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Mitohormesis

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Abstract

For many years, mitochondria were viewed as semi-autonomous organelles, required only for cellular energetics. This view has been largely supplanted by the concept that mitochondria are fully integrated into the cell and that mitochondrial stresses rapidly activate cytosolic signaling pathways that ultimately alter nuclear gene expression. Remarkably, this coordinated response to mild mitochondrial stress appears to leave the cell less susceptible to subsequent perturbations. This response, termed mitohormesis, is being rapidly dissected in many model organisms. A fuller understanding of mitohormesis promises to provide insight into our susceptibility for disease and potentially provide a unifying hypothesis for why we age.

In 120 BC, King Mithridates V held a lavish banquet. Such feasts were not unusual, since as King of Pontus, a region now in modern day Turkey, Mithridates V was extraordinarily wealthy, a result of his strategic alliance with the neighboring Roman Empire. Midway through this particular banquet, however, the seemingly robust and healthy monarch suddenly died. All signs immediately pointed to poisoning. Suspicion naturally fell on the king's wife, who by tradition became the caretaker ruler of Pontus, and would remain so, until the time either of the two young sons of Mithridates V would come of age. A short time after his father's untimely death, the eldest son and potential future king began to notice new, intense abdominal pains after every meal. Convinced his mother was now slowly poisoning him, and determined not to meet the same fate as his recently deceased father, the older son decided to escape. Over the next seven years, while alone in the wild, the young prince attempted to find a way to protect himself against a future assassination. His solution was to regularly ingest small doses of known poisons believing that by doing so he could build up a resistance against larger doses that might someday come his way. After seven years of a self-imposed exile, the son, now Mithridates VI, returned to Pontus. He rapidly retook the throne, whereupon he promptly imprisoned his mother and brother, married his sister and ruled Pontus effectively, albeit ruthlessly, for the next sixty years. It is

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widely believed that when Mithridates VI returned to Pontus, he carried with him a potion containing 54 known poisonous compounds mixed together in small doses. Ingestion of this potion, thereafter called *Antidotum Mithridaticum*, was believed to protect the user against any number of lethal assaults. It would be used in one form or another by royals and common folk for the next 1900 years.

However dysfunctional our particular families may be, few of us today have the particular concerns that beset Mithridates VI. Yet surprisingly, many of the notions that he wrestled with during his seven year sabbatical in the Anatolian woods are becoming increasingly rediscovered and explored. In particular, there is growing scientific interest in the idea that a mild sub-lethal stress can protect against larger, subsequent stresses. This concept, termed hormesis, was originally explored in the context of classical 19th century pharmacology, although the term itself was only coined some seventy years ago (Southam and Ehrlich, 1943). In general, hormesis is defined as any adaptive response exhibiting a biphasic dose response, and this general phenomenon has been the subject of many excellent reviews (Calabrese and Baldwin, 2002). Here, we will explore in-depth one particular form of hormesis, termed mitohormesis. In this paradigm, mild mitochondrial stress that can be triggered by any of a variety of insults, results in a broad and diverse cytosolic and nuclear response (Figure 1). Although varied, this response appears to induce a wide-ranging cytoprotective state resulting in long-lasting metabolic and biochemical changes. Remarkably, rather than being harmful, these changes may reduce our susceptibility for disease, as well as potentially determine how long we live.

Mitochondrial Stress and the Retrograde Response

Mitochondria are entrusted with the difficult task of providing for acute and chronic energetic needs through the generation of ATP, and of producing various biosynthetic intermediates that form part of the TCA cycle and heme biosynthesis. Yet, the genetic complexity of the mitochondria is such that it encodes a mere dozen or so polypeptides, with the other 1000 or so proteins that make up the organelle encoded by the nucleus. This cellular co-dependency suggests that for the cell to grow and divide, any significant deficiency in mitochondrial function might trigger an adaptive nuclear response. How then does the nucleus know that the mitochondria are in trouble? And furthermore, how is this mitochondrial stress signal sent in a retrograde fashion from mitochondria to the nucleus? The first attempt to find answers to these questions came from studying *S. cerevisiae*, an organism in which mitochondrial DNA (mtDNA) is not required for growth as long as a fermentable carbon source is provided, allowing investigators to analyze the presumed adaptive nuclear response in yeast cells engineered to lack mitochondrial DNA (Parikh et al., 1987). These early studies showed that mitochondrial genetic deficiencies induce a coordinated and complex nuclear response that alters the expression of forty or more genes (Epstein et al., 2001). While the exact response depends in part on the specific mitochondrial perturbation, in general, the transcriptional response results in a reconfiguration of metabolism, allowing for the production of essential intermediates such as glutamate, and increasing glycolytic production of ATP (Epstein et al., 2001). In yeast, the coordination of this response depends on the transcription factors Rtg1 andRtg3, two basic helix-loop-helix/leucine zipper proteins (Rothermel et al., 1995; Rothermel et al., 1997). Rtg1 andRtg3 bind

