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Cellular Metabolism and Aging

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Abstract

Metabolic changes are hallmarks of aging and genetic and pharmacologic alterations of relevant pathways can extend life span. In this review, we will outline how cellular biochemistry and energy homeostasis change during aging. We will highlight protein quality control, mitochondria, epigenetics, nutrient-sensing pathways, as well as the interplay between these systems with respect to their impact on cellular health.

Keywords

Mitochondria; Proteostasis; Nutrient-sensing pathways; Epigenetics

Introduction

> "So Nature deals with us, and takes away our playthings one by one…"
>
> from "Nature" by Henry Wadsworth Longfellow

Virtually every aspect of cell biology is affected by aging. Cellular aging is the result of physical and chemical assaults, of molecular exhaustion, and of physiological attempts to compensate for damage. Examples include toxic adducts to macromolecules, attrition of chromosomes, DNA damage, and impaired organelles[1, 2]. Current pharmacological attempts to attenuate aging aim at stimulating cellular repair or at eliminating dysfunctional cells.

Evolutionarily conserved pathways with their built-in redundancies and overlaps appear more resilient to damage. In contrast, phylogenetically newer functions are more vulnerable and developmentally advanced cells seem at a disadvantage when it comes to aging. This vulnerability becomes evident in the functional decline of specialized cells of the adaptive immune system or of cortical neurons, which are more sensitive to age-induced damage than their primal and more resilient counterparts such as myeloid or mesenchymal cells.

Whereas cells of different types may age at different rates, consistent metabolic changes are observed across cell types[3, 4]. In this review, we will discuss key metabolic pathways with relevance for cellular aging and outline how they are connected. Though the effects of aging and metabolism are intertwined, their relationship does not follow a scalable action-and-reaction pattern. Instead, low levels of metabolic impairment can diminish the effects of aging through stimulation of repair systems, a concept known as hormesis, while severe metabolic injury accelerates aging.

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2. Mitochondria and aging

Mitochondria are the remnants of proteobacteria that became endosymbionts 1-2 billion years ago. Mitochondria still retain a small genome that encodes 37 genes in animals but is larger in simpler eukaryotes. The integration of mitochondrial genes into the host's chromosomes comes with advantages as their expression, replication, and repair are under control by the more sophisticated nuclear machinery of eukaryotes. The probable reason why mitochondria retained a small genome has to do with the topology of the encoded proteins: they are part of the respiratory chain complex and translation inside the mitochondrial matrix allows for proper insertion into the inner mitochondrial membrane, whereas nuclear encoded proteins are translated in the cytosol and may require import through the outer and inner mitochondrial membranes[5].

In contrast to their neglect of DNA housekeeping, mitochondria have become the central hub for metabolism of the host cells. They not only produce ATP, but are also essential for the conversion of nutrients into building blocks (intermediary metabolism), for signaling, and for apoptosis. One of the most exciting areas of research involves the regulation of nuclear gene expression by mitochondria through “retrograde communication”. While this pathway is well-defined in yeast, it lacks conserved components in higher eukaryotes and how the expression of nuclear encoded mitochondrial genes is adjusted to respiratory activity in mammalian cells is under intense investigation[6, 7]. Apart from activation or silencing of specific genes, mitochondria also control nuclear activity through metabolites that influence the epigenetic landscape (see 5. Coordination of nuclear activities and metabolism).

Mitochondrial diseases have classically been defined as based on mutations of the mitochondrial genome. However, the majority of the more than 1,000 mitochondrial proteins are encoded in the nucleus and not inherited strictly maternally[8]. The list of diseases that are based on nuclear encoded mitochondrial disorders is growing, as is our understanding of the involvement of this organelle in basic and complex cellular functions. In addition to metabolic dysfunction caused directly by mitochondrial impairment, several diseases are also indirectly influenced by mitochondrial activity, for instance neurodegenerative diseases and cancer. Given their dominant role in metabolism, it is not surprising that mitochondria also play a central role in the aging process[9-11].

ROS theory of aging

One of the most widely published theories of aging involves reactive oxygen species (ROS)[12]. These molecules are byproducts of the respiratory chain in the inner mitochondrial membrane, where redox reactions create a proton gradient that drives ATP generation. Superoxide radicals are produced by complex I and III of the respiratory chain. Three scavenging mechanisms, superoxide dismutase (SOD; mitochondrion and cytosol), catalase (peroxisome) and glutathione peroxidase (mitochondrion and cytosol) act in a stepwise fashion to remove these radicals. First, SOD detoxifies the superoxide and creates hydrogen peroxide. This intermediary can form the more dangerous hydroxyl radical if not removed. Catalase and glutathione peroxidase prevent hydroxyl radical formation by converting hydrogen peroxide into water. Increased SOD activity without changes to catalase or glutathione peroxidase can be harmful due to accumulation of damaging hydroxyl radicals.

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In contrast, elevated levels of glutathione promote glutathione peroxidase's reducing activity and can have beneficial health effects. Patients who were fed bioavailable precursors of glutathione had significantly improved laboratory and clinical parameters in the HIV model of accelerated aging[13-15]. Whether increasing glutathione through supplementation with the precursor amino acids cysteine and glycine will increase life span in this clinical model remains to be seen.

