

REVIEW ARTICLE

Regulation of Age-related Decline by Transcription Factors and Their Crosstalk with the Epigenome

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Abstract: Aging is a complex phenomenon, where damage accumulation, increasing deregulation of biological pathways, and loss of cellular homeostasis lead to the decline of organismal functions over time. Interestingly, aging is not entirely a stochastic process and progressing at a constant rate, but it is subject to extensive regulation, in the hands of an elaborate and highly interconnected signaling network. This network can integrate a variety of aging-regulatory stimuli, *i.e.* fertility, nutrient availability, or diverse stresses, and relay them *via* signaling cascades into gene regulatory events - mostly of genes that confer stress resistance and thus help protect from damage accumulation and homeostasis loss. Transcription factors have long been perceived as the pivotal nodes in this network. Yet, it is well known that the epigenome substantially influences eukaryotic gene regulation, too. A growing body of work has recently underscored the importance of the epigenome also during aging, where it not only undergoes drastic age-dependent changes but also actively influences the aging process. In this review, we introduce the major signaling pathways that regulate age-related decline and discuss the synergy between transcriptional regulation and the epigenetic landscape.

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1. INTRODUCTION

With the advent of modern medicine, acute diseases have become increasingly treatable, leaving aging and age-related diseases as major determinants of our health and longevity. Aging is a highly complex process, thought to result from the exposure to intrinsic and extrinsic stresses that lead to accumulation of molecular damage, deregulation of signaling pathways, loss of cellular homeostasis, stem cell depletion, tissue breakdown and thereby a functional decline of the entire organism over time. Additionally, old individuals are more likely to exhibit age-related diseases, in particular, metabolic disorders (*e.g.* diabetes), neurodegenerative protein aggregation diseases (*e.g.* Alzheimer's and Parkinson's disease), cardiovascular disorders and cancer [1].

The rate at which an organism ages can be highly variable among different environmental conditions, species, or even genotypes, implying that age-related decline is a highly plastic process and subject to extensive regulation. This gives hope for pharmaceutical interventions that target aging and age-related disorders. However, to identify such interventions we must first acquire a thorough understanding of the underlying

mechanisms that can slow aging down. There is an ongoing debate about whether aging itself is regulated or only the mechanisms and pathways that can interfere with it. For simplicity, this review uses the term "aging regulation" for any events that accelerate or decelerate the age-dependent decline of the organism.

Metazoans have evolved sophisticated mechanisms to sense adverse conditions that put their survival and reproduction at risk, such as lack of nutrients, exposure to toxins, irradiation, pathogens, heat, or changes in fertility. Such information is then relayed by various signaling pathways to trigger compensatory measures, to a large extent, the activation of stress responses and repair pathways (Fig. 1). Some of the best-characterized signaling pathways include the nutrient sensing Insulin/IGF Signaling (IIS), mechanistic target of rapamycin (mTOR) signaling, AMP kinase signaling, the unfolded protein response, and fertility-related signals from the germline [2, 3]. The centerpieces of these signaling pathways are downstream transcription factors, the activation of which converts environmental or physiological cues into a wide range of cellular responses that help to combat unfavorable conditions. Loss of such transcription factors tends to profoundly impair the crucial gene expression changes needed for these responses and leads to a shorter lifespan [2, 3].

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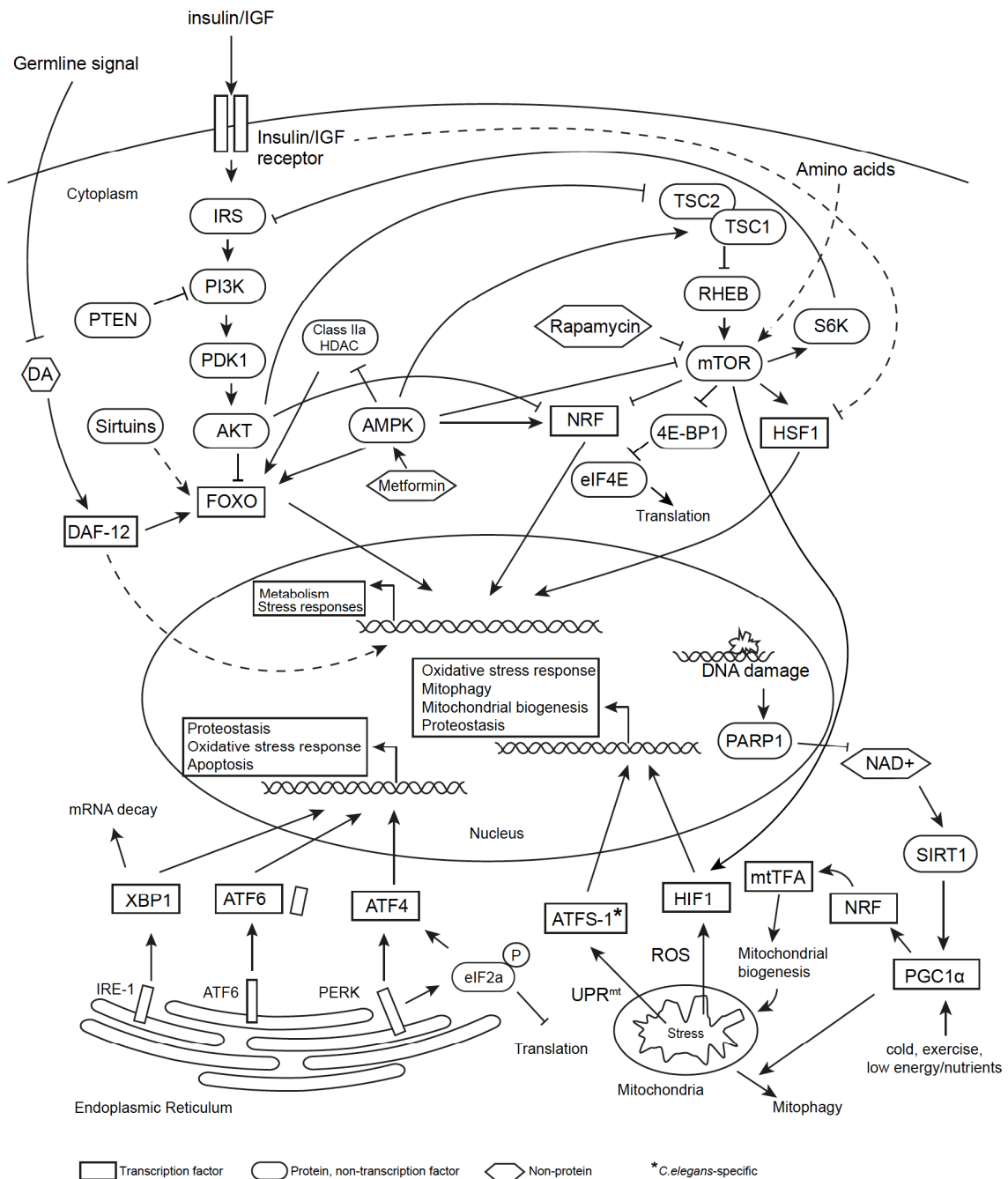


Fig. (1). Overview of the major aging-regulatory signaling pathways and their downstream transcription factors, relating distress signals into aging-preventive transcriptional responses. The various pathways and transcription factors shown are mentioned in the section of ‘transcription factors as central components of aging regulatory signaling pathways’.

It is well established that transcriptional regulation is conferred not only by transcription factors but also by the epigenetic landscape at their target genes. The latter controls accessibility of these genomic loci by transcription factors and the transcription machinery. The epigenetic landscape is regulated through a variety of mechanisms on different levels. First, DNA can be covalently modified, in particular by the methylation of cytosines, commonly leading to inaccessibility and gene repression. DNA is then folded around histone octamers to form nucleosomes, the smallest chromatin entities. Nucleosomes can be covalently modified by a plethora of post-translational histone modifications or the

deposition of histone variants. Furthermore, nucleosomes can be reorganized (assembled, disassembled or repositioned) by ATP-dependent chromatin remodelers [4]. Finally, the spatial organization of chromatin in the nucleus is controlled by dynamic interactions between chromatin regions and their interaction with the nuclear lamina, a filamentous protein meshwork lining the inner nuclear membrane [5]. All of the aforementioned alterations in chromatin compose the epigenome, since the primary DNA sequence remains unchanged. And they confer an additional layer of tightly regulated, dynamic, and reversible gene regulation that interconnects with transcription factor activities.

The epigenome participates in both, short-term and long-term regulatory events, ranging from the response to acute environmental stresses to the involvement in chronic pathologies. Therefore it comes as no surprise that a number of epigenetic changes have been documented in the context of cellular and organismal aging [6-8]. Aged mammalian cells suffer from a general loss of heterochromatin, characterized by loss of repressive histone marks, reduction of nucleosome occupancy, and DNA hypomethylation. Meanwhile, DNA hypermethylation emerges within the transcriptionally active genomic regions [6, 7]. These epigenetic alterations result in significant shifts in gene expression, including the expression of components and targets of aging regulatory signaling pathways. Interestingly, while being heavily influenced by the epigenome, aging regulatory pathways also actively shape the epigenome, often through the activities of their transcription factors that can either recruit chromatin remodelers/modifiers or alter their expression. In this review, we take the opportunity to discuss the current understanding of transcriptional aging regulation with its orchestration of signaling pathways, transcription factors, and epigenetic mechanisms.