DNA in a sequence specific manner as a heterodimer. The activity of Rtg1/Rtg3 is predominantly regulated by dephosphorylation of Rtg3, resulting in translocation of the complex from the cytoplasm to the nucleus. This process is regulated by a third factor, the cytoplasmic protein Rtg2 (Sekito et al., 2000). Interestingly, the activity of Rgt2 appears to be sensitive to variety of metabolic cues, including the concentration of glutamate, as well as regulation through the important nutrient sensitive kinase, Target of Rapamycin complex I (TORC1) (Komeili et al., 2000; Liu et al., 2001). Presently, it is believed that Rtg2 is the proximal sensor of mitochondrial dysfunction, although the exact signal emitted from damaged or dysfunctional mitochondria remains elusive (Jazwinski and Kriete, 2012). One attractive possibility is mitochondrial reactive oxygen species (ROS), whose levels increase in dysfunctional mitochondria. Alternatively, the activating signal might involve a fall in mitochondrial membrane potential, given that this is also a common phenomenon observed in dysfunctional mitochondria. Unlike ROS, mitochondrial membrane potential is not an emitted signal. Nonetheless, recent evidence in mammalian cells suggest that mitochondrial depolarization can serve as a stimulus to recruit and activate cytosolic factors as observed with the PINK1/Parkin system (Jin et al., 2010). In that particular case, loss of mitochondrial membrane potential leads to the accumulation of the mitochondrial targeted serine/threonine kinase PINK1, which in turn, triggers the recruitment of the cytosolic E3 ubiquitin ligase Parkin. Thus, it's conceivable that a fall in membrane potential could similarly recruit Rtg2 to the mitochondrial membrane and allow assembly of a signaling complex required for the retrograde response.

Although the studies discussed above established a way, at least in yeast, that perturbations in mitochondrial function could be sensed and compensated for, the interest in this retrograde pathway was enhanced when it was shown that activating this response could extend the replicative lifespan of yeast(Kirchman et al., 1999). Subsequent studies have demonstrated that a loss of mitochondrial membrane potential during normal yeast replicative aging and showed that this fall in membrane potential correlated with induction of the retrograde response as these organisms aged(Borghouts et al., 2004). Taken together, these observations suggested that mitochondrial stress may trigger a hormetic response that provided both short term metabolic benefits and the potential for long term benefits in increased stress resistance and longevity.

Unfortunately, there are no clear analogs of the Rtg1/2/3 system in mammals. Nonetheless, mutations in mitochondrial DNA that result in stable perturbations of mammalian mitochondrial function can also elicit a coordinated alteration in nuclear gene expression(Heddi et al., 1999). Again, this nuclear response can be globally viewed as an attempt to compensate for the primary metabolic defect caused by impaired mitochondrial function. Subsequent analysis suggested that following treatment with various respiratory chain inhibitors or after mtDNA deletion, the disruption of mammalian mitochondrial function elicited a signaling response involving calcineurin-dependent activation of NF-κB (Biswas et al., 1999; Biswas et al., 2003). Recent systems biology approaches have suggested that the retrograde response in mammals may involve a host of factors including the Retinoid X receptor α (RXRA), the peroxisome proliferator-activated receptor γ coactivator-1 (PGC1α), the signaling kinase c-Jun N-terminal kinase (JNK) and ROS generation (Chae et al., 2013).

Signaling Mitochondrial Stress

Thus far we have discussed various mechanisms by which stressed mitochondria may signal outward to the cytosol and the nucleus. These include altering mitochondrial membrane potential to allow recruitment and assembly of signaling molecules or the production of ROS. These are however, not the only available elements contained within the mitochondrial repertoire. For instance, calcium released from the ER is taken up via the mitochondrial calcium uniporter (MCU) through a recently identified inner mitochondrial protein (Baughman et al., 2011; De Stefani et al., 2011). In these and other ways, mitochondria have the capacity to shape cytosolic calcium transients and ultimately to modulate a host of calcium-dependent signaling events. Further, mitochondrial activity plays a central role in determining the levels of metabolic intermediates including NAD^+/NADH and Acetyl-CoA, which act as obligate cofactors for modifying enzymes in the sirtuin, PARP and histone acetyltransferase families. Although it remains uncertain to what degree enzymatic activity is normally regulated by cofactor availability, there is accumulating evidence that under various stresses, availability of these intermediates shapes biological outcomes (Dolle et al., 2013; Houtkooper and Auwerx, 2012). Besides these energetic intermediates, mitochondria can influence the cell by their underlying structure and distribution. For instance, there is increasing interest in the role of mitochondrial fusion and fission in physiology. Recent evidence suggests that tubular versus fragmented mitochondria differ in their metabolic capacity, ROS production and ability to induce cell death(Picard et al., 2013). Furthermore, other recent studies have determined that mitochondrial distribution within the cell, particularly mitochondrial distance to the nucleus, can alter the ultimate transcriptional response (Al-Mehdi et al., 2012).

The mitochondrial unfolded protein response

In many of the initial studies exploring the cellular response to mitochondrial perturbations, the nuclear response was in general precipitated by altering the integrity of mtDNA or by acutely poisoning the electron transport chain to interrupt ATP generation. However, a distinctly different nuclear response is induced when the mitochondrial stress is the accumulation of misfolded proteins within the mitochondrial matrix. In one early example, cells were engineered to express a mutant form of the mitochondrial matrix protein ornithine transcarbamylase (OTC) (Zhao et al., 2002). This mutant OTC molecule could not fold correctly and elicited a stress response that was similar, in some respects, to the better characterized ER stress response. In particular, the accumulation of misfolded mitochondrial OTC induced a nuclear transcriptional response resulting in the induction of a number of mitochondrial-specific protein chaperones. This mitochondrial unfolded protein response pathway (UPR^{mt}) is found in lower organisms as well, and recent elegant dissection of this pathway has been achieved in *C. elegans* (Haynes et al., 2010; Nargund et al., 2012; Yoneda et al., 2004). In particular activation of this response in worms requires a unique transcription factor termed Activating Transcription Factor associated with Stress-1 (ATFS-1) (Haynes et al., 2010; Nargund et al., 2012). ATFS-1 is unique in the sense that it has both a mitochondrial targeting sequence and a nuclear localization signal. In the absence of mitochondrial stress, ATFS-1 is imported into the mitochondria and rapidly degraded by resident proteases. In some ways, this is analogous to factors such as nuclear p53 or

cytosolic Hif-1α, both of which are subjected to proteasomal degradation in the absence of their respective stresses, DNA damage and hypoxia. In response to mitochondrial dysfunction, mitochondrial import of ATFS-1 is reduced causing cytosolic accumulation, followed by nuclear translocation. Once in the nucleus, ATFS-1 promotes a transcriptional response that attempts to restore homeostasis by upregulating a host of mitochondrial chaperones and proteases, as well as genes involved in mitochondrial protein importation and ROS metabolism.