Increased ROS production through desynchronized respiration and/or lower ROS scavenging capacity with age offers an attractive model to explain damage to proteins through carbonylation or to DNA through guanine modifications[16, 17]. With their proximity to the respiratory chain, mitochondrial proteins and mitochondrial DNA that lacks protective nucleosomes are especially prone to damage. Indeed, mice with error-prone mitochondrial DNA replication age prematurely[18, 19]. However, the theory of ROS-induced aging has been reevaluated over the past decade. Genetic alterations in ROS scavengers or treatment with antioxidants failed to show consistent effects on life span regulation[20]. Different species' life expectancies do not correlate with ROS levels. Moreover, there is evidence that modest levels of ROS have an anti-aging effect by triggering a stress-relieving response (hormesis). Combined, it appears that the dosage is critical when evaluating ROS in the context of aging, but reduction of ROS alone does not extend life span under physiological conditions.

Mitochondrial aging

Mitochondria replicate independently of the cell cycle. In addition, they undergo fusion-fission cycles, which serve to adapt ATP production levels, allow for repair of mitochondrial DNA damage, and adjust the level of heteroplasmy (i.e. the degree to which multiple different mitochondrial DNA species coexist in the same cell)[21]. Mitochondrial removal by autophagy also requires fission of the organelle (see 3. Proteostasis network). Aged cells have impaired fusion and fission, thus reducing overall metabolic flexibility. As a consequence, mitochondria fail to adapt to nutrient availability or signaling cues and switch between oxidization of the substrates fatty acids, glucose, and amino acids[22].

There is solid evidence that mitochondrial activity declines with age in tissues as well as in individual cells[23]. Well documented types of damage include replication errors of mitochondrial DNA and toxic adducts on mitochondrial proteins. The elevated pH and high levels of acetyl-CoA and succinyl-CoA in the mitochondrial matrix promote non-enzymatic acylation of ε-amino groups. These lysine modifications can prove harmful to the function of proteins. The removal of such adducts is catalyzed by sirtuins, a class of protein de-ac(et)ylases that are particularly enriched in mitochondria (SIRT3, SIRT4, and SIRT5). Their activity improves mitochondrial function and contributes to healthy aging, though not necessarily to extended life expectancy[24]. Sirtuins require NAD^+ as coenzyme and this metabolite is a key anti-aging effector (see 4. Nutrient-sensing pathways). In addition to the mitochondrial sirtuins, SIRT1 promotes mitochondrial activity in the cytosol by deacetylating the transcriptional coactivator PGC1α, allowing it to promote the expression of NRF-1 target genes. NRF-1 is a master transcription factor of numerous nuclear encoded mitochondrial genes. PGC1α, together with increasing levels of ROS, also stimulates NRF-2, which activates a support pathway and increases the expression of anti-oxidant

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stress response genes[25]. Combined, sirtuins increase mitochondrial activity and preserve their function by adapting the stress response (Figure 1). SIRT1 and SIRT3 in particular have been linked to maintaining metabolic health, though initial findings on their ability to extend life span have been disproven[26, 27].

3. Proteostasis network

In many cells, protein synthesis and removal are the most resource-consuming processes, tightly connecting them to energy metabolism. Furthermore, proteins are the main executors of cell function and dysregulated production or protein dysfunction have been implicated in aging. In particular, the highly specialized neurons of the mammalian brain seem to be sensitive to protein damage[28]. The expression of aggregation-prone polypeptides and the inability of these cells to divide and dilute protein accumulation are the root causes of several neurodegenerative diseases. Protein stress by itself may not damage neurons, but makes these frail cells more susceptible to a second toxic injury, such as inflammation or metabolic insults. Apart from neurons, most cells show consistent changes to protein homeostasis (proteostasis) with age, such as impaired proteasome and chaperone function[29-34].

Translation control

Proteostasis involves protein synthesis, structural and topological changes, and polypeptide removal. Lowering the biogenesis of polypeptides indeed alleviates stress and inhibition of global translation has positive effects on life span extension[35]. Experimental reduction of translation includes genetic manipulation of ribosomes or translation factors, as well as pharmacological interventions, most notably through inhibition of the mTOR signaling pathway (see 4. Nutrient-sensing pathways). Cell stress also reduces overall protein synthesis and the reduction of translation is accomplished by phosphorylation of the translation initiation factor eIF2α by kinases such as GCN2 and PKR. However, select proteins may be translated at higher rates under these conditions as their synthesis is either independent of eIF2α or even inhibited by native eIF2α[36]. Among them is the transcription factor ATF4 that drives the integrated stress response (ISR) that favors expression of life span-extending factors such as transcription factors and executors that deal with oxidative damage. This longevity-promoting effect of the ISR is also triggered by caloric restriction, the most successful intervention thus far to improve longevity and health span.

UPR

The main purpose of the unfolded protein response (UPR) is to reduce protein stress in the endoplasmic reticulum (ER) by altering protein production in a manner that is similar and partially overlapping with the ISR (Figure 2)[37]. Triggered by misfolding of proteins within the ER, the UPR attenuates global translation through phosphorylation of initiation factor eIF2α by the ER-resident kinase PERK. A second arm of the UPR involves nuclear translocation of the transcription factor ATF6, which increases expression of ER-resident chaperones. Third, activation of the RNase IRE1 leads to alternative splicing of the transcription factor XBP1, which alters the proteostatic milieu in the ER[38]. Slight activation of the UPR, in particular higher expression of XBP1, has beneficial effects on survival and

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life span[37]. Interestingly, XBP1 also acts in a cell non-autonomous manner as a stress sensor in the nervous system of nematodes. Upregulation of XBP1 in neurons leads to UPR activation in peripheral organs[39].