2. TRANSCRIPTION FACTORS AS CENTRAL COMPONENTS OF AGING-REGULATORY SIGNALING PATHWAYS

2.1. Insulin/IGF1-like Signaling

Aging is subject to regulation by a broad network of signaling pathways, many of which involve downstream transcription factors that convert signals of unfavorable conditions into appropriate gene expression changes, *i.e.* of genes involved in metabolism and stress responses, to protect the organism from these conditions, slow down aging, and thereby ensure its survival. Notably, when triggered under favorable conditions, these pathways can also dramatically extend the lifespan of an animal. The first aging-associated pathway, namely the highly conserved Insulin/IGF Signaling (IIS) pathway, was discovered in the nematode *Caenorhabditis elegans* [9-11]. Mutations in several IIS components, such as the insulin/IGF receptor homolog *daf-2* [11] and the PI3 kinase *age-1* [9, 10], led to dramatic lifespan extension and increased stress resistance. Similar effects were later confirmed in other metazoan species [12]. The main lifespan-regulatory output of the IIS pathway is conferred by forkhead box protein O (FOXO) transcription factors and their gene regulatory activities, as FOXO loss-of-function mutations in diverse organisms, *e.g.* in *C. elegans* (where the only FOXO transcription factor is called DAF-16), suppress most of the longevity phenotypes [13]. In line with the FOXO/DAF-16-dependent effects observed in *C. elegans*, population studies of various human centenarian cohorts revealed a strong association between IIS polymorphisms and longevity [14-21]. In particular, several genetic variants of FOXO3 are more frequently found in centenarians than in younger individuals and are linked to longevity-related traits [19]. Briefly, under favorable conditions that maintain high insulin/IGF signaling, the insulin receptor tyrosine kinase recruits and phosphorylates insulin receptor substrate (IRS) proteins, which lead to the activation of AKT kinases through a PI3 kinase-PDK1-AKT cascade [22]. Eventually, FOXOs are phosphorylated by AKT [23-25] and SGK [26,

27] kinases, which sequesters the transcription factors by binding to 14-3-3 proteins in the cytoplasm, away from their target genes [28-30]. Such effects are negatively regulated by various phosphatases, most notably PTEN that reverts the effects of PI3 kinase [31]. Under low IIS, these phosphorylation events on FOXO no longer take place, leading to FOXOs' release from cytoplasmic sequestration and permitting its entry into the nucleus for transcriptional regulation of aging-preventive and thus longevity-promoting genes. FOXOs predominantly activate gene expression by promoter binding, promotion of HDAC activity, and the recruitment of co-activators [32]. A study in *C. elegans* identified a broad variety of FOXO/DAF-16 binding partners, including co-activators, involved in diverse biological processes [33], which illustrates the potential complexity of the mechanisms used by FOXO/DAF-16.

In addition to FOXOs, IIS also regulates other transcription factors involved in aging regulation. In *C. elegans*, such transcription factors include the heat shock transcription factor HSF-1 [34-36] and the Nrf family transcription factor SKN-1 [37]. Both transcription factors contribute to the lifespan extension induced by low IIS. Along with FOXO/DAF-16, HSF-1 activates the expression of small heat shock proteins [38] and other stress resistance genes, such as PAT-10 [39], while SKN-1 mainly regulates oxidative stress response and is required for lifespan extension induced by dietary restriction [40, 41]. Notably, the two factors seem to act in distinct manners: 1) HSF-1, but not SKN-1, extends lifespan in a DAF-16-dependent manner [35, 37]. 2) High IIS prevents HSF-1 and SKN-1 from nuclear entry through different mechanisms: For HSF-1 it promotes the formation of an inactive DDL-1/DDL-2/HSF-1 protein complex in the cytoplasm [36], while SKN-1 undergoes phosphorylation by AKT kinases and 14-3-3-dependent sequestration in a manner similar to FOXOs [37].

2.2. Mechanistic Target of Rapamycin (mTOR) Signaling

The mTOR pathway was first linked to aging in the yeast *S. cerevisiae*, in which deletion of a major downstream factor, a ribosomal protein S6 kinase (S6K) homolog, doubled chronological lifespan [42]. mTOR is a serine/threonine kinase that regulates metabolism through nutrient and hormone-sensing [43]. It functions in two protein complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) [44], promoting anabolic processes (*e.g.* protein, lipid, and nucleotide synthesis) and repressing catabolic processes such as autophagy, when activated by nutrients and growth factor signals [44-46]. mTORC1 can be activated by amino acids through RAG GTPases, which allows it to respond to the availability of nutrients across eukaryotes. However, in metazoans, mTOR receives and coordinates yet additional upstream growth signals, including insulin/IGF, EGF, and multiple cytokines [47]. Notably, mTOR signaling and IIS are intertwined [48], with IIS regulating mTORC1 [49] and with mTORC1/2 influencing IIS at multiple points [44, 48, 50]. Under high IIS, AKT inhibits tuberous sclerosis protein 2 (TSC2), a suppressor of the mTORC1 activator RHEB, and thereby allows for the activation of mTORC1 [49]. Most effects of mTOR activity are conferred by two means: 1) direct impact on protein synthesis, and 2) transcriptional regulation. Regarding protein synthesis,

mTORC1 activation leads to the phosphorylation of the translation repressor protein, eukaryotic translation initiation factor 4E-binding protein 1 (4EBP1), thus derepressing the eukaryotic translation initiation factor 4E (eIF4E) to promote protein synthesis [51]. The full picture of transcriptional regulation by mTOR, however, remains elusive. Nevertheless, the mTOR pathway, like IIS, deploys transcription factors to regulate downstream target genes. We give some examples in the later parts of this section.

Inhibition of mTORC1 by rapamycin and mutations in mTOR or the mTORC1 component Raptor exhibit lifespan-extending effects in yeast [52, 53], *C. elegans* [54, 55], *D. melanogaster* [56] and mice [57-60], establishing mTORC1 as a major regulator of aging. Knockdown of the mTORC2 component Rictor also extends lifespan in *C. elegans* [61]. Dietary restriction (DR), an environmental influence that can extend lifespan in multiple organisms [62, 63], largely acts through mTORC1 signaling, as ablation of mTOR or S6K attenuates the lifespan extending effect of dietary restriction in several species [53, 56]. Much of the longevity by mTOR inhibition has been attributed to the global reduction of protein synthesis, as conditions that inhibit translation (e.g. reduced levels of ribosomal proteins or treatment with protein synthesis inhibitor) are sufficient to induce lifespan extension in *C. elegans* [64]. Interestingly, while overall protein synthesis is reduced under mTOR inhibition, subsets of stress response and metabolic genes have been shown to be translated at higher efficiency in multiple species [65], suggesting selectivity in translation regulation by mTOR.

In addition to protein synthesis, mTOR inhibition confers transcriptional regulation of various genes, many of which have the ability to combat stress conditions. For example, inhibition of mTORC1 helps to activate the heat shock transcription factor HSF1 upon heat stress in mammalian cells [66] as well as Nrf2/SKN-1 in mice and *C. elegans* [61], whereas mTORC1 activates the hypoxic response transcription factor HIF1 [67]. Moreover, in *C. elegans* lifespan extension by mTOR inhibition was found to depend on the activities of Nrf2/SKN-1 [61] and FOXA/PHA-4, the latter being a forkhead transcription factor [68] that engages in dietary restriction-mediated longevity and promotes autophagy in response to TOR inhibition and germline removal [69, 70].

2.3. AMP-activated Protein Kinase (AMPK) Signaling

AMP-activated protein kinase (AMPK), as indicated by its name, is triggered when the intracellular ATP/AMP ratio is low. It is crucial for energy metabolism as well as stress responses. The activity of AMPK can be stimulated by dietary restriction and has been found to decline with age, implying a connection between AMPK and aging regulation [71]. Indeed, AMPK counteracts aging *via* an integrated signaling network that involves several well-known aging regulatory pathways. A prime example is the lifespan extending effect of AMPK through mTOR inhibition. Activated AMPK confers phosphorylation of the mTORC1 component Raptor and the mTORC1 inhibitor tuberous sclerosis protein 2 (TSC2), which entails repression of mTOR signaling [72, 73]. Also among the various AMPK targets, direct or indi-

rect, are several transcription factors. The mammalian FOXO3 transcription factor of the IIS pathway as well as its *C. elegans* ortholog DAF-16 have been identified as direct targets of AMPK. Under signals that activate FOXO/DAF-16, phosphorylation by AMPK at multiple regulatory sites promotes FOXO/DAF-16-mediated transcription without affecting its nuclear localization [74, 75]. In addition to such direct regulation, AMPK can also influence regulators of FOXO. For example, in the liver, where AMPK plays a slightly different role, it can be activated in response to the presence of adipokines and as a consequence phosphorylates and thereby inhibits class II histone deacetylases (HDACs), which prevents their nuclear entry and activation of FOXO by deacetylation [76]. In *C. elegans*, AMPK also directly phosphorylates CRTC, a co-activator of the transcription factor cAMP response element-binding protein CREB/CRH-1. This detains CRTC in the cytoplasm and thereby prevents CREB/CRH-1 from transcriptional regulation, leading to lifespan-extending gene expression changes [77]. Finally, AMPK activates Nrf2/SKN-1 [78, 79] and represses NF- κ B [80], the latter being a transcription factor involved in inflammaging - a phenomenon that we will discuss in a later paragraph.

2.4. Sirtuin Activity

Sirtuins are NAD-dependent protein deacetylases that regulate a wide range of biological functions. They first caught attention as anti-aging factors in yeast, where the founding member of this protein family, SIR2, extends lifespan by suppressing the generation of toxic extrachromosomal rDNA circles [81]. The pro-longevity effects of sirtuins were confirmed in metazoan species, in spite of distinct mechanisms as well as some discordances in *C. elegans* and *D. melanogaster* [82, 83]. Nevertheless, some evidence suggests that overexpression of sirtuins in *C. elegans* and *D. melanogaster* promotes longevity, too [82]. The dependence on NAD suggests a link between sirtuin activity and the metabolic state of the organism. Indeed, in yeast, nematodes, and flies dietary restriction leads to increased sirtuin activity, which is required for dietary restriction to extend lifespan. Sirtuins regulate a variety of protein substrates, including several transcription factors involved in aging-related signaling pathways. In *C. elegans*, overexpression of the sirtuin gene sir-2.1 is thought to increase lifespan by activating FOXO/DAF-16 [29, 84]. SIR-2.1 directly interacts with 14-3-3 and FOXO/DAF-16, and by NAD-dependent deacetylation of DAF-16 it promotes expression of its target genes - an energy- and DAF-16-dependent longevity control mechanism independent of IIS [85, 86]. In mammals, the closest SIR2 ortholog SIRT1 deacetylates several transcription factors involved in stress response and metabolism: By deacetylation of p53 and FOXOs, SIRT1 activity leads to reduced apoptosis and activation of DNA repair genes [87-90]. Furthermore, by deacetylation of PGC1 α , SIRT1 promotes mitochondrial biogenesis and gluconeogenesis [91]. The hypoxic response factor HIF1 α , on the contrary, is suppressed by SIRT1 activity. This suppression is lost in hypoxia due to NAD depletion, allowing the activation of HIF-1 in such conditions [92]. Yet another negatively regulated SIRT1 target is NF- κ B [93]. Beyond SIRT1, mammals express six additional sirtuins (SIRT2-7). Although less understood than

SIRT1, they confer aging-related functions, too. In mitochondria, SIRT3, 4, and 5 deacetylate and activate enzymes involved in energy metabolism and oxidative stress resistance [94]. SIRT6 targets several sites on the histone H3 (K9, K18 and K56) and non-histone proteins to maintain telomere stability and promote chromatin changes required for DNA repair [95]. Overexpression of SIRT6 extends the lifespan of male mice [96].