The above experimental paradigms represent situations of relatively severe mitochondrial damage. Evidence suggests that milder forms of mitochondrial stress are also sensed and can also elicit a signaling cascade. In yeast, the ATP-binding cassette (ABC) transporter protein Mdl1 exports peptides across the inner mitochondrial membrane (Young et al., 2001). Proteins degraded by specific proteases within the mitochondrial matrix generate peptides of various sizes (600–2100 kD) that can exit into the cytosol through Mdl1. In worms, the analogous protein HAF-1 appears to be important in mediating the response to mild mitochondrial dysfunction (Haynes et al., 2010). Like Mdl1, HAF-1 is an inner mitochondrial membrane protein that belongs to the ABC transporter family, and, like Mdl1, HAF-1 appears capable of exporting matrix generated peptides into the cytosol. Through yet undefined mechanisms, peptide release from the mitochondria triggers a transcriptional response that involves several proteins including the ubiquitin-like protein UBL-5, the homeobox containing transcription factor DVE-1 and ATFS-1(Haynes et al., 2007; Haynes et al., 2010). While much remains to be learned, the use of released peptides from the mitochondrial matrix to trigger a response is vaguely reminiscent of another biological phenomenon, namely quorum sensing in gram-positive bacteria(Battersby and Richter, 2013). In this situation, oligopeptides are released into the environment through an ABC transporter located on the surface of the bacteria (Henke and Bassler, 2004). Release of these peptides into the extracellular environment triggers the activation of a histidine kinase sensor located on the bacterial surface of other gram-positive bacteria. This histidine kinase is part of a bacterial two-component response system that ultimately regulates gene expression. In this fashion, the behavior and biology of multiple gram positive bacteria can be coordinated and these multiple dispersed genomes can communicate with each other. Given that most cells contain hundreds, if not thousands of mitochondria, and given the endosymbiotic theory of mitochondrial origin, it is intriguing to consider that an analogous system to quorum sensing may be in place in order to allow mitochondria within the cell to communicate with each other and with the nucleus (Figure 2). Interestingly, for bacteria, the peptides released often have unique side-chain modification including isoprenyl groups or thio-lactone rings. Whether similar modifications occur for mitochondrial secreted peptides remains unknown.

There are a number of tantalizing clues that activation of the UPR^{mt} might provide biologically important short and long term adaptation. In particular, there is a growing body of evidence suggesting that activation of the UPR^{mt} might be an important determinant of lifespan. For instance, using *C. elegans* as a model, recent work has suggested that NAD^+ levels decline as worms age (Mouchiroud et al., 2013). Restoration of NAD^+ levels extended longevity through a pathway that required activation of the UPR^{mt} response.

Interestingly, this study further demonstrated that overexpression of the NAD-dependent deactylase sir-2.1 in *C. elegans* also extended lifespan in a UPR^{mt} dependent fashion. In another recent study, strains of inbred mice that differ in their longevity were analyzed to identify potential genes that regulate longevity. This analysis identified the mitochondrial ribosomal protein S5 (Mrps5) as a candidate gene regulating mouse lifespan (Houtkooper et al., 2013). As we will discuss later, mitochondrial ribosomal proteins are involved in the translation of those specific electron transport components that are encoded by mtDNA. In worms, it was subsequently demonstrated that knockdown of Mrps5, as well as related mitochondrial ribosomal proteins, could extend lifespan (Houtkooper et al., 2013). When a transgenic worm was used so that the expression of mitochondrial chaperone proteins could be easily visualized, it could be demonstrated that knockdown of *mrps-5* triggered the constitutive activation of the UPR^{mt} response. Further, genetic inhibition of the UPR^{mt} response abrogated the ability of *mrps-5* to modulate lifespan. Interestingly, the antibiotic doxycycline, which works therapeutically by blocking bacterial translation but also interferes with mitochondrial translation, could also activate UPR^{mt} and extend the life of worms. These observations may help explain the results of previous unbiased screens for longevity genes in *C. elegans*. For instance, in one such screen, roughly 15% of the genes identified that extended lifespan were functionally linked to the mitochondria or cellular metabolism (Lee et al., 2003). This frequency of mitochondrial and metabolic ‘hits’ represents an approximate 10-fold enrichment of this functional class of gene products. While these earlier large scale unbiased screens did not directly assess the UPR^{mt} response, it remains possible that any variety of genetic, environmental or pharmacological stresses that impair mitochondrial protein quality could trigger a hormetic response that at least in model organisms, appears to extend lifespan.

Mitokines for stresses near and far

So far we have discussed cell autonomous responses in which perturbation of mitochondrial function caused by altering mtDNA, respiratory function or mitochondrial protein quality, triggered a cytoplasmic and nuclear response within the affected cell. Recent evidence suggests however that cell non-autonomous signals can also be generated by mitochondrial stress. As mentioned above, in various systems including yeast(Kirchman et al., 1999), worms(Feng et al., 2001; Lee et al., 2003), flies (Copeland et al., 2009) and mice(Lapointe et al., 2009; Liu et al., 2005) inhibition of elements of the electron transport chain result in lifespan extension. How does altering mitochondrial function regulate longevity? One potential clue came from a recent study in worms in which the UPR^{mt} response was activated and lifespan extended by knocking down a component of the nuclear-encoded cytochrome c oxidase (*cco-1*) complex (Durieux et al., 2011). Further analysis revealed that tissue specific knockdown of *cco-1* in the brain or intestine was sufficient to increase lifespan. Moreover, and quite remarkably, knockdown of *cco-1* in the brain could trigger the activation of the UPR^{mt} response in the intestine. The author postulated that stressed mitochondria in the brain might release soluble factors they termed mitokines that somehow govern both the induction of the UPR^{mt} response in distal tissues, and lifespan of the entire organism. Recent evidence suggests that cell non-autonomous signaling stimulated by

proteotoxic stress may actually extend beyond the UPR^{mt} response (van Oosten-Hawle et al., 2013).