Chaperone network

Protein synthesis requires 30-50% of cellular energy and is even under optimal conditions error-prone. By some estimates, a third of polypeptides fail to fold properly during translation in mammalian cells[40-43]. From the cradle to the grave, a network of chaperones supports protein folding and activity. Initially, ribosome-associated chaperones and foldases ensure proper structural assembly of a newly synthesized polypeptide. The nascent polypeptide-associated complex (NAC) accounts for most of the chaperone-assisted protein folding of newly translated proteins[44]. A second protective layer is provided by chaperones such as HSP70 and HSP40, which fold proteins in an ATP-dependent manner. Finally, if nascent proteins require additional assistance, they are transferred into chaperonins, closed nanocages that allow protein folding in isolation without interference from the otherwise crowded protein environment in the cytosol[45]. Failure to fold proteins eventually leads to their removal through the ubiquitin-proteasome system (UPS) or autophagy (see below).

Sentinel chaperones such as HSP90 scan the mature proteome for misfolded polypeptides. These chaperones can attempt to refold client proteins or direct them for removal. Approximately 332 chaperones and associated proteins are encoded in the human genome[46]. This “chaperome” consists of constitutive elements but is also enriched for stress response factors that are upregulated by heat shock or by the transcription factors ATF4 (for the ISR) and ATF6 (for the UPR). The dynamic response to protein stress is reduced with age and transgenic overexpression of chaperones improves life span[47-49]. However, it should be noted that abnormally high levels of chaperones come at a cost: they dampen signaling by the heat shock transcription factor HSF1 through feedback mechanisms and eliminate the ability to mount a proper stress response[50]. Further, overexpressed chaperones can soak up client polypeptides and thus reduce the bioavailability of critical proteins.

UPS

The UPS (ubiquitin-proteasome system) is the primary pathway to eliminate proteins in a specific fashion. A decrease of UPS activity with age has been linked to deficiencies in proteostasis. Further, one of the functions that distinguishes the long-lived naked mole rat from shorter lived rodents is the robustness of its UPS[51, 52]. Similarly, healthy centenarians have been shown to maintain high proteasomal activity[53].

Proteins that are destined for degradation by the proteasome are first tagged with several copies of the small polypeptide ubiquitin in a chain-like fashion. The covalent attachment of ubiquitin to target proteins occurs through a series of enzymatic events, involving ubiquitin-activating enzymes, conjugating enzymes, and finally ubiquitin ligases. Approximately 600 ubiquitin ligases exist in human cells. These ligases can associate with hundreds of different substrate recognition domains, allowing for a substantial combinatorial diversity that ensures specificity of the tagging process[29]. Similar to the chaperone network, several proteins of the UPS are upregulated upon stress. For instance, the UPR activates ubiquitination enzymes

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that allow for the specific extraction, ubiquitination, and proteasomal degradation of ER-resident proteins in a process called ERAD (Endoplasmic reticulum-associated protein degradation). The UPS also regulates chaperone activity with ubiquitin ligases such as CHIP (STUB1), which tags chaperone client proteins for degradation during stress and ubiquitinates the chaperone HSP70 for removal during recovery from stress[54]. The ability of the UPS to target specific substrates also triggers the removal of organelles or bulk protein aggregates through autophagy (see below), where ubiquitination serves as a ligand for autophagosome receptors.

The UPS is a critical regulator of gene expression through the removal of short-lived transcription factors. Degradation therefore has wide-ranging effects on cellular activity and metabolism. One example of metabolic feedback mechanisms between mitochondria, the UPS, and gene activity involves ROS. These chemical radicals can dampen the activity of the UPS, which in turn stabilizes transcriptional repressors. This reduces the expression of nuclear encoded mitochondrial genes, attenuating oxidative metabolism. Replacement of carbonylated proteasome subunits through new rounds of transcription and translation, and the activation of transcription factor NRF-2, which leads to the production of ROS scavengers and executors of autophagy and the UPS, eventually normalize oxidative metabolism following ROS exposure [29, 55, 56].

Mitochondrial proteostasis

Mitochondria have a select number of proteases and chaperones that are expressed in the cytosol and imported into the intermembrane or matrix chambers, or anchored to the membranes. These mitochondrial proteases ensure the import and activity of proteins into mitochondria, and maintain the homeostasis of the respiratory chain complex, which is partly encoded by the mitochondrial genome. Protein stress inside mitochondria triggers a mitochondrial version of the UPR (UPR^{mt}), which increases expression of chaperones, proteases, and ROS detoxifying factors[57]. The elements triggering the UPR^{mt} are surprisingly different between species, but the response to stress appears overall conserved. The UPR^{mt} is responsible for refolding or destroying misfolded proteins and thereby improving the efficiency and the health of mitochondria. Notably, a recent publication pointed out this stress response might also have deleterious effects on mitochondrial health. When healthy and damaged mitochondria coexist (heteroplasmy), the UPR^{mt} can provide sufficient buffering capacity to maintain dysfunctional organelles, which, in the absence of UPR^{mt}, would have been competitively replaced by healthy mitochondria[58]. Regarding aging, the involvement of the UPR^{mt} remains contested. Upregulation of some UPR^{mt} elements promotes resilience to ROS and increases life span (mitohormesis), while other elements accomplish the opposite. More work will be necessary before a verdict can be reached on the role of the UPR^{mt} in aging[59, 60].