2.5. Signals from the Gonad

Removal of the germline has lifespan-extending effects in *C. elegans* and *Drosophila* [97, 98]. However, the connection between reproduction and longevity reaches beyond the commonly speculated competition between germline and soma for the same resources. The first evidence came from the nematode *C. elegans*, where elimination of the germ cells, genetically (by *glp-1* or *mes-1* mutation) or physically (by laser ablation), significantly extends lifespan [98, 99]. However, removal of the entire gonad does not extend lifespan, suggesting that the somatic parts of the gonad are required for longevity induced by germline removal. Additionally in mice, transplantation of ovaries from young females prolongs the lifespan of old recipients [100]. These phenomena imply that the reproductive system produces aging-regulatory signals which eventually influence the lifespan of the whole organism. In search for the gonadal cell types contributing to such signals in *C. elegans*, surprisingly, sperm and oocyte-deficient mutant animals exhibited no lifespan changes, whereas genetic manipulations of germline stem cells (GSCs) were found sufficient to change lifespan [99]. GLP-1, the *C. elegans* homologue of Notch, is required for the maintenance of a normal GSC identity [101]. *glp-1* loss-of-function mutants have arrested GSCs and live longer than wild-type, while *glp-1* gain-of-function mutations can cause GSC overexpansion and shorten lifespan. Such observations directly connect GSCs and presumably their crosstalk with the somatic gonad to organismal aging regulation. In the tissues receiving these signals from the germline, two transcription factors are essential for the gonad-mediated longevity: FXR/DAF-12 [98, 102, 103] and FOXO/DAF-16 [98, 104, 105]. FXR/DAF-12 is a nuclear hormone receptor downstream of TGF β signaling [106], which is consistent with the existence of an endocrine signaling axis between the gonad and other parts of the organism. Search for the signal in *C. elegans* eventually showed that loss of components in the synthesis pathway of dafachronic acid (DA), a known activator to DAF-12, completely abolishes the longevity of germline-less worms [102]. DA supplementation restores the negative effects of DA synthesis pathway mutations in a DAF-12 dependent manner. Likewise, DAF-12 dependent lifespan extension is observed with DA supplementation in worms with whole gonad loss [103]. It could be concluded that DA biosynthesis and DAF-12 are essential for the longevity mediated by the absence of the germline, and that the source of the DA signal is likely to be the somatic gonad, secreting DA in the absence of GSCs in their vicinity. One of the identified downstream mechanisms goes through FOXO/DAF-16 and the transcription elongation factor TCERG1/TCER-1. In *C. elegans*, particularly intestinal DAF-16 and TCER-1 work together to enhance the expression of genes involved in lipid synthesis and breakdown that

are important for promoting longevity of germline-less animals [104, 105]. Consistently, nuclear translocation of DAF-16 is observed specifically in the intestine in adult *glp-1* mutant animals, and expression of a constitutively nuclear DAF-16 protein in the intestine is sufficient to fully restore longevity in germline-less DA-deficient *glp-1; daf-16; daf-9* animals. In short, DA-DAF-12 signaling promotes the nuclear translocation of DAF-16 in response to germline removal [107-109]. However, expression of a constitutive nuclear DAF-16 protein is unable to restore the longevity in *glp-1; daf-16; daf-12* mutant animals [109], suggesting that DAF-12 has an additional role, either in parallel or downstream of DAF-16, to achieve longevity upon germline loss.

2.6. Signals Regulating Mitochondrial Maintenance

Mitochondria, as the power plants of the cell, not only govern the energy metabolism, but also play an important role during aging. Their dysfunction is considered one of the hallmarks and may even be a driver of aging [110]. Thus it is important for every cell to maintain a pool of healthy mitochondria. Several mechanisms are in place to achieve this, regulating the biogenesis of mitochondria, the structure of the mitochondrial network [111], the maintenance of a healthy mitochondrial proteome, and the removal of old and damaged mitochondria. In this paragraph, we will discuss the mechanisms controlling mitochondrial biogenesis and removal, while we focus on the mitochondrial protein homeostasis in a later section of this review.

It is widely accepted that there is a master regulator of mitochondrial biogenesis, the transcriptional coactivator PGC1 α [112]. It induces the expression of the transcription factors Nrf1 and Nrf2 that drive, besides other aging-preventive targets, the expression of various mitochondrial respiratory chain components. Furthermore, PGC1 α binds and functions as a coactivator to Nrf1 on the promoter of the nuclearly encoded mitochondrial transcription factor A (mtTFA or TFAM), which translocates into mitochondria and is required for mitochondrial DNA replication and gene expression [113, 114], crucial rate-limiting steps in mitochondrial biogenesis. PGC1 α activity is predominantly regulated at the transcriptional level, but also subject to fine-tuning by posttranslational modifications [115]. Multiple energy-related signaling pathways can alter PGC1 α expression, by converging on a number of transcription factors that can bind to the promoter and impact the transcription of PGC1 α [115, 116]. One of the most prominent signals that regulate mitochondrial biogenesis is the exposure to cold, which induces transcription of PGC1 α upon neuronal perception, predominantly *via* a cAMP-PKA (protein kinase A)-CREB-PGC1 α signaling axis [112]. Physical exercise and thus increased nerve-stimulated calcium signaling also leads to increased PGC1 α transcription, through two axes: a Ca²⁺-calcineurin A-MEF2 (myocyte enhancer transcription factors 2)-PGC1 α axis [117] and a Ca²⁺-CaMKIV (calmodulin-dependent protein kinase IV)-REB-PGC1 α axis [118]. In addition, the availability of nutrients influences PGC1 α expression. Insulin signaling inhibits the PGC1 α -activating transcription factor FOXO1, while glucagon promotes PGC1 α transcription through a glucagon-glucagon receptor-cAMP-PKA-CREB-PGC1 α axis [115]. Furthermore, the energy sensor AMPK relays a low ATP/AMP ratio into mi-

tochondrial biogenesis, activating PGC1 α by direct phosphorylation and increasing PGC1 α expression [115]. Pharmacological activation of AMPK in muscle has been shown to promote mitochondrial biogenesis through PGC1 α [119], whereas such effects were abolished by overexpression of a dominant-negative AMPK [120]. Notably, AMPK agonists become less effective in inducing AMPK activity and mitochondrial biogenesis in old animals [121], supporting the notion that AMPK function declines during aging and potentially contributes to age-related mitochondrial dysfunction.

Maintaining a pool of healthy mitochondria depends not only on their biogenesis but also the removal of damaged or superfluous ones. Such removal is conferred by a specialized type of autophagy, named mitophagy, which targets mitochondria for lysosomal degradation. Mitophagy might play crucial roles in longevity. Genetic studies from *C. elegans* have shown that components of the mitophagy inducing pathways, *i.e.* PINK-1 and DCT-1, are required for lifespan extension due to reduced IIS or mild mitochondrial defects [122]. Interestingly, mitochondrial biogenesis and mitophagy are tightly coordinated processes. In *C. elegans*, mitophagy impairment triggers the activation of the transcription factor SKN-1/Nrf2 to enhance both mitochondrial biogenesis and mitophagy and thus mitochondrial turnover [122]. In mammals, mitophagy is additionally regulated by a NAD-SIRT1-PGC1 α signaling axis [123], establishing also PGC1 α as a common regulator of mitochondrial biogenesis and mitophagy.

Even stimuli from outside the mitochondria can influence mitophagy, *i.e.* nuclear DNA damage. Nuclear DNA damage activates the NAD-utilizing Poly(ADP-ribose) polymerase PARP1, and thereby leads to depletion of NAD. This has been found to reduce NAD-SIRT1-PGC1 α signaling and thereby to reduce mitophagy [123].

2.7. Signaling Pathways Regulating Protein Homeostasis

Protein damage occurs under conditions of stress or simply as a byproduct of normal cellular activities. Protein homeostasis or proteostasis - the maintenance of proper synthesis, folding, compartmentalization, and degradation of all proteins - is essential for the normal functions of every cell. Thus, the proteome is under tight surveillance by multiple dedicated cellular systems that actively prevent or eliminate protein misfolding and its toxic effects. Loss of protein homeostasis is strongly linked to aging and late-onset diseases, and consistent with this observation, the underlying protein quality control mechanisms have been proven crucial to confer stress resistance and longevity [124]. Eukaryotes have developed intricate systems to maintain protein homeostasis in the cytosol as well as in organelles including mitochondria and the endoplasmic reticulum. In the next three sections, we will introduce the signaling pathways and their transcription factors that are responsible for the regulation of protein quality control.