Why would stressed mitochondria in the brain of a worm need to communicate this stress to the rest of the soma? At present, there are no definitive answers. One possibility is that mitochondria in the nervous system of *C. elegans* might be tuned to act as sensors of overall metabolic status. Disruption of energy generation in this tissue would generate a signal that could modulate the energy demand or overall stress defenses of other tissues. In many ways, this would function in a fashion not too dissimilar to the control of body temperature. In that case, the stress of cold temperature activates the neuronal release of catecholamines that in turn, increase mitochondrial activity in tissues such as brown fat in order to generate heat. Certainly, it maybe beneficial that disruption of mitochondrial capacity not only triggers a response within the cell with impaired mitochondria but also signals to the rest of the body that a metabolic crisis is at hand. Perhaps this metabolic danger signal could in turn reduce overall energetic demand by altering or delaying local signals that regulate proliferation or other cell fate decisions that require increased energy consumption.

Although intriguing, it remains uncertain what mitokines are and whether they exist in other species. However, there are some hints to suggest that factors secreted from the mitochondria may indeed have systemic biological effects in higher species. One such candidate is humanin, a peptide of approximately 24 amino acids believed to derive from a short, cryptic open reading frame within the mitochondrial 16S rRNA gene. Originally isolated in the context of a protective factor for Alzheimer's disease (Hashimoto et al., 2001), it is now clear that humanin circulates in plasma and has in various experimental paradigms cytoprotective effects, as well as affording potentially beneficial metabolic protection (Lee et al., 2013). Humanin was proposed to be a founding member of a class of mitochondrially-derived peptides causing systemic effects in mammals (Lee et al., 2013). Exactly how and where humanin is synthesized within cells remains unclear, but there is a growing appreciation that mitochondrial transcription, once thought to be composed of a few relatively bland polycistronic transcripts, in fact has a surprisingly complex and varied transcriptome (Mercer et al., 2011). Whether other mitochondrial peptides and regulatory noncoding RNAs exist remains to be determined.

Very recently yet another stress generated in the mitochondria has been shown to trigger a coordinated nuclear response. These studies centered on the biological effects of actinonin, an antibiotic that inhibits mitochondrial translation. As noted earlier, mitochondria synthesize 13 polypeptides that function as components of the electron transport chain, as well as two ribosomal RNAs and 22 mitochondria-specific tRNAs. Actinonin specifically blocks the translation of the mitochondrial polypeptides. It does so by inhibiting a unique peptide deformylase that catalyzes the removal of a formyl group from the initial N-terminal methionine. Interestingly, actinonin and related compounds are being developed as a new class of anticancer agents (Lee et al., 2004). Indeed, certain tumors appear uniquely sensitive to inhibition of mitochondrial translation (Skrtic et al., 2011). A recent study demonstrated that treating fibroblasts with actinonin causes stalling of mitochondrial ribosomes (Richter et al., 2013). The stalling triggers subsequent depletion and decay of mitochondrial ribosomal subunits and mitochondrial mRNAs. Furthermore, actinonin induced a block in cell

proliferation, which may represent part of a mitochondrial ribosome quality control mechanism. This proliferative block appears to precede any fall in cellular energetics and may involve, at least based on gene expression studies, the activation of the tumor suppressor p53 (Richter et al., 2013).

Thus a number of mitochondrial perturbations - including inhibiting mitochondrial function, incorrect folding of mitochondrial proteins, or stalling of mitochondrial ribosomes - elicit a nuclear response (Figure 3). In addition, mitochondrial number is regulated by the balance between mitochondrial biogenesis and mitophagy. The mechanisms underlying biogenesis have been reviewed elsewhere (Scarpulla et al., 2012) with a number of studies demonstrating a central role for the PGC-1 family of coactivators. The activity of PGC-1α is modulated by energy availability as sensed by factors including AMPK and Sirt1 that modify PGC-1α by either phosphorylation or acetylation to regulate the coactivator's activity (Jeninga et al., 2010; Nemoto et al., 2005; Rodgers et al., 2005). Therefore, mitochondrial biogenesis triggered by energetic stress represents another hormetic response, especially since besides increasing mitochondrial number, PGC-1α can also induce a potent antioxidant stress resistance program (St-Pierre et al., 2006). Interestingly, starvation and energetic stress can also result in the biogenesis of new lysosomes. This response appears to be orchestrated not by PGC-1α, but rather by transcription factor EB (TFEB). Outside their biogenesis, mitochondria and lysosomes share the property that both organelles can trigger cell death when their outer membranes become permeable. For mitochondria, this occurs through the classical mitochondrial outer membrane permeabilization (MOMP) pathway, leading to caspase activation, whereas for lysosomes, permeabilization leads to the release of various cathepsins and other enzymes that can induce cell death through various means (Boya and Kroemer, 2008). As discussed above, mitochondria also share some similarity with the endoplasmic reticulum as the UPR^{mt} response and the classic ER stress response share numerous features. As such, it is likely that each organelle within the cell is capable of perceiving stress signals and communicating stress to the nucleus. Furthermore, for each organelle, unresolved stress can be a potent inducer of cell death.