Cross-talk between the mitochondrial and cytosolic proteostasis systems occurs at multiple layers and may also play an important role in aging (Figure 3). A dedicated cytosolic stress response exists to deal with mitochondrial proteins that have failed to enter the organelle and mitochondria-associated degradation involves the extraction of proteins from the organelle for cytosolic degradation by the UPS, in a mechanism resembling the UPR[61, 62]. Further,

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mitochondrial dysfunction can elicit a cytosolic stress response that enhances the performance of non-mitochondrial proteins and increases cellular fitness[63].

Mitochondria have also been suggested to assist cytosolic proteostasis by importing protein aggregates and digesting them with matrix proteases. This observation might explain how mitochondrial defects impact neurodegenerative diseases, not only through weakening the metabolism of neurons but also by failing to clear protein aggregates. Indeed, mitochondrial dysfunction accelerates the course of some protein aggregate diseases[64]. How these aggregated proteins mechanistically enter mitochondria and how this pathway affects aging and disease awaits further clarification[65].

Autophagy

Autophagy is the proteostatic mechanism with the strongest ties to longevity. In simpler eukaryotes, life span extension by rapamycin requires induction of autophagy[66, 67]. In addition, direct overexpression of regulators and executors of autophagy have been shown to have beneficial effects on health and life span[68]. Autophagy can be divided into three subtypes. First, chaperone-mediated autophagy targets individual proteins through interaction with heat shock proteins for lysosomal import and degradation. Second, microautophagy involves direct engulfment of proteins by the lysosome. The third, macroautophagy, is the most important mechanism for metabolic control and life span regulation[69]. Following initiation of the phagosome at mitochondrial-ER contact surfaces, a growing vesicle engulfs macromolecular complexes or organelles and eventually fuses to the lysosome for degradation. Macroautophagy is important for the recycling of lipids, sugars, amino acids, and metals, and its contribution to life span extension is based on the removal of damaged proteins, superfluous lipids, impaired organelles, and the regulation of inflammation and cell death.

An important aspect of macroautophagy is the removal of damaged or excess mitochondria. Mitochondrial dysfunction reduces the ability of these organelles to import proteins. The kinase PINK1 acts as an indicator of import stress and accumulates on the outer membrane. PINK1 phosphorylates ubiquitin and activates the ubiquitin ligase PARKIN. PARKIN conjugates a plethora of accessible mitochondrial proteins with phospho-ubiquitin, which attracts phagosome receptors for internalization of the organelle[70, 71]. Mutations in this pathway lead to early onset Parkinson's disease. The control of mitochondrial numbers and the overall state of aerobic metabolism of cells is also regulated through mitophagy. One study exemplified how aged hematopoietic stem cells with increased autophagy display healthier, more juvenile features. The authors argued that removal of mitochondria and shifting of the overall metabolism towards glycolysis contributed to increased cellular health[72]. Apart from the engulfment of entire mitochondria, smaller portions can also be pinched off in vesicles containing oxidized proteins for lysosomal targeting in a process that is independent from autophagy or the fusion/fission cycle. These carriers are referred to as mitochondria-derived vesicles[73].

The scale of autophagy has been studied best in the liver, where up to 70% of proteome turn-over occurs through this mechanism. Inhibition of autophagy leads to the accumulation of poly-ubiquitinated inclusions, indicating that the proteasome system alone is insufficient for

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bulk protein removal, but instead functions mainly in selective polypeptide degradation or in ubiquitination as a recognition tag for the autophagosome. Autophagy has also been implicated in restructuring of the nuclear architecture. However, it remains to be seen whether nuclear autophagy is involved in the aging process[74, 75].

Lysosomes are the endpoint of phagosome breakdown and have remarkable capacity to extract and recycle individual nutrients and building blocks[76]. Recently, the role of lysosomes in the aging process has been extended to a lysosome-to-nucleus signaling function and additional lysosomal pathways with relevance for aging are likely awaiting discovery[77].

4. Nutrient-sensing pathways

Pathways regulating energy metabolism and adaptation to nutrients are commonly associated with life span control. The main players are the insulin-IGF1 pathway, mTOR complexes, AMPK, and sirtuins (Figure 4). The mechanisms of these pathways have been covered in detail in a series of excellent reviews[3, 4, 78-83]. Here, we will briefly outline their function and their interplay with other cellular systems pertaining to life span regulation.