2.8. Signals Promoting Protein Quality Control in the Cytosol

Early studies in the cellular response to thermal stress, also known as Heat Shock Response (HSR), have opened the door to our understanding of protein homeostasis at the mo-

lecular level [125]. Acute thermal stress changes the thermodynamics of protein folding, leading to rapid accumulation of misfolded proteins. This induces transcription of Heat Shock Proteins (HSPs), many of which are chaperones that help proteins to fold correctly, so that protein homeostasis is restored [126]. Such robust transcriptional activation of HSPs relies on the evolutionarily conserved transcription factor Heat Shock Factor 1 (HSF1) [127]. HSF1 has to trimerize, in order to function as a transcription factor in the HSR. However, under non-stressed conditions, HSF1 is kept from trimerization through sequestration by chaperones, most importantly HSP90. Only when unfolded proteins accumulate, HSP90 dissociates from HSF1 to engage in the correct folding of these new client proteins, which then allows the freed HSF1 to trimerize and rapidly turn on the expression of a broad panel of HSPs [128]. Although discovered for its roles in HSR, HSF1 has emerged as a crucial regulator for various biological processes under non-stress conditions, from development to aging [127]. Given the importance of protein homeostasis in longevity, it comes as no surprise that HSF1 turns out to be an anti-aging transcription factor. In *C. elegans*, lifespan positively correlates with HSF-1 levels. Loss of HSF-1 drastically decreases lifespan and accelerates protein aggregation, while HSF-1 overexpression leads to lifespan extension with increased proteotoxic stress resistance [34, 35]. Multiple aging-regulatory pathways utilize HSF1 to regulate stress resistance and lifespan. As mentioned previously in the section 'Insulin/IGF1-like signaling', HSF1 is subject to regulation by IIS [36], in that high IIS prevents the nuclear translocation and thereby activity of HSF1. Loss of HSF-1 abolishes lifespan extension under low IIS in *C. elegans* [34, 35]. This suggests a crucial interdependence between HSF-1 and other transcription factors downstream of IIS, *i.e.* FOXO/DAF-16. Indeed, HSF-1 overexpression fails to extend *C. elegans* lifespan in the absence of FOXO/DAF-16 [35]. Such phenotypes may in part arise from cell non-autonomous functions of HSF-1. Notably, in *C. elegans*, overexpression of HSF-1 in neurons is sufficient to extend lifespan, and this requires the presence of DAF-16 in peripheral tissues [129]. Together with transcriptional profiling of the two transcription factors [130, 131], these findings above indicate partly overlapping but non-redundant functions of HSF-1 and DAF-16 in protein homeostasis and lifespan regulation. Apart from regulation by IIS, mTORC1, as a major protein synthesis regulator, can also directly phosphorylate and activate HSF1 to enhance protein homeostasis during phases of growth [66]. Besides by mTOR, HSF1 is also subject to post-translational modification by other key regulators of aging, metabolism, and development, *i.e.* MAPK and SIRT1. Several reviews on HSF1 regulation provide more insight [127, 132].

Besides facilitation of protein folding, another essential aspect of protein homeostasis is the removal of damaged proteins. A cellular catabolic process named autophagy and in the context of aging particularly macroautophagy plays an important role in protein degradation and the maintenance of homeostasis [133]. During macroautophagy, damaged organelles or macromolecules are engulfed by a double-membrane structure called autophagosome, which later fuses to lysosomes for degradation [134]. Loss of macroautophagy is linked to age-related protein aggregation diseases such as

Parkinson's, Alzheimer's and Huntington's disease [135]. Therefore unsurprisingly macroautophagy has emerged as a key player in the aging process. Induction of macroautophagy by overexpressing specific constituents is sufficient to extend lifespan in metazoans [136, 137]. Moreover, various longevity paradigms, including mTOR inhibition, reduced IIS, mitochondrial respiration deficiency, and germline removal have been shown to require macroautophagy for their full lifespan-extending effects [138, 139]. Macroautophagy is a constitutive process and the sustained expression of its components depends on transcriptional regulation [138]. The helix-loop-helix transcription factor TFEB has emerged as a key regulator that controls genes of all stages of macroautophagy [140, 141]. Consistently, in *C. elegans*, the TFEB homolog HLH-30 is responsible for the longevity of all lifespan extension regimens that require macroautophagy [142]. Overexpression of TFEB/HLH-30 leads to induction of macroautophagy and lifespan extension, as well as improved clearance of pathological proteins in protein aggregation disease models. Interestingly, HSF1 is also able to promote autophagy. A recent study in *C. elegans* found that macroautophagy can be induced by mild heat stress or HSF-1 overexpression and contributes to longevity and heat stress resistance in such treatments [143]. This finding implicates the orchestration of HSR and macroautophagy in stress responses and aging.

2.9. Mitochondrial Unfolded Protein Response

A healthy proteome within the mitochondria is crucial for their proper functions. Particularly challenging is that the vast majority of proteins within mitochondria are encoded in the nucleus and thus needs to be imported from the cytoplasm - a multi-stage process that requires many aspects of mitochondrial physiology to be intact [144]. Therefore, protein import and processing efficiency are under tight surveillance and also serve as good indicators of mitochondrial health. Any stress that perturbs these processes triggers protective mechanisms, most importantly the mitochondrial unfolded protein response (UPR^{mt}) that aims to restore the mitochondrial protein homeostasis. Although first characterized in mammalian cells [145], UPR^{mt} has been most extensively studied in *C. elegans*.

C. elegans mutants with moderate mitochondrial dysfunction often display a longer lifespan [146-149]. While seemingly counterintuitive, these phenotypes could be explained by activation of the UPR^{mt} and additional mechanisms, whose stress resistance benefits would outweigh the mitochondrial defects. The transcription factor ATFS-1 is in large part responsible for the activation of the UPR^{mt} [150]. ATFS-1, normally imported into mitochondria, translocates into the nucleus when there is decreased mitochondrial import efficiency and triggers UPR^{mt}-related gene expression [151]. Notably, even though UPR^{mt} is important for mitochondria-induced longevity [148], it alone is insufficient to prolong lifespan [152], indicating its need to synergize with other longevity promoting pathways. Indeed, hypoxia-induced factor HIF-1 is activated by increased ROS production and contributes to longevity in ROS-generating *C. elegans* mutants of the electron transport chain, *i.e.* *isp-1* and *clk-1* [153]. Consistent with the observations in *C. elegans*, loss-of-function mutations in *coq7/clk-1* also regulates mito-

chondrial respiration and ROS production in mice [154]. Only the functional homologue of ATFS-1 and thus a potential master regulator of UPR^{mt} in mammals remains unknown.

2.10. Protein Homeostasis-related Signals from the Endoplasmic Reticulum

The endoplasmic reticulum (ER) is central to the processing and trafficking of proteins to many destinations, including the ER, Golgi apparatus, plasma membrane, or for secretion. Proteotoxic stress in the ER, such as an accumulation of misfolded proteins, triggers the ER unfolded protein response (UPR^{ER}), which helps the cell to restore ER proteostasis. The UPR^{ER} pathway encompasses three branches, initiated by three factors respectively - inositol-requiring enzyme 1 (IRE1), PKR-like ER kinase (PERK), and activating transcription factor 6 (ATF6). Each branch controls specific downstream transcription factors to regulate the expression of stress response genes. IRE1 activates the transcription factor X-box binding protein 1 (XBP1) by splicing an intron out of the XBP1 mRNA. The fully processed XBP1 mRNA is then translated, and the resulting protein controls the expression of various target genes related to protein processing and stress resistance [155]. In parallel, IRE1 mediates IRE1-dependent mRNA decay (RIDD) to reduce protein load in the ER and activate JNK and NF-κB [156, 157]. Likewise, the PERK branch reduces protein load, mainly by downregulating translation through phosphorylation of the translation initiation factor 2α (eIF2α) [158]. However, activating transcription factor 4 (ATF4) is preferably translated under these conditions to further activate the pro-apoptotic transcription factor CHOP [159]. The third branch of the UPR^{ER} activates the transcription factor ATF6 by promoting its translocation into the Golgi apparatus and its subsequent cleavage. The cleaved active form of ATF6 is translocated into the nucleus to drive the expression of stress response genes [160]. The ability of UPR^{ER} activation decreases with age, suggesting that this may contribute to the aging process [161]. Indeed, several longevity pathways rely on UPR^{ER}. For instance, longevity mediated by reduction of IIS requires IRE-1 and XBP-1 in *C. elegans* [162], and longevity mediated by dietary restriction depends on IRE-1 in *C. elegans* and *D. melanogaster* [67, 163]. Moreover, activation of the UPR^{ER} can be sufficient to promote longevity. For example, expression of the spliced active form of XBP-1 in the *C. elegans* nervous system extends lifespan in a cell-nonautonomous manner through UPR^{ER} activation in the intestine [164].

2.11. Inflammaging

Aging is accompanied by a progressive increase of unresolved chronic inflammation. Such phenomenon is named inflammaging [165]. While the underlying cause of inflammaging remains unclear, it has been determined as a major culprit of biological aging in mammals [166]. On the transcriptional level, inflammation is regulated by a signaling network centered around the transcription factor NF-κB [167]. NF-κB is downstream of a variety of signals that sense pathogens, cytokines, and growth factors. When activated, it mediates the expression of a wide range of target genes involved in inflammatory response, apoptosis, and cell growth. The activity of NF-κB is mainly regulated post-

translationally [168]. In the inactive state, NF- κ B binds the inhibitor of κ B (I κ B) proteins and is sequestered in the cytoplasm. Under upstream activation signals, I κ B is phosphorylated by I κ B kinase (IKK) and degraded by the proteasome. Consequentially, NF- κ B is freed and translocates into the nucleus to activate its target genes. Increased constitutive activation of NF- κ B and inflammation have been observed in multiple tissues during aging [169-171]. Moreover, inhibition of NF- κ B attenuates aging phenotypes in normal and accelerated aging [172, 173], posing NF- κ B as a driver of aging as well as a potential therapeutic target. Despite the incomplete understanding of how NF- κ B and resulting inflammation promote aging, NF- κ B activities and the secretion of pro-inflammatory cytokines have been shown to account for certain aging-related processes, such as cellular senescence [174] - an irreversible cell cycle arrest that leads to aging-related functional deterioration (*e.g.* stem cell depletion) - and immunosenescence [165, 175] - the functional decline of the adaptive immune system during aging. Notably, NF- κ B signaling crosstalks with other aging regulatory pathways. SIRT1 has been shown to bind and deacetylate the NF- κ B complex component p65/RelA and thereby reduce NF- κ B activity [176], whereas IIS activates NF- κ B *via* an Akt-IKK axis [177]. In addition, mTOR can directly stimulate IKK to inhibit NF- κ B [178], while active IKK, in turn, promotes mTOR activity by phosphorylating the mTOR suppressor TSC1 [179]. For more detailed discussions on NF- κ B and inflammaging, readers are encouraged to turn to [175, 180].