Mitochondria as internal sensors of external threats

The above discussion illustrates stresses generated within the mitochondria that can elicit a cellular response. In many cases, this cellular response involves upregulation of a set of genes that alters cellular metabolism and intrinsic stress resistance. However, mitochondria also play a key role in orchestrating the response to perceived external threats. One well studied example involves the mitochondrial antiviral signaling (MAVS) complex. The MAVS protein is an outer mitochondrial membrane protein that serves as an adaptor and platform orchestrating a response to viral infection(Seth et al., 2005). In particular, MAVS can bind to several members of retinoic-acid-inducible protein I-like receptor (RLR) family of pattern recognition receptors. The RLR family in turn binds to unique RNA structures that are generated during viral infection. Once the RLR family engages dsRNA it is believed to trigger a conformational change in the RLR that enables subsequent interaction with MAVS and the mitochondria. This interaction activates MAVS, and in a prion-type fashion, leads to a self-propagating signal (Hou et al., 2011). The MAVS self-assembled polymer can subsequently recruit additional signaling components including TNF-associated factors

(TRAF2 and TRAF6) and RIPK1 to activate an innate immune response(Hou et al., 2011; Seth et al., 2005). Another example in which mitochondria are activated by potential external threats involves activation of the inflammasome. The inflammasome is a large protein complex whose assembly is triggered by a wide range of stimuli including uric acid, potentially released from dying cells or lipopolysaccharide (LPS) stimulation that mimics bacterial infection (Lamkanfi and Dixit, 2012). Activation of the inflammasome results in the enzymatic activation of caspase-1, and the subsequent proteolytic cleavage of interleukin 1β. Mitochondrial ROS plays an important role in inflammasome activation, although the precise target remains unidentified (Bauernfeind et al., 2011; Zhou et al., 2011). Indeed, there are a growing number of examples where the generation of mitochondrial ROS appears to be a tightly regulated process that is essential for tuning the magnitude or effectiveness of the immune response (Bulua et al., 2011; West et al., 2011).

Mitochondrial Oxidants

One of the best described mechanisms for mitochondrial communication with its cellular host is through the release of ROS. We have already discussed several examples in which mitochondrial ROS act as downstream effector molecules. Indeed, oxidants in general (Finkel, 2011), and mitochondrial oxidants in particular (Finkel, 2012), can function in numerous signaling pathways. These include diverse processes such as the regulation of cytosolic stress kinases (Kamata et al., 2005), modulation of hypoxic signaling (Chandel et al., 1998), and activation of macroautophagy (Scherz-Shouval et al., 2007). Several recent examples suggest that mitochondrial oxidants are active participants in mitohormesis. One of the first clear examples came from studies in which glucose metabolism was impaired either pharmacologically by exposing worms to 2-deoxy-D-glucose (2DG), or by simply restricting glucose availability(Schulz et al., 2007). Both maneuvers resulted in an extension of lifespan. A more detailed examination of metabolism in these animals demonstrated that restricting glucose availability resulted in a presumed compensatory increase in mitochondrial respiration, with evidence for increased utilization of fat through β-oxidation. These metabolic changes appeared to require activation of *aak-2*, the *C. elegans* homolog of the well characterized energy sensor AMP-dependent kinase (AMPK). Consistent with the observed increase in mitochondrial respiration, treatment of worms with 2DG resulted in an increase in ROS levels. Following this oxidative stress, the level of the hydrogen peroxide scavenging enzyme catalase was elevated approximately one week after 2DG exposure. Worms given 2DG but pre-treated with the antioxidant N-acetylcysteine (NAC) showed no evidence of a rise in ROS levels or the subsequent induction of catalase expression. Remarkably, antioxidant treatment also blocked the extension of lifespan by 2DG treatment. These observations support the notion that a shift away from glucose utilization resulted in a transient state of increased mitochondrial metabolism and subsequent oxidative stress. Mitochondrial oxidants in turn induced a hormetic response that ultimately resulted in increased resistance to oxidative stress and increased overall longevity. Others have come to similar conclusions, although it remains to be determined if the relevant mitochondrial oxidant species is hydrogen peroxide or superoxide anion (Yang and Hekimi, 2010). Recent studies have also implicated the phenomenon of mitohormesis in at least part of the life span increase seen in the classic long-lived *C. elegans* mutant *daf-2*, which has alterations in the

insulin/IGF-1 pathway (Zarse et al., 2012). In another example, long-lived mutants induced through inhibition of mitochondrial respiration were found to increase the activity of the hypoxia-inducible factor HIF-1 (Lee et al., 2010). In this setting, the activation of HIF-1 was seemingly dependent on the release of mitochondrial oxidants. A similar hormetic response involving mitochondrial ROS dependent activation of HIF-1 was shown to be important in rescuing AMPK-null mutant of *C. elegans* (Xie and Roy, 2012). Finally, a recent study has demonstrated that a redox-dependent, mitohormetic response can also regulate the lifespan of Drosophila (Owusu-Ansah et al., 2013).

From a strictly metabolic viewpoint these studies appear contradictory as they would suggest that increased mitochondrial respiration (e.g. 2DG) or decrease mitochondrial respiration (e.g. respiratory chain mutants) can both correlate with an increase in an organism's lifespan. Perhaps the only unifying factor is that both conditions appear to result in an inappropriate release of ROS, thus triggering a hormetic response. Another potential source of confusion is that, as previously discussed, disruption of mitochondrial function was thought to induce lifespan extension through the ROS-independent activation of the UPR^{mt}. Nonetheless, some recent evidence suggests that stimuli that activate the previously describe ATFS-1 pathway, also activate a parallel ROS-dependent signaling network (Baker et al., 2012). It is also important to stress that release of mitochondrial oxidants is likely important in the regulation of multiple pathway. One system that is clearly activated by oxidative stress and participates in the subsequent hormetic induction of increased stress resistance involves the nuclear factor erythroid 2-related factor (Nrf2). This leucine zipper transcription factor is capable of regulating the expression of a host of gene products that help mediate resistance to oxidative stress (Ma, 2013). Furthermore, the worm homolog SKN-1 directly binds mitochondria (Paek et al., 2012), and is required to mediate the longevity benefits associated with mitochondrial oxidant release (Schmeisser et al., 2013b; Zarse et al., 2012).