Growth pathways

The insulin-IGF1 pathway regulates growth in times of ample nutrient supply. Through intermediaries such as PI3K and Akt, this pathway suppresses FOXO transcription factors. FOXO transcription factors have multiple downstream effects: they activate autophagy, the UPS, and the ROS stress response, are essential for stem cell function, have tumor-suppressive activities, and promote life span extension[84]. Phosphorylation by Akt prohibits nuclear translocation of FOXOs and instead activates the mTOR complex[85]. The mTOR kinase complex is a master regulator of cell growth and mTOR activation increases protein synthesis, energy expenditure and induces a metabolic switch from frugality to anabolic processes that accelerate aging. The insulin-IGF1 pathway responds to high glucose levels, while mTOR responds directly to high amino acid concentrations and indirectly to glucose levels through Akt. To date, the mTOR inhibitor rapamycin has shown the most promising pharmacologic effect on life span extension in mammals. As mentioned above, the positive impact of rapamycin is autophagy-dependent. The other highly effective intervention, caloric restriction, slows cell growth by reducing both insulin-IGF1 and mTOR signaling[80]. However, the life span extension mediated by these interventions is limited and sustained inhibition of vital systems can become harmful, increase insulin resistance, lower cellular fitness, and accelerate aging over time[3].

Restrictive pathways

Whereas insulin-IGF1 and mTOR represent anabolic “high energy” pathways, the catabolic “low energy” factors AMPK and sirtuins[86, 87] counteract mTOR and enhance mitochondrial activity to produce more ATP through fatty acid oxidation, and induce autophagy to recycle nutrients[88-90]. Unfortunately, the westernized lifestyle, consisting of a hypercaloric diet and limited exercise, downregulates AMPK and sirtuins. Caloric restriction, on the other hand, activates both pathways, stimulating efficient ATP production through glucose uptake and

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glycolysis, fatty acid oxidation, and inducing recycling pathways to replenish energy[91, 92]. AMPK is a structural sensor of the AMP/ATP ratio and low energy (high AMP) allows AMPK to be phosphorylated by its kinase LKB1. Pharmacologic activation of AMPK can be achieved by the anti-diabetic drug metformin, which will be used in the first life span-extension study in humans (TAME - targeting aging with metformin)[4, 93]. As a kinase, AMPK phosphorylates a number of target proteins to increase catabolic metabolism and inhibit mTOR. AMPK is a key mediator of longevity and induction of autophagy is an important downstream effect[94]. The recycling of cellular organelles increases lysosomal amino acid levels, which are detected by the mTOR complex. Amino acid-induced activation of mTOR then terminates the catabolic reaction in a homeostatic feedback loop.

Sirtuins are NAD^+-dependent de-ac(et)ylases that exert several beneficial effects, such as detoxifying mitochondria predominantly via SIRT3 (see 2: Mitochondria and aging), increasing genomic stability through chromatin-associated SIRT6, and transcriptional activation of mitochondria by SIRT1[24, 95, 96]. The additional function of sirtuins as ADP-ribosyltransferases is outside the scope of this review. With their dependence on NAD^+, sirtuins effectively act as sensors for this coenzyme[95]. NAD^+ synthesis is under circadian control and can be quickly increased by fasting and AMPK activation. Importantly, NAD^+ levels are depleted with age, partially through competition between sirtuins and other enzymes such as the NAD^+-dependent DNA repair protein PARP[4]. Increased NAD^+ supply, on the other hand, has been shown to improve health and life span. Some of the immediate metabolic changes following NAD^+ repletion involve enhanced mitochondrial activity through deacetylation and activation of PGC1α by SIRT1, as well as improved mitochondrial proteostasis by SIRT3. Recently, SIRT7 has also been shown to improve mitochondrial health and aging in hematopoietic stem cells[97].

5. Coordination of nuclear activities and metabolism

The nuclear-metabolic axis

Disruption of the nuclear architecture can have profound effects on aging, as shown by progeria-causing laminopathies. These diseases cause juvenile-onset aging, as in Hutchinson-Gilford Progeria Syndrome. Similar to DNA repair defects, affected patients age at an accelerated pace and die prematurely[98, 99]. Laminopathies interfere with autophagy and impede mitochondrial activity through only partially understood mechanisms[100]. The mTOR inhibitor rapamycin has been shown to improve the cellular function of progeroid fibroblasts and treatment protocols are under development for these currently incurable diseases[101].

Several pathways linked to cancer, specifically cell cycle control genes $p16^{INK4a}$, $p19^{ARF}$ and the tumor suppressor p53, also play important roles in the aging process[3, 102-104]. The expression levels of $p16^{INK4a}$ and $p19^{ARF}$ correlate with age and using them as chronological markers has been proposed. Polymorphisms in these genes are associated with age-related diseases. Mild increases of $p16^{INK4a}$, $p19^{ARF}$, and p53 have beneficial effects on aged cells, independent of their tumor-suppressive effects, but more significant upregulation accelerates aging. The mechanistic basis of this phenomenon remains unclear.

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Attrition of telomeres is a consequence of cell replication and aging. Shortened telomeres induce senescence and trigger a p53-dependent response that shuts down mitochondrial activity[105]. However, p53 can also increase mitochondrial output through association with the mitochondrial transcription factor TFAM in the matrix[106]. Therefore, key regulators of the cell cycle appear to have varied roles in metabolism and aging, depending on the context. Assembling a unifying model that explains all these activities poses a major challenge in this field.

