8.

Trifunovic, A., Wredenberg, A., Falkenberg, M., Spelbrink, J. N., Rovio, A. T., Bruder, C. E., Bohlooly, Y. M., Gidlof, S., Oldfors, A., Wibom, R., Tornell, J., Jacobs, H. T. and Larsson, N. G. 2004. Premature ageing in mice expressing defective mitochondrial DNA polymerase. *Nature,* 429, 417-23.

Tsai, C. W., Lin, A. H., Wang, T. S., Liu, K. L., Chen, H. W. and Lii, C. K. 2010. Methionine restriction up-regulates the expression of the pi class of glutathione S-transferase partially via the extracellular signal-regulated kinase-activator protein-1 signaling pathway initiated by glutathione depletion. *Mol Nutr Food Res,* 54, 841-50.

Tucci, P. 2012. Caloric restriction: is mammalian life extension linked to p53? *Aging (Albany NY),* 4, 525-34.

Tullet, J. M., Hertweck, M., An, J. H., Baker, J., Hwang, J. Y., Liu, S., Oliveira, R. P., Baumeister, R. and Blackwell, T. K. 2008. Direct inhibition of the longevity-promoting factor SKN-1 by insulin-like signaling in C. elegans. *Cell,* 132, 1025-38.

Turner, N., Li, J. Y., Gosby, A., To, S. W., Cheng, Z., Miyoshi, H., Taketo, M. M., Cooney, G. J., Kraegen, E. W., James, D. E., Hu, L. H., Li, J. and Ye, J. M. 2008. Berberine and its more biologically available derivative, dihydroberberine, inhibit mitochondrial respiratory complex I: a mechanism for the action of berberine to activate AMP-activated protein kinase and improve insulin action. *Diabetes,* 57, 1414-8.

Twig, G., Elorza, A., Molina, A. J., Mohamed, H., Wikstrom, J. D., Walzer, G., Stiles, L., Haigh, S. E., Katz, S., Las, G., Alroy, J., Wu, M., Py, B. F., Yuan, J., Deeney, J. T., Corkey, B. E. and Shirihai, O. S. 2008. Fission and selective fusion govern mitochondrial segregation and elimination by autophagy. *EMBO J,* 27, 433-46.

Udelsman, R., Blake, M. J., Stagg, C. A., Li, D. G., Putney, D. J. and Holbrook, N. J. 1993. Vascular heat shock protein expression in response to stress. Endocrine and autonomic regulation of this age-dependent response. *J Clin Invest,* 91, 465-73.

Vakhrusheva, O., Smolka, C., Gajawada, P., Kostin, S., Boettger, T., Kubin, T., Braun, T. and Bober, E. 2008. Sirt7 increases stress resistance of cardiomyocytes and prevents apoptosis and inflammatory cardiomyopathy in mice. *Circ Res,* 102, 703-10.

van der Horst, A., Tertoolen, L. G., de Vries-Smits, L. M., Frye, R. A., Medema, R. H. and Burgering, B. M. 2004. FOXO4 is acetylated upon peroxide stress and deacetylated by the longevity protein hSir2(SIRT1). *J Biol Chem,* 279, 28873-9.

Mitochondrial Hormesis and Lifespan

van Heemst, D., Beekman, M., Mooijaart, S. P., Heijmans, B. T., Brandt, B. W., Zwaan, B. J., Slagboom, P. E. and Westendorp, R. G. 2005. Reduced insulin/IGF-1 signalling and human longevity. *Aging Cell,* 4, 79-85.

Vanfleteren, J. R. and De Vreese, A. 1995. The gerontogenes age-1 and daf-2 determine metabolic rate potential in aging Caenorhabditis elegans. *FASEB J,* 9, 1355-61.

Various, Heart Protection Study Collaborative Group. 2002. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet,* 360, 23-33.

Vincent, H. K., Powers, S. K., Demirel, H. A., Coombes, J. S. and Naito, H. 1999. Exercise training protects against contraction-induced lipid peroxidation in the diaphragm. *Eur J Appl Physiol Occup Physiol,* 79, 268-73.

Virtamo, J., Edwards, B. K., Virtanen, M., Taylor, P. R., Malila, N., Albanes, D., Huttunen, J. K., Hartman, A. M., Hietanen, P., Maenpaa, H., Koss, L., Nordling, S. and Heinonen, O. P. 2000. Effects of supplemental alpha-tocopherol and beta-carotene on urinary tract cancer: incidence and mortality in a controlled trial (Finland). *Cancer Causes Control,* 11, 933-9.