3. INTERPLAY BETWEEN AGING REGULATORY SIGNALING PATHWAYS AND THE EPIGENOME

In eukaryotic cells, nuclear DNA is packaged into nucleoprotein complexes known as chromatin, which helps to compact the genome, to maintain its integrity, and also to regulate the accessibility to its DNA sequences by other proteins, including transcription factors and the transcription machinery. As a result, chromatin and the processes that control it provide an additional epigenetic layer of gene regulation, which is highly dynamic and is thought to affect most biological processes, including aging.

In eukaryotes, DNA is wrapped around a histone octamer containing two copies of the histone proteins H2A, H2B, H3 and H4 respectively, making up the nucleosome, the smallest building block of chromatin [181]. A fifth histone, histone H1, binds the linker DNA regions between nucleosomes to stabilize chromatin structure and aid its further folding and condensation [182]. Association with additional proteins or non-coding RNAs eventually helps chromatin to fold into higher order arrangements and to position within the nucleus. Chromatin and thereby transcription can be influenced through several mechanisms, most importantly covalent modification of its DNA or histones, usage of histone variants, repositioning of nucleosomes, its tethering to the nuclear envelope, and its association with non-coding RNAs [183].

Aging-regulatory signaling pathways to large extent influence aging through the regulation of gene expression. Since the accessibility of target genes is strongly influenced by the epigenome and the resulting chromatin states at their

genomic loci, the epigenome can strongly influence the output of these signaling pathways. Conversely, pro-longevity signals can also actively remodel the epigenome in the course of transcriptional regulation (Fig. 2). During organismal and cellular aging, the epigenome undergoes substantial changes, characterized by the general loss of heterochromatin as well as alterations in histone marks and DNA methylation [6, 7]. Although it remains challenging to determine the causal roles of epigenetic regulation for aging, it is feasible to slow down or accelerate aging through epigenetic manipulations, such as mutations in certain histone modifying enzymes [7]. Furthermore, the Yamanaka factors (Oct3/4, Sox2, Klf4 and c-Myc), which can substantially alter the epigenome of highly differentiated cells to induce a pluripotent state, have been shown to ameliorate aging phenotypes *in vitro* [184] and *in vivo* [185] through partial epigenetic reprogramming. Both examples illustrate the power of the epigenome in aging regulation and suggest that it has causal roles - at least in part. Here we give an overview of the intertwined relationship between the epigenome, aging, and aging-regulatory signaling pathways, with a particular focus on how the epigenome may influence aging-regulatory transcription factors and *vice versa*.

3.1. DNA Methylation

The bases of DNA are subject to a variety of chemical modifications, among which the 5mC methylation of CpG dinucleotides in mammalian cells has the best characterized connection to gene expression. Although varying across metazoans, methylation is found on 60-80% of all CpGs in mammalian genomes [186]. CpG methylation in promoter regions is usually linked to gene repression [186, 187]. Frequently expressed genes commonly have an abundance of non-methylated CpGs in their promoter regions, whereas frequently silent genes tend to have highly methylated promoters. CpG methylation is symmetric on both DNA strands and heritable to the daughter cells during DNA replication, owing to the activity of DNA methyltransferase 1 (DNMT1) [188]. Apart from this maintained methylation, *de novo* methylation can occur by two *de novo* methyltransferases, DNMT3a and DNMT3b [189]. Both mechanisms assist the maintenance of epigenetic memory and the temporal and spatial control of gene expression [190]. CpG methylation can affect gene expression by either physically obstructing the binding of transcription factors and the transcription machinery [191] or recruiting methyl-CpG-binding domain proteins (MBDs) that further recruit histone modifiers and chromatin remodelers to form heterochromatin, a generally more compact and thus transcriptionally repressive chromatin state [192]. Notably, some specific transcription factors are actually methyl-CpG-binding proteins, mediating activation or repression of gene expression in the vicinity to methylated CpGs [193].

DNA methylation, particularly the CpG methylation found in mammals, undergoes a variety of changes with age. These changes have been studied extensively. Although DNA methylation is strongly influenced by environmental factors, they cannot explain the age-associated epigenetic changes. Instead, they seem to be, at least partially, the result of aging regulatory mechanisms [194, 195]. For instance, the

sion - at least in the regions in which the changes occur. Instead, they may need to synergize with additional factors or epigenetic mechanisms. In support of such notion, broad-scale genomic changes in DNA methylation were found to impact recruitment of the polycomb repressive complex 2 (PRC2) and resulting gene repression by H3K27 methylation, not wherever DNA methylation had changed but specifically at PRC2 target genes [201].

Although it remains undetermined whether DNA methylation changes are a cause or consequence of the aging processes, they at least have been highly predictive of chronological and biological age in mammals [202-204]. Most notably, an epigenetic clock could be established by the characterization of DNA methylation at 353 CpG sites in a data collection from different tissues [204, 205]. Furthermore, this clock associates with specific age-related diseases, e.g. the neurodegenerative Huntington's disease [206]. Such intriguing correlation between DNA methylation at specific sites and age strongly implies a functional involvement of DNA methylation in aging regulation, although more studies are needed to fully clarify this matter.

3.2. Histone Modifications and Histone Variants

Similar to DNA, histones can be covalently modified. In particular the N-terminal tails of histones are subject to various post-translational modifications (PTMs) that serve as anchors for other chromatin-associated proteins [207]. Although a variety of histone PTMs have been described, methylations and acetylations of lysines on histones H3 and H4 are the most prominent and characterized in the context of gene regulation. Acetylation of histones generally facilitates gene activation by relaxing the nucleosome structure and thereby improving DNA accessibility [208]. Methylation poses different effects depending on the location and number of methyl groups [209]. For instance, di- and tri-methylation of H3K9 and H3K27 are thought to repress gene expression, whereas H3K4me3 marks gene activation. In addition to various modifications, replacement of canonical histones by variants is another mechanism that changes the chromatin state and exerts epigenetic regulation [183].

Deposition of canonical histones only occurs during DNA replication and thus requires for cells to be actively dividing. In contrast, deposition of histone variants such as H3.3 occurs in a DNA replication-independent manner and thus in post-mitotic cells, too [210]. Histone variants provide additional control over epigenetic regulation. For extensive reviews on gene regulation by histone modifications and variants, readers can turn to [207, 211].

Post-translational histone modifications form perhaps the most intensely studied aspect of epigenetic regulation, also in the context of aging. They influence gene expression by altering chromatin structure (e.g. promoting eu- or heterochromatin formation), aiding or blocking the recruitment of transcription factors and the transcription machinery. For instance, at the onset of reproduction maturity in *C. elegans*, trimethylation of H3K27 (H3K27me3) occurs at the promoters of heat shock protein genes, resulting in reduced binding of HSF-1 and thereby repression of the heat shock response [212]. Overall, a variety of age-related changes in histone marks have been observed. However, the interpretation of

these changes has remained difficult. First, their function can be highly context dependent. Second, these changes can both drive aging regulation and be driven by aging regulatory signaling pathways. For instance, in a study of human FOXO3 [213], preexisting histone marks that confer open chromatin have been shown to dictate the binding of FOXO3 to enhancer regions. In turn, FOXO3 binding further enhances these active chromatin marks to facilitate gene expression (Fig. 2d). Recent studies of histone methylation in mitochondria-mediated longevity in *C. elegans* may serve as another good example. Widespread H3K9me2 conferred by the methyltransferase MET-2 and removal of H3K27me3 by the two demethylases JMJD-1.2 and JMJD-3.1 are essential for mitochondrial stress resistance and longevity [214, 215]. Moreover, elevated activity of these demethylases was sufficient to extend lifespan via the UPR^{mt} pathway. On the contrary, another histone demethylase, UTX-1, negatively regulates *C. elegans* lifespan. Decreased UTX-1 levels promote FOXO/DAF-16-dependent longevity and increase the repressive mark H3K27me3 at the insulin/IGF receptor gene, *daf-2* [216]. The most prominent histone mark in the context of aging might be H3K4me3. This mark, linked to active chromatin, is remodeled during organismal and cellular aging in animals [8, 198]. Deficiency of H3K4me3 induces longevity transgenerationally in *C. elegans* [217, 218], by promoting the accumulation of mono-unsaturated fatty acids [219]. Histone acetylation, usually associated with gene activation, also participates in aging regulation. This is suggested by the roles of class III histone deacetylases (HDACs), sirtuins, in caloric restriction (CR)-mediated longevity in multiple organisms [7]. Furthermore, histone acetylation modifiers have been shown to interact with aging regulatory transcription factors in various contexts. For example, the histone acetyl transferase CBP/p300, a factor implicated in aging regulation in *C. elegans* [220], can be recruited by the transcription factor CREB to chromatin, where it confers histone acetylation to promote transcription of CREB target genes [221]. Furthermore, the H3K9ac and H4K16ac deacetylase SIRT1 forms a complex with the transcription factor FOXO in response to oxidative stress [222]. Although SIRT1 is thought to deacetylate FOXO in this case, it remains possible that histone deacetylation at the FOXO target promoters is involved, too. The NF- κ B member RELA (p65) recruits and interacts with the HDAC SIRT6 under stress conditions to mount a transcriptional response [173]. Loss of SIRT6 enhances RELA-dependent apoptosis and senescence in cell culture. This is in line with an increased NF- κ B activity observed in aging adult stem cells. Similarly, a nuclear receptor TLX, crucial for Neural Stem Cell (NSC) maintenance with age, interacts with histone modifiers including HDAC3, HDAC5, and the histone demethylase LSD1 to modify the promoter regions of p21^{CIP1} and PTEN to promote NSC proliferation [223].

A general caveat of understanding histone modifier-transcription factor interactions is the difficulty in determining whether the histone modifying enzyme acts on histones at the target promoters or actually on the transcription factor itself. For many such interactions this issue still needs to be addressed.