The metabolic-nuclear axis

Studies on cancer metabolism and aging have converged on the link between the intermediary metabolism and epigenetics. DNA- and histone-modifying enzymes are key modifiers of the epigenetic landscape and require intermediary metabolites. There is growing interest in dissecting how metabolism affects gene expression and vice versa. One hallmark of aged cells is the loss of gene silencing[107]. Increased transcriptional noise exists due to a lack of heterochromatin, reactivation of transposons, dysregulated splicing, and other impairments[108-111]. In addition, epigenetic modifications can promote the inheritance of transgenerational longevity and metabolic traits in model organisms as well as in humans[112-114]. Among the epigenetic changes that occur during aging are loss of H3K9me3 modifications (a marker of gene repression), global loss of DNA methylation, and enhanced H4K16 acetylation (a marker of active genes)[115-117]. How these alterations are affected by the overall metabolic state and how they in turn regulate cell function is not entirely understood. Still, distinct metabolic pathways generate intermediates that are required for the enzymatic reactions that add or remove methyl or acetyl residues[118-121].

The metabolites S-adenosyl methionine and acetyl-CoA are required for DNA and histone methylation, and for protein acetylation, respectively. Both are produced under nutrient-rich conditions. Their antagonists are alpha-ketoglutarate, which is required for protein and DNA demethylation and NAD^+, a co-enzyme of sirtuin-dependent protein deacetylation. Both intermediates can increase under nutrient-low conditions: alpha-ketoglutarate levels are replenished by metabolic reactions that feed into the TCA cycle (anaplerosis) and NAD^+ availability is regulated through AMPK-dependent synthesis[122, 123]. While caloric restriction and elevated NAD^+ may attenuate aging by reducing protein acetylation, the effects on histone acetylation and gene activity are less obvious and await further clarification[124, 125].

NAD^+ also serves as a coenzyme of the DNA repair enzyme PARP and NAD^+ loss has been linked to genomic damage with age[126]. The TCA cycle intermediate alpha-ketoglutarate displays metabolic fluctuations. Hypoxia, for instance, favors the generation of its antagonist 2-hydroxyglutarate (L2HG), which inhibits demethylase activity[127, 128]. Formation of 2HG is also enhanced in certain cancers with mutations of the TCA enzyme IDH. These IDH mutations convert alpha-ketoglutarate into R2HG, which like L2HG blocks demethylation[129].

Epigenetic changes during aging affect the genome globally, but also locally. For instance, some genes defy global trends and are under direct regulation by metabolic pathways, such as FOXO target genes or stress response genes that are induced by ROS through the

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transcription factor NRF-2. Further, the cell cycle as well as senescence can be regulated by metabolism and mitochondrial activity through p53[130, 131]. For instance, under starvation AMPK phosphorylates p53 to induce p21, causing a cell cycle arrest. Mitochondrial stress in form of increased ROS levels also induces cell cycle arrest using mediators such as p53 and p27[130]. Mitochondria can stimulate the expression of nuclear UPR^{mt} genes through alterations in the epigenetic code[132]. It has been shown in worms that mitochondrial dysfunction increases histone demethylases to promote these UPR^{mt} factors. Interestingly, to extend lifespan this effect needs to occur in the nervous system. The complex and sometimes contradictory effects of global and local epigenetic changes, as well as their connections with metabolism, chromatin, and aging defy summarization in a simple model[133].

6. Summary

Genome-wide genetic studies in yeast and in worms have led to the discovery of the major pathways that govern longevity. Hormesis is a common principle across systems that applies to several of the described longevity pathways: limited metabolic impairment extends life span due to compensatory stress responses, whereas too much damage is harmful. Research findings based on blunt knock-out experiments may therefore require reevaluation in systems that allow for gene dosage adjustments. Still, the most exciting aspect of metabolism remains in the interconnectivity of pathways. How these different systems communicate with each other to synchronize their activity is the target of ongoing studies. Indeed, we are likely to make the most exciting discoveries about metabolic regulation of aging and find new avenues for therapeutic intervention at the intersection of these pathways.

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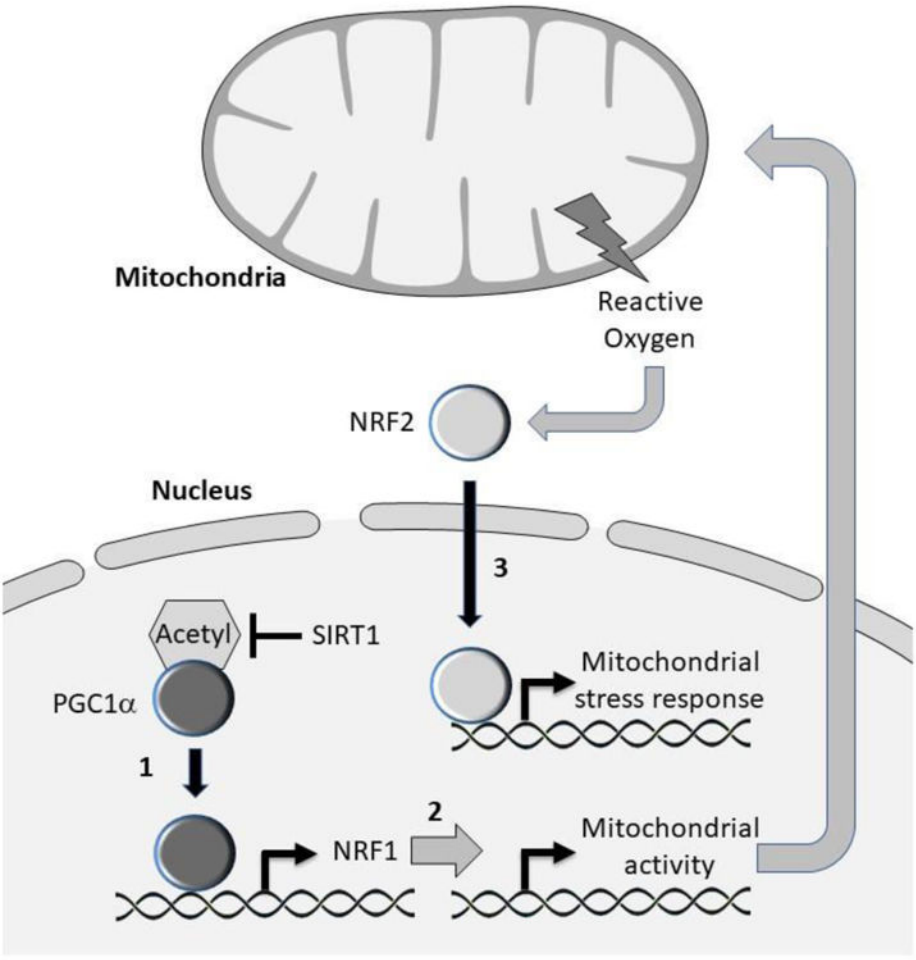