Viswanathan, M. and Guarente, L. 2011. Regulation of Caenorhabditis elegans lifespan by sir-2.1 transgenes. *Nature,* 477, E1-2.

Vivekananthan, D. P., Penn, M. S., Sapp, S. K., Hsu, A. and Topol, E. J. 2003. Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials. *Lancet,* 361, 2017-23.

Volek, J. S., Phinney, S. D., Forsythe, C. E., Quann, E. E., Wood, R. J., Puglisi, M. J., Kraemer, W. J., Bibus, D. M., Fernandez, M. L. and Feinman, R. D. 2009. Carbohydrate restriction has a more favorable impact on the metabolic syndrome than a low fat diet. *Lipids,* 44, 297-309.

Walker, G., Houthoofd, K., Vanfleteren, J. R. and Gems, D. 2005. Dietary restriction in C. elegans: from rate-of-living effects to nutrient sensing pathways. *Mech Ageing Dev,* 126, 929-37.

Wang, F., Nguyen, M., Qin, F. X. and Tong, Q. 2007. SIRT2 deacetylates FOXO3a in response to oxidative stress and caloric restriction. *Aging Cell,* 6, 505-14.

Wang, G. L., Jiang, B. H., Rue, E. A. and Semenza, G. L. 1995. Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O2 tension. *Proc Natl Acad Sci U S A,* 92, 5510-4.

Wang, Y., Kaneko, T., Wang, P. Y. and Sato, A. 2002. Decreased carbohydrate intake is more important than increased fat intake in the glucose intolerance by a low-carbohydrate/high-fat diet. *Diabetes Res Clin Pract,* 55, 61-3.

Warburton, D. E., Nicol, C. W. and Bredin, S. S. 2006. Health benefits of physical activity: the evidence. *Can Med Ass J (CMAJ),* 174, 801-9.

Ward, N. C., Wu, J. H., Clarke, M. W., Puddey, I. B., Burke, V., Croft, K. D. and Hodgson, J. M. 2007. The effect of vitamin E on blood pressure in individuals with type 2 diabetes: a randomized, double-blind, placebo-controlled trial. *J Hypertens,* 25, 227-34.

Watson, J. D. 2013. Antioxidant antidote. *New Scientist,* 28-29.

Webster, B. R., Lu, Z., Sack, M. N. and Scott, I. 2012. The role of sirtuins in modulating redox stressors. *Free Radic Biol Med,* 52, 281-90.

Weindruch, R. 2006. Will dietary restriction work in primates? *Biogerontology,* 7, 169-71.

Weindruch, R. and Walford, R. L. 1988. The retardation of aging and disease by dietary restriction. Springfield, Illinois, Charles C Thomas Pub Ltd.

Westbrook, R., Bonkowski, M. S., Strader, A. D. and Bartke, A. 2009. Alterations in oxygen consumption, respiratory quotient, and heat production in long-lived GHRKO and Ames dwarf mice, and short-lived bGH transgenic mice. *J Gerontol A Biol Sci Med Sci,* 64, 443-51.

Westerheide, S. D. and Morimoto, R. I. 2005. Heat shock response modulators as therapeutic tools for diseases of protein conformation. *J Biol Chem,* 280, 33097-33100.

Wick, A. N., Drury, D. R., Nakada, H. I. and Wolfe, J. B. 1957. Localization of the primary metabolic block produced by 2-deoxyglucose. *J Biol Chem,* 224, 963-9.

Wiederkehr, A. and Wollheim, C. B. 2006. Minireview: implication of mitochondria in insulin secretion and action. *Endocrinology,* 147, 2643-9.

Willette, A. A., Bendlin, B. B., Colman, R. J., Kastman, E. K., Field, A. S., Alexander, A. L., Sridharan, A., Allison, D. B., Anderson, R., Voytko, M. L., Kemnitz, J. W., Weindruch, R. H. and Johnson, S. C. 2012. Calorie restriction reduces the influence of glucoregulatory dysfunction on regional brain volume in aged rhesus monkeys. *Diabetes,* 61, 1036-42.

M. Ristow and K. Schmeisser

Winder, W. W. and Hardie, D. G. 1996. Inactivation of acetyl-CoA carboxylase and activation of AMP-activated protein kinase in muscle during exercise. *Am J Physiol,* 270, E299-304.