Besides post-translational modifications on histones, the properties of nucleosomes can be altered by histone variants

that sometimes substitute the canonical histones. Several histone variants have been implicated as regulators of cellular and organismal aging-related processes. For example, the H2A variant macroH2A, enriched in Senescence-Associated Heterochromatin Foci (SAHF), is presumed to ensure gene repression in these regions [224]. Increased incorporation of the H3 variant H3.3 is observed in aged mammalian brain as well as aged *C. elegans* [225, 226]. H3.3 is particularly interesting, as it is incorporated independently of DNA replication and thus could participate also in chromatin changes that occur in post-mitotic or senescent cells. Indeed, overexpression of H3.3 alone is sufficient to drive cellular senescence [227]. Moreover, in *C. elegans*, although H3.3 has little impact on lifespan in wild type, it is required for the prevention of aging in several longevity regimens, including low IIS, lack of germline, and mitochondrial perturbations. H3.3 assures the aging-preventive transcriptomic changes that occur under these conditions [225]. All of the above underscores H3.3 incorporation as an epigenetic mechanism that can regulate the aging process.

3.3. Chromatin Remodeling and Pioneer Transcription Factors

The positioning and density of nucleosomes on DNA is another important mechanism that affects gene expression, as the presence of nucleosomes commonly obstructs DNA binding by transcription factors or the transcription machinery itself. In particular, ATP-dependent chromatin remodeling enzymes control the distribution of nucleosomes [4] by activities such as histone exchange, nucleosome eviction, or sliding of the nucleosomes along the DNA. In total, there are four families of chromatin remodelers known to date, distinguished by the domain structures of their catalytic subunits: the SWI/SNF, ISWI, CHD, and INO80 families. While they have partially distinct physiological roles, each of them can both free and block DNA sequences of importance from nucleosome occupancy, and thus can cast either activating or repressive effects on gene expression [228].

While extensively influenced by the epigenome, signaling pathways can take an active role in shaping the epigenome through pioneer transcription factors. Pioneer transcription factors, in contrast to regular transcription factors, are capable of binding their target loci even in compacted transcriptionally inactive chromatin regions and decondensating the chromatin, usually by recruitment of chromatin remodelers but also histone modifiers, in order to allow for binding of downstream transcriptional regulators and the transcription machinery itself [229]. Several central aging regulators may presumably act as pioneer transcription factors [230]: The most prominent examples are the forkhead box proteins, all of which have important functions in processes like development, growth, and aging regulation. Of these, especially FOXA has long been considered the prototype of a pioneer transcription factor [229], which during important developmental transitions is the first transcription factor to get activated, to bind its target genes, open the chromatin in these regions, initiate recruitment of epigenome altering enzymes, and thereby trigger a cascade of downstream transcriptional events that allow development to proceed. As we already mentioned earlier in this review, in addition to the role in development, FOXA/PHA-4 is required

for longevity in response to dietary restriction in *C. elegans* [69]. Therefore, the epigenome-altering activity of PHA-4 at its target promoters is likely to be an essential step in the aging-preventive effects of dietary restriction, too. Another, yet detrimental, function of FOXA was observed in aged mouse liver: Here FOXA2 binds nuclear receptor target loci with decreased nucleosome occupancy, presumably contributing to metabolic dysfunction by driving the eviction of nucleosomes [231]. More recently, FOXO has also been shown to have pioneering capabilities in the context of aging: In *C. elegans* exposed to stress or a lack of insulin/IGF signaling, FOXO/DAF-16 is activated and recruits the chromatin remodeler SWI/SNF, to activate the expression of stress response and longevity promoting genes [33]. Knock-down of SWI/SNF subunits impairs FOXO/DAF-16-mediated longevity, suggesting chromatin remodeling as a requirement for the activation of DAF-16 target genes. In another recent *C. elegans* study, the chromatin modifier AF10/ZFP-1 has been shown to be regulated by both FOXO/DAF-16 and FOXA/PHA-4 [232]. In turn, AF10/ZFP-1 impairs the binding of FOXO/DAF-16 and FOXA/PHA-4 to their target sites, forming a feed-forward loop that controls the amplitude and duration of their target gene expression. Besides forkhead box proteins, NRF/SKN-1 is another anti-aging transcription factor with pioneer factor capability. In human cells, NRF2 is able to recruit BRG1, the catalytic subunit of the SWI/SNF complex to some target sites in response to oxidative stress [233].

These findings nicely illustrate how pioneer transcription factors can break through epigenetic barriers to initiate transcriptional regulatory including epigenome-changing cascades, and that the use of such factors is an integral part of many aging-regulatory pathways.

3.4. Long Non-coding RNAs

Studies of the non-coding genome have revealed diverse roles for non-coding RNAs in shaping the epigenome. Long non-coding RNAs (lncRNAs) have drawn increasing attention as regulators of gene expression. One classic example is a lncRNA, X-inactive specific transcript (Xist), that mediates inactivation of the X chromosome [234]. It binds multiple loci across the entire X chromosome and recruits polycomb repressive complexes. The latter add repressive histone marks to the inactivated X chromosome, leading to silencing of gene expression. Other lncRNAs are involved in the phenomenon of genomic imprinting, binding to imprinted regions and silencing neighboring genes *in cis* by promoting histone modifications, conferring parent-of-origin specific gene expression patterns [235].

Moreover, lncRNAs also bear roles beyond dosage compensation and imprinting. For instance, transcription factors can use them to fine-tune the expression of their target genes. A prime example is found in the senescence regulating p53 pathway. The transcription factor p53 induces the expression of several lncRNAs [236] that in turn use diverse mechanisms to modulate the p53 target gene network [237]. Most notably, they can recruit the polycomb repressive complex 2 (PRC2) to place the repressive histone mark H3K27me3. For instance, the p53-induced noncoding transcript (Pint) recruits PRC2 to repress genes in the TGF β , AMPK, and p53 pathways, to promote cell proliferation [238].

Besides conferring gene repression, lncRNAs can activate gene expression by epigenetic alterations, too. A pro-senescence lncRNA named VAD inhibits the incorporation of the repressive histone variant H2A.Z in INK4 promoter regions, which promotes the expression of p16 and p14 to maintain senescence [239].

3.5. Nuclear Organization

In the nucleus, chromosomes occupy defined chromosomal territories [5]. Active regions are usually at the surface of the territory, whereas silent regions are buried in the interior. Furthermore, lowly-expressed heterochromatin tends to locate near the nuclear lamina. Alterations of the nuclear architecture are observed in *C. elegans* during aging and in human senescent cells [240, 241]. Disrupted nuclear organization may disturb aging-regulatory transcriptional events, for instance, prevent the access of aging-preventive transcription factors to their target genes or lead to loss of repression of otherwise nuclear lamina-associated aging-promoting genes, both of which would accelerate aging [242]. Strong evidence for this hypothesis is provided by several progeric syndromes in humans. The most prominent of these is Hutchinson-Gilford Progeria Syndrome (HGPS), in which a mutant form of the lamin A protein, called progerin, is expressed and leads to defects in the nuclear lamina, misshapen nuclei, changes in nuclear chromatin structure and organization, and eventually accelerated aging [243]. HGPS displays features reminiscent of normal aging [244]. Notably, progerin has been shown to also accumulate during normal aging and disrupt cellular functions [245, 246], indicating potential common mechanisms between HGPS and normal aging. Recent work showed that progerin and the resulting nuclear defects lead to misexpression of oxidative stress response genes, controlled by the aging-preventive transcription factor NRF2, and that inactivation of NRF2 signaling in wild type cells mimics HGPS pathology [247]. In another progeria syndrome, Néstor-Guillermo Progeria Syndrome (NGPS), again the causal mutation was found in a nuclear lamina associated protein, BANF1 [248]. Given its DNA and histone binding ability as well as key roles in nuclear assembly [249-251], BANF1 is likely to ensure the functions of aging regulatory pathways by maintaining nuclear organization. Another nuclear lamin protein, lamin B1, is strongly associated with cellular senescence [252]. Loss of lamin B1 profoundly alters the chromatin landscape and drives proliferating cells into senescence [253].

CONCLUSION AND FUTURE PERSPECTIVES

Aging is undoubtedly an intricate and complex process. While it describes the organism's general decay over time, it is highly plastic - subject to regulation in multiple layers and by various mechanisms and pathways. Here we have focused on the transcriptional regulatory events that lie in the center of many aging regulatory signaling pathways, converting aging-related stimuli into the expression of stress resistance genes. These events are conferred not only by transcription factors, but also by the chromatin landscape and the epigenome that they interact with. Transcription factors and the epigenome are in constant crosstalk, with the epigenome strongly influencing the behavior of aging-regulatory tran-

scription factors, e.g. by controlling their binding or binding of their coregulators to promoter regions; concurrently, the activity of aging-regulatory transcription factors can shape the epigenome, e.g. by recruiting chromatin remodelers or modifiers, to control the expression of its target genes.

During aging, the epigenome undergoes drastic changes. Several attempts have been made to identify the root of these changes [7], with limited success. Due to the interconnected nature of aging-regulatory pathways, it has remained challenging to distinguish causes from consequences and to determine the degree to which epigenetic alterations drive the aging process. Nevertheless, one outcome of the age-related epigenetic changes is a general loss of precise transcriptional control, which is thought to strongly contribute to aging phenotypes [6, 254]. It will be of great importance that future studies further address the causality of epigenetic changes for the physiological aging process.

Another future direction should be to expand our studies of the aging-related epigenetic repertoire beyond the most common marks and modifications. While most aging-related efforts regarding histone modifications focus on acetylation, methylation, or phosphorylation of their N-terminal tails, modifications by rarer moieties or modifications in the core regions of histones [255] remain an unexplored territory. Furthermore, mammalian genomes had long been thought to contain only one form of DNA methylation, 5mC, until recent work described the epigenetic silencing by Adenine methylation, 6mA [256]. Studies of such less common modifications may further aid our understanding of the aging epigenome. What is also worth noting is the connection between metabolism and epigenetic regulation. Many epigenetic modifiers utilize metabolites as substrates or co-factors (e.g. NAD-dependent sirtuins, Acetyl-CoA-dependent HATs, etc.) and thus are able to relay metabolic changes to the epigenome [257]. It would be of great value to further elucidate the cross talk between metabolism and epigenetic regulation that may in turn influence aging-regulatory transcription factors.

Finally, crosstalk between the transcription machinery and the epigenome can have an impact beyond the transcriptional level. Post-transcriptional processing, in particular pre-mRNA splicing, is tightly coupled to transcription [258, 259]. Especially, the splice site choice and recruitment of splicing factors are largely determined by a combination of transcriptional and epigenetic properties [259-262]. This implies changes in mRNA splicing as an underappreciated but important component of aging-regulatory events. Indeed, recent studies of human diseases [263] and aging in *C. elegans* [264, 265] seem to support such notion.