Although the preceding examples have come largely from studies in *C. elegans*, other recent elegant studies in yeast have come to similar conclusions regarding the potential hormetic role for mROS. For instance, in yeast, a reduction in target of rapamycin (TOR) signaling results in an extension of chronological lifespan. A careful analysis of such long-lived yeast strains with impaired TOR signaling revealed that reducing TOR signaling led to initial increase in mitochondrial ROS production(Pan et al., 2011). Again, rather than being harmful, this mROS production was required for the increased lifespan observed. Remarkably, in this setting, expression of the antioxidant protein manganese superoxide dismutase reduced lifespan while treatment with the redox-cycling compound menadione extended lifespan. A further dissection of the role of mROS in yeast longevity demonstrated that mROS are sensed by the two kinases, Tel1p and Rad53p (Schroeder et al., 2013). These proteins are known to sense DNA damage and are the yeast homologs of the well known mammalian proteins, ATM and Chk2, respectively. Activation of this pathway results in alterations in epigenetic silencing through a mechanism involving the sirtuin family of deacetylases. Interestingly, recent work in *C. elegans* suggest that sirtuin overexpression in that organism may extend lifespan through a mechanism involving mitohormesis(Schmeisser et al., 2013a).

Mitohormesis in human biology

What are the implications of mitohormesis for human health? Clearly, in model organisms, the evidence is consistent with the idea that a variety of mild stresses can protect the organism from subsequent larger stresses, and thus translate to a longer lifespan. In this context, antioxidants appear to have a negative effect presumably by preventing the hormetic response. Indeed, in *C. elegans*, there is significant evidence that an augmented cytoprotective response, be it the induction of chaperones, xenobiotic detoxification or antioxidant defenses, is tightly coupled and required for most, if not all, lifespan extensions (Shore et al., 2012). These observations may provide an explanation for the thoroughly disappointing clinical experience with antioxidant therapies. Numerous randomized studies have, in general, failed to demonstrate a benefit from antioxidant therapy and large meta-analysis studies suggests that in some cases, certain antioxidants may actually increase mortality(Bjelakovic et al., 2007; Lippman et al., 2009; Lonn et al., 2005). There are a number of possible explanations for why antioxidants have in general been ineffective including issues of improper dosing or insufficient localization to the mitochondrial source of ROS. Similarly, it is possible that the hint that antioxidants might increase cancer incidence may be a result of the ability of antioxidants to protect genetically damaged pre-cancerous cells from undergoing apoptosis. Nonetheless, it is also possible that chronic low dose antioxidants inhibit the normal hormetic response and therefore block the induction of a broad array of cytoprotective measures the organism would normally undertake. This is supported by some human experimentation in which physical exercise is viewed as a stress and where the salutary benefits of exercise appeared to be inhibited in those subjects given antioxidant supplements(Gomez-Cabrera et al., 2008; Ristow et al., 2009). In these experiments, whereas exercise by itself increased the levels of antioxidant proteins such as superoxide dismutase and glutathione peroxidase in the patient’s skeletal muscle, this response was not observed in individuals taking a combination of vitamin C and vitamin E (Ristow et al., 2009). Again, returning to the large-scale human trials, Vitamin E appears to be associated with an increased risk of developing heart failure in patients with vascular disease or diabetes (Lonn et al., 2005). Given the evidence presented earlier, is it possible that the ischemic myocardium is generating ROS in a fashion similar to cells exposed to hypoxia (Chandel et al., 1998)and that these beneficial hormetic signals are actually inhibited by Vitamin E?

It may also be interesting to assess how mitohormesis regulates disease susceptibility. For instance, nutritional overload contributes to obesity, and obesity contributes to susceptibility for diabetes. Yet, not all obese individuals develop clinically apparent disease. Increased nutrient supply presumably results in increased mitochondrial respiration and increased mitochondrial ROS production. Indeed, ROS production has been tightly linked mechanistically to diabetes (Houstis et al., 2006). Some have further suggested that individual variation in the mitohormesis response might explain why it is that not all obese individual developed clinically apparent disease (Kolb and Eizirik, 2012). A similar line of reasoning could be applied to a host of diseases where patients have multiple risk factors for the disease but no evidence of the condition. Interestingly, certain naturally occurring plant compounds that appear to have medicinal value appear to induce a hormetic response when

ingested. Since these compounds are often synthesized under conditions in which the plants are undergoing some form of environmental stress, this has led to the hypothesis known as xenohormesis (Howitz and Sinclair, 2008). In this scenario, these naturally synthesized, plant small molecules represent a form of cross-species signaling. Their production is stimulated when the plant is stressed, as might happen during a prolonged drought. In turn, when consumed they stimulate a hormetic response in the recipient animals, thereby helping to prepare the animal for the presumed worsening of environmental conditions (e.g. drought for the plant, famine for the animal).

Could other effective man-made drugs represent examples of such a strategy? One potential candidate might be the widely used anti-diabetic drug metformin that is thought to work by inhibiting mitochondrial function (Owen et al., 2000). Could the known beneficial effects of this agent for both diabetes and cancer prevention (Franciosi et al., 2013)be through a hormetic mechanism? Although this mechanism to our knowledge has not been suggested, evidence in both lower organisms and mice suggest that treatment with metformin induces an increase in oxidant defenses as well as an extension of lifespan (Martin-Montalvo et al., 2013; Onken and Driscoll, 2010). Does this agent therefore represent the first example of exploiting hormesis to broadly treat a range of age-related diseases and even aging itself? Will other molecules emerge that gently perturb mitochondrial function and generate a mitohormetic signal that results in abroad therapeutic benefit? Will these molecules represent an entirely new approach for how we treat various diseases and as such, are we now on the verge of a new era of therapy and understanding? Or, perhaps, after 2000 years, we have simply re-discovered the ancient secret of King Mithridates VI.