Figure 1. Master regulators of mitochondrial activity

SIRT1 activates expression of nuclear encoded mitochondrial genes through deacetylation of PGC1α. The sirtuins SIRT3, SIRT4, and SIRT5 reduce proteotoxic stress by removing protein acetylation in mitochondria (not shown).

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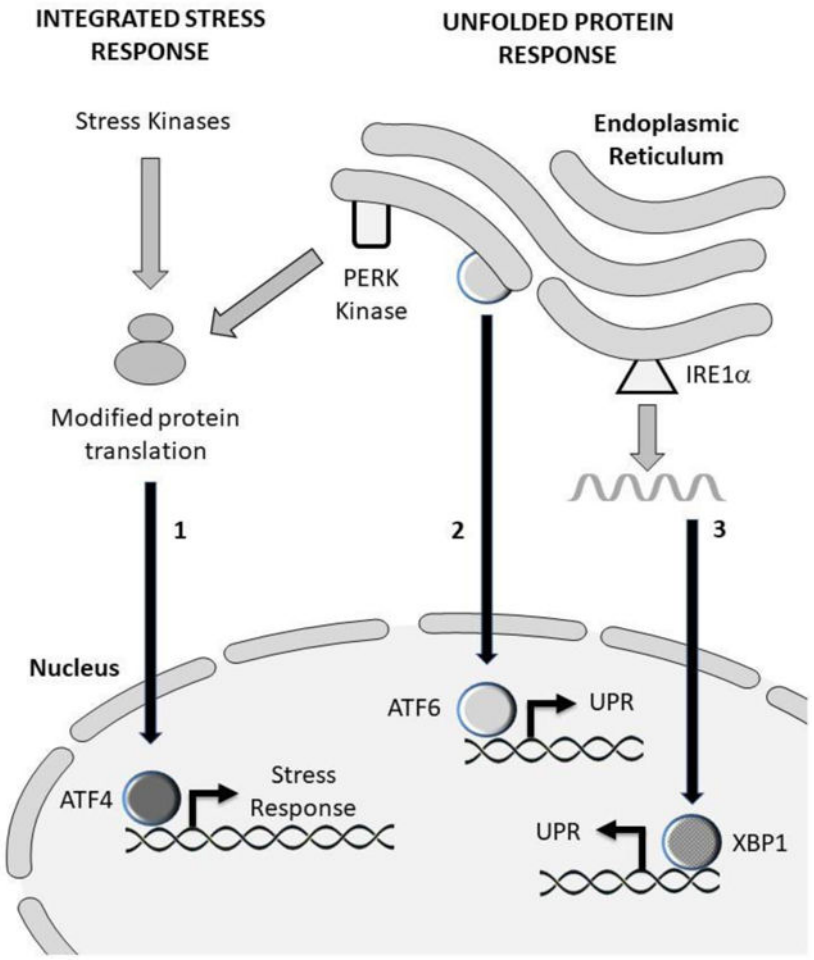

Figure 2. ISR and UPR effectors

Upstream stress kinases such as GCN2 and PKR, as well as the ER-bound kinase PERK, phosphorylate eIF2α. This reduces overall protein translation, while favoring the expression of the transcription factor ATF4 and several chaperones. Additional elements of the UPR include the transcription factor ATF6, which translocates from the ER to the nucleus upon stress, and IRE1α, which allows for alternative splicing of the mRNA encoding the transcription factor XBP1, leading to its activation.