We conclude that aging-regulatory transcription factors, age-related changes in the epigenome, and their crosstalk form an extremely important aspect of aging regulation, resulting in a tightly controlled multilayered network that converts aging-regulatory signals into gene expression events and physiological outcomes. Up to now, we still have a rather incomplete understanding of this network and thus still have a long but exciting road ahead to fully chart it.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

- [1] Fulop, T.; Larbi, A.; Witkowski, J.M.; McElhaney, J.; Loeb, M.; Mitnitski, A.; Pawelec, G. Aging, frailty and age-related diseases. *Biogerontology*, **2010**, *11*(5), 547-563.
- [2] Uno, M.; Nishida, E. Lifespan-regulating genes in *C. elegans*. *NPJ Aging Mech. Dis.*, **2016**, *2*, 16010. Available from: <https://www.nature.com/articles/npjamd201610>
- [3] Riera, C.E.; Merkwirth, C.; De Magalhaes Filho, C.D.; Dillin, A.C. Signaling networks determining life span. *Annu. Rev. Biochem.*, **2016**, *85*, 35-64. Available from: <https://www.annualreviews.org/doi/10.1146/annurev-biochem-060815-014451>
- [4] Narlikar, G.J.; Sundaramoorthy, R.; Owen-Hughes, T. Mechanisms and functions of ATP-dependent chromatin-remodeling enzymes. *Cell*, **2013**, *154*(3), 490-503.
- [5] Cavalli, G.; Misteli, T.G. Functional implications of genome topology. *Nat. Struct. Mol. Biol.*, **2013**, *20*(3), 290-299.
- [6] Booth, L.N.; Brunet, A. The aging epigenome. *Mol. Cell.*, **2016**, *62*(5), 728-744.
- [7] Pal, S.; Tyler, J.K. Epigenetics and aging. *Sci. Adv.*, **2**(7), e1600584. Available from: <http://advances.sciencemag.org/content/2/7/e1600584>
- [8] Benayoun, B.A.; Pollina, E.A.; Brunet, A.B. Epigenetic regulation of ageing: Linking environmental inputs to genomic stability. *Nat. Rev. Mol. Cell. Biol.*, **2015**, *16*(10), 593-610.
- [9] Johnson, T.E. Increased life-span of age-1 mutants in *Caenorhabditis elegans* and lower Gompertz rate of aging. *Science*, **1990**, *249*(4971), 908-912. Available from: <http://science.sciencemag.org/content/249/4971/908/tab-article>
- [10] Klass, M.R. A method for the isolation of longevity mutants in the nematode *Caenorhabditis elegans* and initial results. *Mech. Ageing Dev.*, **1983**, *22*(3-4), 279-286.
- [11] Kenyon, C.; Chang, J.; Gensch, E.; Rudner, A.; Tabtiang, R. A *C. elegans* mutant that lives twice as long as wild type. *Nature*, **1993**, *366*(6454), 461-464. Available from: <https://www.nature.com/articles/366461a0>
- [12] Giannakou, M.E.; Partridge, L. Role of insulin-like signalling in *Drosophila* lifespan. *Trends Biochem. Sci.*, **2007**, *32*(4), 180-188.
- [13] Martins, R.; Lithgow, G.J.; Link, W. Long live FOXO: Unraveling the role of FOXO proteins in aging and longevity. *Ageing Cell*, **2016**, *15*(2), 196-207.
- [14] Suh, Y.; Atzmon, G.; Cho, M.O.; Hwang, D.; Liu, B.; Leahy, D.J.; Barzilai, N.; Cohen, P. Functionally significant insulin-like growth factor I receptor mutations in centenarians. *Proc. Natl. Acad. Sci. U.S.A.*, **2008**, *105*(9), 3438-3442.
- [15] Kojima, T.; Kamei, H.; Aizu, T.; Arai, Y.; Takayama, M.; Nakazawa, S.; Ebihara, Y.; Inagaki, H.; Masui, Y.; Gondo, Y.; Sakaki, Y.; Hirose, N. Association analysis between longevity in the Japanese population and polymorphic variants of genes involved in insulin and insulin-like growth factor I signaling pathways. *Exp. Gerontol.*, **2004**, *39*(11-12), 1595-1598.
- [16] Pawlikowska, L.; Hu, D.; Huntsman, S.; Sung, A.; Chu, C.; Chen, J.; Joyner, A.H.; 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.; Ziv, E.; Study of Osteoporotic Fractures. Association of common genetic variation in the insulin/IGF1 signaling pathway with human longevity. *Ageing Cell*, **2009**, *8*(4), 460-472.
- [17] Willcox, B.J.; Donlon, T.A.; He, Q.; Chen, R.; Grove, J.S.; Yano, K.; Masaki, K.H.; Willcox, D.C.; Rodriguez, B.; Curb, J.D. FOXO3A genotype is strongly associated with human longevity. *Proc. Natl. Acad. Sci. U.S.A.*, **2008**, *105*(37), 13987-13992.
- [18] Anselmi, C.V.; Malovini, A.; Roncarati, R.; Novelli, V.; Villa, F.; Condorelli, G.; Bellazzi, R.; Puca, A.A. Association of the FOXO3A locus with extreme longevity in a southern Italian centenarian study. *Rejuvenation Res.*, **2009**, *12*(2), 95-104.
- [19] Flachsbarth, F.; Caliebe, A.; Kleindorp, R.; Blanché, H.; von Eller-Eberstein, H.; Nikolaus, S.; Schreiber, S.; Nebel, A.F. Association of FOXO3A variation with human longevity confirmed in German centenarians. *Proc. Natl. Acad. Sci. U.S.A.*, **2009**, *106*(8), 2700-2705.
- [20] Li, Y.; Wang, W.J.; Cao, H.; Lu, J.; Wu, C.; Hu, F.Y.; Guo, J.; Zhao, L.; Yang, F.; Zhang, Y.X.; Li, W.; Zheng, G.Y.; Cui, H.; Chen, X.; Zhu, Z.; He, H.; Dong, B.; Mo, X.; Zeng, Y.; Tian, X.L. Genetic association of FOXO1A and FOXO3A with longevity trait in Han Chinese populations. *Hum. Mol. Genet.*, **2009**, *18*(24), 4897-4904.
- [21] Lunetta, K.L.; D'Agostino, R.B., Sr; Karasik, D.; Benjamin, E.J.; Guo, C.Y.; Govindaraju, R.; Kiel, D.P.; Kelly-Hayes, M.; Massaro, J.M.; Pencina, M.J.; Seshadri, S.; Murabito, J.M. Genetic correlates of longevity and selected age-related phenotypes: A genome-wide association study in the Framingham Study. *BMC Med. Genet.*, **2007**, *8*(Suppl 1), S13. Available from: <https://bmcmmedgenet.biomedcentral.com/articles/10.1186/1471-2350-8-S1-S13>
- [22] Manning, B.D.; Cantley, L.C. AKT/PKB signaling: Navigating downstream. *Cell*, **2007**, *129*(7), 1261-1274.
- [23] Gottlieb, S.; Ruvkun, G. daf-2, daf-16 and daf-23: Genetically interacting genes controlling Dauer formation in *Caenorhabditis elegans*. *Genetics*, **1994**, *137*(1), 107-120.
- [24] Ailion, M.; Thomas, J.H. Isolation and characterization of high-temperature-induced Dauer formation mutants in *Caenorhabditis elegans*. *Genetics*, **2003**, *165*(1), 127-144.
- [25] Manning, B.D.; Toker, A. AKT/PKB Signaling: Navigating the Network. *Cell*, **2017**, *169*(3), 381-405.
- [26] Hertweck, M.; Göbel, C.; Baumeister, R. *C. elegans* SGK-1 is the critical component in the Akt/PKB kinase complex to control stress response and life span. *Dev. Cell.*, **2004**, *6*(4), 577-588.
- [27] Brunet, A.; Park, J.; Tran, H.; Hu, L.S.; Hemmings, B.A.; Greenberg, M.E. Protein kinase SGK mediates survival signals by phosphorylating the forkhead transcription factor FKHL1 (FOXO3a). *Mol. Cell. Biol.*, **2001**, *21*(3), 952-965.
- [28] Brunet, A.; Bonni, A.; Zigmond, M.J.; Lin, M.Z.; Juo, P.; Hu, L.S.; Anderson, M.J.; Arden, K.C.; Blenis, J.; Greenberg, M.E. Akt promotes cell survival by phosphorylating and inhibiting a Forkhead transcription factor. *Cell*, **1999**, *96*(6), 857-868.
- [29] Berdichevsky, A.; Viswanathan, M.; Horvitz, H.R.; Guarente, L. *C. elegans* SIR-2.1 interacts with 14-3-3 proteins to activate DAF-16 and extend life span. *Cell*, **2006**, *125*(6), 1165-1177.
- [30] Li, J.; Tewari, M.; Vidal, M.; Lee, S.S. The 14-3-3 protein FTT-2 regulates DAF-16 in *Caenorhabditis elegans*. *Dev. Biol.*, **2007**, *301*(1), 82-91.
- [31] Ogg, S.; Ruvkun, G. The *C. elegans* PTEN homolog, DAF-18, acts in the insulin receptor-like metabolic signaling pathway. *Mol. Cell*, **1998**, *2*(6), 887-893.
- [32] Eijkelenboom, A.; Burgering, B.M. FOXOs: Signalling integrators for homeostasis maintenance. *Nat. Rev. Mol. Cell. Biol.*, **2013**, *14*(2), 83-97.
- [33] Riedel, C.G.; Downen, R.H.; Lourenco, G.F.; Kirienko, N.V.; Heimbucher, T.; West, J.A.; Bowman, S.K.; Kingston, R.E.; Dillin, A.; Asara, J.M.; Ruvkun, G. DAF-16 employs the chromatin remodeller SWI/SNF to promote stress resistance and longevity. *Nat. Cell. Biol.*, **2013**, *15*(5), 491-501.
- [34] Morley, J.F.; Morimoto, R.I. Regulation of longevity in *Caenorhabditis elegans* by heat shock factor and molecular chaperones. *Mol. Biol. Cell.*, **2004**, *15*(2), 657-664.
- [35] Hsu, A.L.; Murphy, C.T.; Kenyon, C. Regulation of aging and age-related disease by DAF-16 and heat-shock factor. *Science*, **2003**, *300*(5622), 1142-1145. Available from: <http://science.sciencemag.org/content/300/5622/1142>
- [36] Chiang, W.C.; Ching, T.T.; Lee, H.C.; Mousigian, C.; Hsu, A.L. HSF-1 regulators DDL-1/2 link insulin-like signaling to heat-shock responses and modulation of longevity. *Cell*, **2012**, *148*(1-2), 322-334.
- [37] Tullet, J.M.; Hertweck, M.; An, J.H.; Baker, J.; Hwang, J.Y.; Liu, S.; Oliveira, R.P.; Baumeister, R.; Blackwell, T.K. Direct inhibition of the longevity-promoting factor SKN-1 by insulin-like signaling in *C. elegans*. *Cell*, **2008**, *132*(6), 1025-1038.
- [38] Hsu, J.M.; Huang, J.; Meluh, P.B.; Laurent, B.C. The yeast RSC chromatin-remodeling complex is required for kinetochore function in chromosome segregation. *Mol. Cell. Biol.*, **2003**, *23*(9), 3202-3215.
- [39] Baird, N.A.; Douglas, P.M.; Simic, M.S.; Grant, A.R.; Moresco, J.J.; Wolff, S.C.; Yates, J.R., 3rd; Manning, G.; Dillin, A.N. HSF-1-