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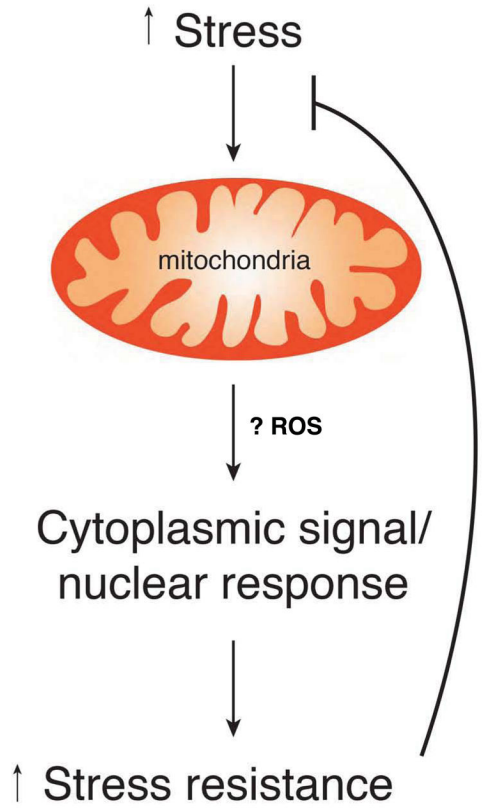

Figure 1.

The basis of mitohormesis. Any of a number of endogenous or exogenous stresses can perturb mitochondrial function. These perturbations are relayed to the cytosol through at present, poorly understood mechanisms that may involve mitochondrial ROS as well as other mediators. These cytoplasmic signaling pathways and subsequent nuclear transcriptional changes induce various long lasting cytoprotective pathways. This augmented stress resistance allows for protection from a wide array of subsequent stresses.

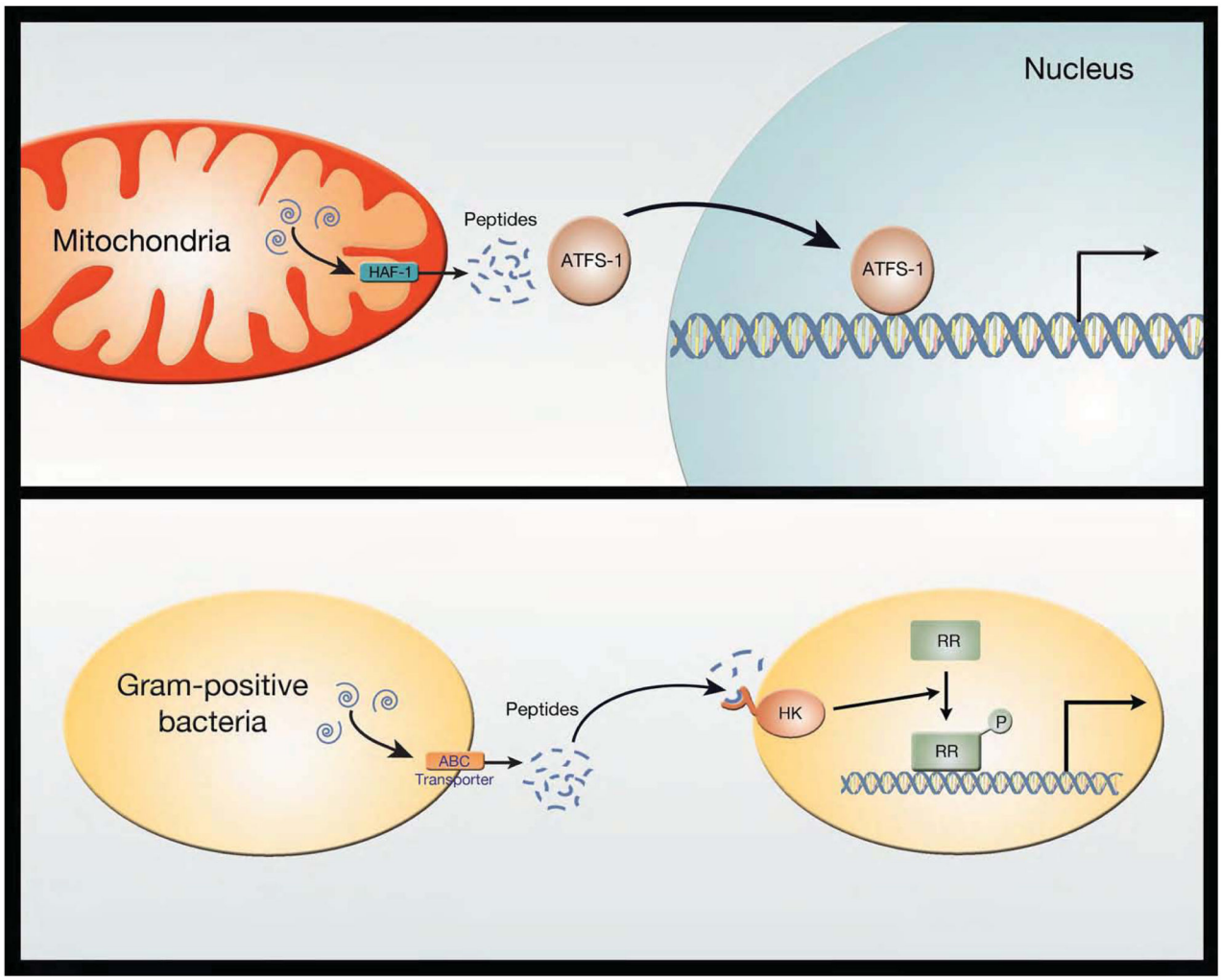

Figure 2.