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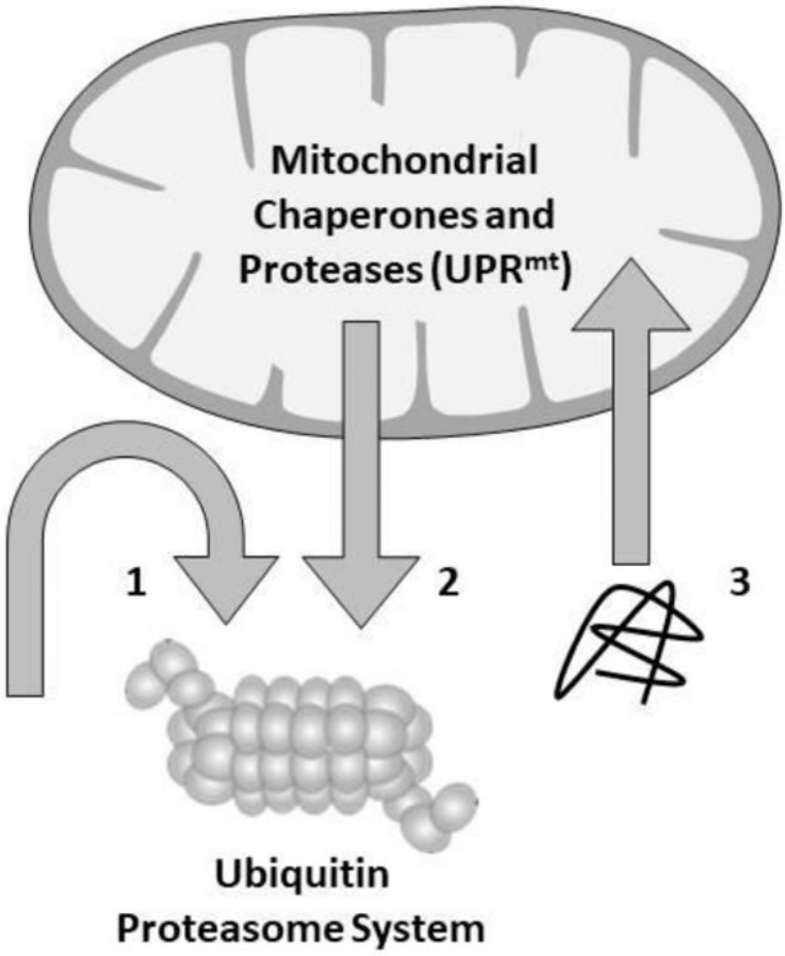

Figure 3. Cooperation between mitochondrial proteostasis and the UPS

Mitochondrial proteins that fail to import into the organelle are removed by the UPS (1). Misfolded proteins can be extracted from mitochondria for proteasomal degradation, similar to the way misfolded proteins are extracted from the ER (2). Protein aggregates can be imported by mitochondria and destroyed by resident proteases (3).

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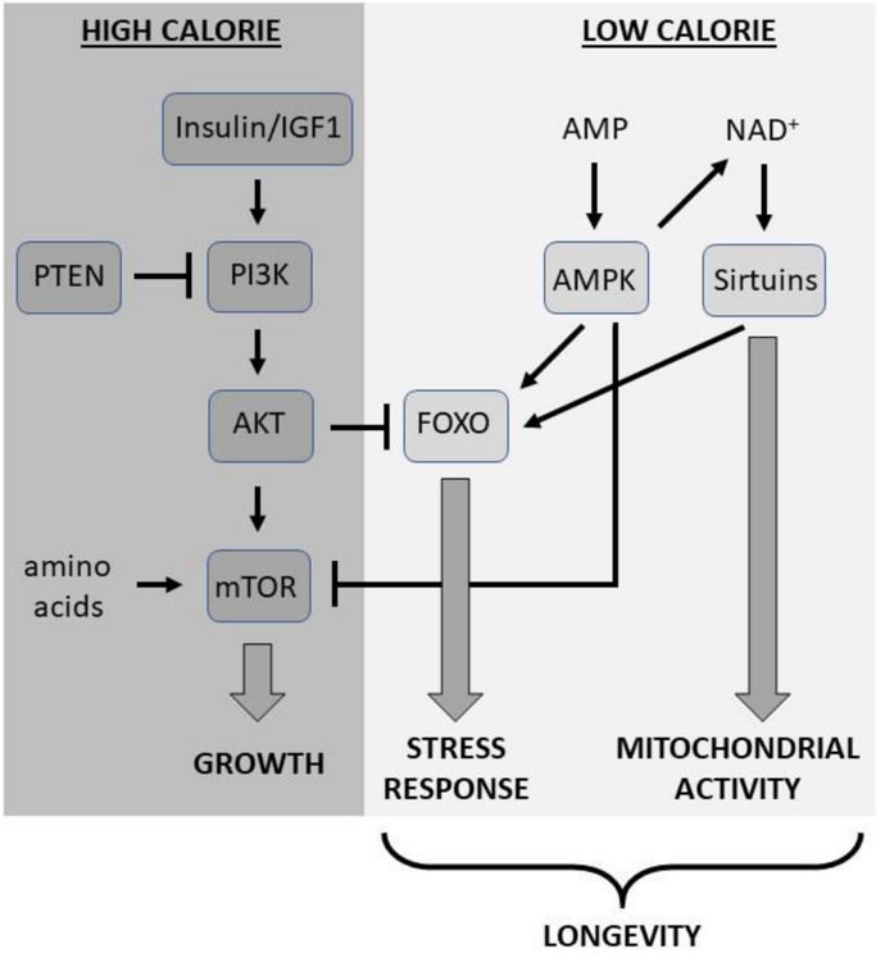

Figure 4. Nutrient-sensing pathways

Overview of the main pathways that sense sugar levels (insulin/IGF1) and amino acids (mTOR) or loss of bioavailable energy (AMPK) and NAD^+ depletion (sirtuins). High calorie conditions favor growth, while low calorie conditions improve the stress response, optimize energy metabolism, and have the potential to increase the life span.