Winder, W. W., Holmes, B. F., Rubink, D. S., Jensen, E. B., Chen, M. and Holloszy, J. O. 2000. Activation of AMP-activated protein kinase increases mitochondrial enzymes in skeletal muscle. *J Appl Physiol,* 88, 2219-26.

Wojtaszewski, J. F., Higaki, Y., Hirshman, M. F., Michael, M. D., Dufresne, S. D., Kahn, C. R. and Goodyear, L. J. 1999. Exercise modulates postreceptor insulin signaling and glucose transport in muscle-specific insulin receptor knockout mice. *J Clin Invest,* 104, 1257-64.

Wood, J. G., Rogina, B., Lavu, S., Howitz, K., Helfand, S. L., Tatar, M. and Sinclair, D. 2004. Sirtuin activators mimic caloric restriction and delay ageing in metazoans. *Nature,* 430, 686-9.

Woods, A., Johnstone, S. R., Dickerson, K., Leiper, F. C., Fryer, L. G., Neumann, D., Schlattner, U., Wallimann, T., Carlson, M. and Carling, D. 2003. LKB1 is the upstream kinase in the AMP-activated protein kinase cascade. *Curr Biol,* 13, 2004-8.

Wouters, B. G. and Koritzinsky, M. 2008. Hypoxia signalling through mTOR and the unfolded protein response in cancer. *Nat Rev Cancer,* 8, 851-64.

Wu, D., Cypser, J. R., Yashin, A. I. and Johnson, T. E. 2009a. Multiple mild heat-shocks decrease the Gompertz component of mortality in Caenorhabditis elegans. *Exp Gerontol,* 44, 607-12.

Wu, J. J., Quijano, C., Chen, E., Liu, H., Cao, L., Fergusson, M. M., Rovira, II, Gutkind, S., Daniels, M. P., Komatsu, M. and Finkel, T. 2009b. Mitochondrial dysfunction and oxidative stress mediate the physiological impairment induced by the disruption of autophagy. *Aging (Albany NY),* 1, 425-37.

Xia, E., Rao, G., Van Remmen, H., Heydari, A. R. and Richardson, A. 1995. Activities of antioxidant enzymes in various tissues of male Fischer 344 rats are altered by food restriction. *J Nutr,* 125, 195-201.

Xiao, R., Zhang, B., Dong, Y., Gong, J., Xu, T., Liu, J. and Xu, X. Z. 2013. A genetic program promotes C. elegans longevity at cold temperatures via a thermosensitive TRP channel. *Cell,* 152, 806-17.

Xie, M. and Roy, R. 2012. Increased Levels of Hydrogen Peroxide Induce a HIF-1-dependent Modification of Lipid Metabolism in AMPK Compromised C. elegans Dauer Larvae. *Cell Metab,* 16, 322-35.

Yanase, S., Hartman, P. S., Ito, A. and Ishii, N. 1999. Oxidative stress pretreatment increases the X-radiation resistance of the nematode Caenorhabditis elegans. *Mutat Res,* 426, 31-9.

Yang, W. and Hekimi, S. 2010. Two modes of mitochondrial dysfunction lead independently to lifespan extension in Caenorhabditis elegans. *Aging Cell,* 9, 433-47.

Yang, Y. Y., Gangoiti, J. A., Sedensky, M. M. and Morgan, P. G. 2009. The effect of different ubiquinones on lifespan in Caenorhabditis elegans. *Mech Ageing Dev,* 130, 370-6.

Yechoor, V. K., Patti, M. E., Ueki, K., Laustsen, P. G., Saccone, R., Rauniyar, R. and Kahn, C. R. 2004. Distinct pathways of insulin-regulated versus diabetes-regulated gene expression: an in vivo analysis in MIRKO mice. *Proc Natl Acad Sci U S A,* 101, 16525-30.

Yfanti, C., Akerstrom, T., Nielsen, S., Nielsen, A. R., Mounier, R., Mortensen, O. H., Lykkesfeldt, J., Rose, A. J., Fischer, C. P. and Pedersen, B. K. 2010. Antioxidant Supplementation Does Not Alter Endurance Training Adaptation. *Med Sci Sports Exerc,* 42, 1388-95.