Potential parallels between the mitochondrial unfolded protein response and quorum sensing in gram positive bacteria. In the *C. elegans* UPR^{mt} response, mitochondrial proteins (indicated by blue swirls) are degraded by matrix proteases and the oligopeptides that are generated are then exported through the ABC transporter family member HAF-1. Once in the cytosol, these peptides can influence the subcellular localization of the transcription factor ATFS-1. Nuclear ATFS-1 is capable of orchestrating a broad transcriptional response to mitochondrial stress. As such, this pathway establishes a method for mitochondrial and nuclear genomes to communicate. In some gram positive bacteria, intracellularly generated peptides can be similarly exported through an ABC transporter protein. These peptides can be detected in the environment by a membrane-bound histidine kinases (HK) sensor. The activation of the HK sensor leads to phosphorylation of a response regulator (RR) protein that, in turn, can alter gene expression. This program allows communication between dispersed gram positive bacteria and thus coordinated behavior of widely dispersed bacterial genomes.

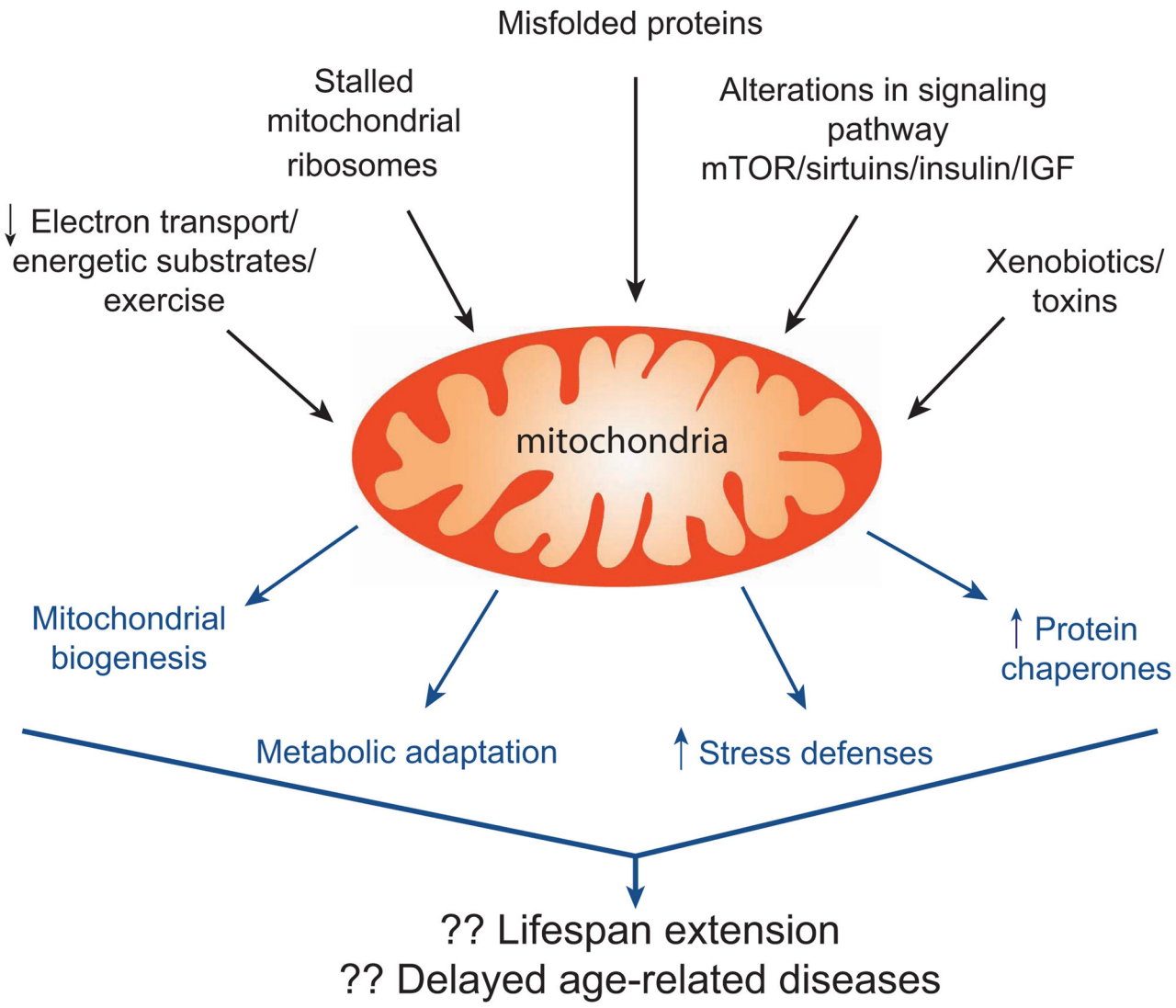

Figure 3.

The complexity of mitochondrial stresses and responses. A wide array of extrinsic and intrinsic mitochondrial perturbations can elicit cellular responses. As detailed in the text, genetic or pharmacological disruption of electron transport, incorrect folding of mitochondrial proteins, stalled mitochondrial ribosomes, alterations in signaling pathways or exposure to toxins, all appear to elicit specific cytoprotective programs within the cell. These adaptive responses include increased mitochondrial number (biogenesis), alterations in metabolism, increased antioxidant defenses and augmented protein chaperone expression. The cumulative effect of these adaptive mechanisms might be an extension of lifespan and a decreased incidence of age-related pathologies.