Yoneda, T., Benedetti, C., Urano, F., Clark, S. G., Harding, H. P. and Ron, D. 2004. Compartment-specific perturbation of protein handling activates genes encoding mitochondrial chaperones. *J Cell Sci,* 117, 4055-66.

Youngman, L. D., Park, J. Y. and Ames, B. N. 1992. Protein oxidation associated with aging is reduced by dietary restriction of protein or calories. *Proc Natl Acad Sci U S A,* 89, 9112-6.

Zarse, K., Schmeisser, S., Groth, M., Priebe, S., Beuster, G., Guthke, R., Platzer, M., Kahn, C. R. and Ristow, M. 2012. Impaired insulin/IGF1-signaling extends life span by promoting mitochondrial L-proline catabolism to induce a transient ROS signal. *Cell Metab,* 15, 451-465.

Zhang, D. D. 2006. Mechanistic studies of the Nrf2-Keap1 signaling pathway. *Drug Metab Rev,* 38, 769-89.

Zhang, Y., Shao, Z., Zhai, Z., Shen, C. and Powell-Coffman, J. A. 2009. The HIF-1 hypoxia-inducible factor modulates lifespan in C. elegans. *PLoS ONE,* 4, e6348.

Zhong, L., D'Urso, A., Toiber, D., Sebastian, C., Henry, R. E., Vadysirisack, D. D., Guimaraes, A., Marinelli, B., Wikstrom, J. D., Nir, T., Clish, C. B., Vaitheesvaran, B., Iliopoulos, O., Kurland, I., Dor, Y., Weissleder, R., Shirihai, O. S., Ellisen, L. W., Espinosa, J. M. and Mostoslavsky, R. 2010. The histone deacetylase Sirt6 regulates glucose homeostasis via Hif1alpha. *Cell,* 140, 280-93.

Mitochondrial Hormesis and Lifespan

Zid, B. M., Rogers, A. N., Katewa, S. D., Vargas, M. A., Kolipinski, M. C., Lu, T. A., Benzer, S. and Kapahi, P. 2009. 4E-BP extends lifespan upon dietary restriction by enhancing mitochondrial activity in Drosophila. *Cell,* 139, 149-60.

Zimmerman, J. A., Malloy, V., Krajcik, R. and Orentreich, N. 2003. Nutritional control of aging. *Exp Gerontol,* 38, 47-52.

Zini, R., Morin, C., Bertelli, A., Bertelli, A. A. and Tillement, J. P. 1999. Effects of resveratrol on the rat brain respiratory chain. *Drugs Exp Clin Res,* 25, 87-97.

Zmijewski, J. W., Banerjee, S., Bae, H., Friggeri, A., Lazarowski, E. R. and Abraham, E. 2010. Exposure to hydrogen peroxide induces oxidation and activation of AMP-activated protein kinase. *J Biol Chem,* 285, 33154-64.

Zong, H., Ren, J. M., Young, L. H., Pypaert, M., Mu, J., Birnbaum, M. J. and Shulman, G. I. 2002. AMP kinase is required for mitochondrial biogenesis in skeletal muscle in response to chronic energy deprivation. *Proc Natl Acad Sci U S A,* 99, 15983-7.

Zou, S., Sinclair, J., Wilson, M. A., Carey, J. R., Liedo, P., Oropeza, A., Kalra, A., de Cabo, R., Ingram, D. K., Longo, D. L. and Wolkow, C. A. 2007. Comparative approaches to facilitate the discovery of prolongevity interventions: effects of tocopherols on lifespan of three invertebrate species. *Mech Ageing Dev,* 128, 222-6.

Zuin, A., Carmona, M., Morales-Ivorra, I., Gabrielli, N., Vivancos, A. P., Ayte, J. and Hidalgo, E. 2010. Lifespan extension by calorie restriction relies on the Sty1 MAP kinase stress pathway. *EMBO J,* 29, 981-91.

Zureik, M., Galan, P., Bertrais, S., Mennen, L., Czernichow, S., Blacher, J., Ducimetiere, P. and Hercberg, S. 2004. Effects of long-term daily low-dose supplementation with antioxidant vitamins and minerals on structure and function of large arteries. *Arterioscler Thromb Vasc Biol,* 24, 1485-91.

Zuryn, S., Kuang, J., Tuck, A. and Ebert, P. R. 2010. Mitochondrial dysfunction in Caenorhabditis elegans causes metabolic restructuring, but this is not linked to longevity. *Mech Ageing Dev,* 131, 554-61.

341