- mediated cytoskeletal integrity determines thermotolerance and life span. *Science*, **2014**, *346*(6207), 360-363. Available from: <http://science.sciencemag.org/content/346/6207/360>
- [40] An, J.H.; Blackwell, T.K. SKN-1 links *C. elegans* mesodermal specification to a conserved oxidative stress response. *Genes Dev.*, **2003**, *17*(15), 1882-1893.
- [41] Bishop, N.A.; Guarente, N. Two neurons mediate diet-restriction-induced longevity in *C. elegans*. *Nature*, **2007**, *447*(7144), 545-549. Available from: <https://www.nature.com/articles/nature05904>
- [42] Fabrizio, P.; Pozza, F.; Pletcher, S.D.; Gendron, C.M.; Longo, V.D. Regulation of longevity and stress resistance by Sch9 in yeast. *Science*, **2001**, *292*(5515), 288-290. Available from: <http://science.sciencemag.org/content/292/5515/288>
- [43] Howell, J.J.; Manning, B.D. mTOR couples cellular nutrient sensing to organismal metabolic homeostasis. *Trends Endocrinol. Metab.*, **2011**, *22*(3), 94-102.
- [44] Bhaskar, P.T.; Hay, N.P. The two TORCs and Akt. *Dev. Cell*, **2007**, *12*(4), 487-502.
- [45] Johnson, S.C.; Rabinovitch, P.S.; Kaeberlein, M. mTOR is a key modulator of ageing and age-related disease. *Nature*, **2013**, *493*(7432), 338-345. Available from: <http://www.nature.com/nature/journal/v493/n7432/nature11861/metrics/citations?page=2>
- [46] McCormick, M.A.; Tsai, S.-Y.; Kennedy, B.K. TOR and ageing: A complex pathway for a complex process. *Philos. Trans. R Soc. Lond. B Biol. Sci.*, **2011**, *366*(1561), 17-27. Available from: <http://rsta.royalsocietypublishing.org/content/366/1561/17>
- [47] Saxton, R.A.; Sabatini, D.M. mTOR signaling in growth, metabolism, and disease. *Cell*, **2017**, *169*(2), 361-371.
- [48] Hay, N. Interplay between FOXO, TOR, and Akt. *Biochim. Biophys. Acta*, **2011**, *1813*(11), 1965-1970.
- [49] Huang, J.; Manning, B.D. A complex interplay between Akt, TSC2 and the two mTOR complexes. *Biochem. Soc. Trans.*, **2009**, *37*(Pt 1), 217-222.
- [50] Takano, A.; Usui, I.; Haruta, T.; Kawahara, J.; Uno, T.; Iwata, M.; Kobayashi, M. Mammalian target of rapamycin pathway regulates insulin signaling via subcellular redistribution of insulin receptor substrate 1 and integrates nutritional signals and metabolic signals of insulin. *Mol. Cell. Biol.*, **2001**, *21*(15), 5050-5062.
- [51] Shaw, R.J. mTOR signaling: RAG GTPases transmit the amino acid signal. *Trends Biochem. Sci.*, **2008**, *33*(12), 565-568.
- [52] Powers, R.W., 3rd; Kaeberlein, M.; Caldwell, S.D.; Kennedy, B.K.; Fields, S. Extension of chronological life span in yeast by decreased TOR pathway signaling. *Genes Dev.*, **2006**, *20*(2), 174-184.
- [53] Kaeberlein, M.; Powers, R.W., 3rd; Steffen, K.K.; Westman, E.A.; Hu, D.; Dang, N.; Kerr, E.O.; Kirkland, K.T.; Fields, S.; Kennedy, B.K. Regulation of yeast replicative life span by TOR and Sch9 in response to nutrients. *Science*, **2005**, *310*(5751), 1193-1196. Available from: <http://science.sciencemag.org/content/310/5751/1193.full>
- [54] Jia, K.; Chen, D.; Riddle, D.L. The TOR pathway interacts with the insulin signaling pathway to regulate *C. elegans* larval development, metabolism and life span. *Development*, **2004**, *131*(16), 3897-3906.
- [55] Vellai, T.; Takacs-Vellai, K.; Zhang, Y.; Kovacs, A.L.; Orosz, L.; Müller, F. Genetics: Influence of TOR kinase on lifespan in *C. elegans*. *Nature*, **2003**, *426*(6967), 620. Available from: <https://www.nature.com/articles/426620a>
- [56] Kapahi, P.; Zid, B.M.; Harper, T.; Koslover, D.; Sapin, V.; Benzer, S. Regulation of lifespan in *Drosophila* by modulation of genes in the TOR signaling pathway. *Curr. Biol.*, **2004**, *14*(10), 885-890.
- [57] Miller, R.A.; Harrison, D.E.; Astle, C.M.; Baur, J.A.; Boyd, A.R.; de Cabo, R.; Fernandez, E.; Flurkey, K.; Javors, M.A.; Nelson, J.F.; Oriuela, C.J.; Pletcher, S.; Sharp, Z.D.; Sinclair, D.; Starnes, J.W.; Wilkinson, J.E.; Nadon, N.L.; Strong, R. Rapamycin, but not resveratrol or simvastatin, extends life span of genetically heterogeneous mice. *J. Gerontol. A Biol. Sci. Med. Sci.*, **2011**, *66*(2), 191-201.
- [58] Zhang, Y.; Bokov, A.; Gelfond, J.; Soto, V.; Ikeno, Y.; Hubbard, G.; Diaz, V.; Sloane, L.; Maslin, K.; Treaster, S.; Rendon, S.; van Remmen, H.; Ward, W.; Javors, M.; Richardson, A.; Austad, S.N.; Fischer, K. Rapamycin extends life and health in C57BL/6 mice. *J. Gerontol. A Biol. Sci. Med. Sci.*, **2014**, *69*(2), 119-130.
- [59] Anisimov, V.N.; Zabezhinski, M.A.; Popovich, I.G.; Piskunova, T.S.; Semenchenko, A.V.; Tyndyk, M.L.; Yurova, M.N.; Rosenfeld, S.V.; Blagosklonny, M.V. Rapamycin increases lifespan and inhibits spontaneous tumorigenesis in inbred female mice. *Cell Cycle*, **2011**, *10*(24), 4230-4236.
- [60] 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.; Miller, R.A. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. *Nature*, **2009**, *460*(7253), 392-395. Available from: <https://www.nature.com/articles/nature08221>
- [61] Robida-Stubbs, S.; Glover-Cutter, K.; Lamming, D.W.; Mizunuma, M.; Narasimhan, S.D.; Neumann-Haefelin, E.; Sabatini, D.M.; Blackwell, T.K. TOR signaling and rapamycin influence longevity by regulating SKN-1/Nrf and DAF-16/FoxO. *Cell Metab.*, **2012**, *15*(5), 713-724.
- [62] Lakowski, B.; Hekimi, S. The genetics of caloric restriction in *Caenorhabditis elegans*. *Proc. Natl. Acad. Sci. U.S.A.*, **1998**, *95*(22), 13091-13096.
- [63] Fontana, L.; Partridge, L.; Longo, V.D. Extending healthy life span--from yeast to humans. *Science*, **2010**, *328*(5976), 321-326. Available from: <http://science.sciencemag.org/content/328/5976/321>
- [64] Hansen, M.; Taubert, S.; Crawford, D.; Libina, N.; Lee, S.J.; Kenyon, C. Lifespan extension by conditions that inhibit translation in *Caenorhabditis elegans*. *Aging Cell*, **2007**, *6*(1), 95-110.
- [65] Gonskikh, Y.; Polacek, N. Alterations of the translation apparatus during aging and stress response. *Mech. Ageing Dev.*, **2017**, *168*, 30-36.
- [66] Chou, S.D.; Prince, T.; Gong, J.; Calderwood, S.K. mTOR is essential for the proteotoxic stress response, HSF1 activation and heat shock protein synthesis. *PLoS One*, **2012**, *7*(6), e39679. Available from: <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0039679>
- [67] Chen, D.; Thomas, E.L.; Kapahi, P. HIF-1 modulates dietary restriction-mediated lifespan extension via IRE-1 in *Caenorhabditis elegans*. *PLoS Genet.*, **2009**, *5*(5), e1000486. Available from: <http://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1000486>
- [68] Sheaffer, K.L.; Updike, D.L.; Mango, S.E. The target of Rapamycin pathway antagonizes pha-4/FoxA to control development and aging. *Curr. Biol.*, **2008**, *18*(18), 1355-1364.
- [69] Panowski, S.H.; Wolff, S.; Aguilaniu, H.; Durieux, J.; Dillin, A. PHA-4/Foxa mediates diet-restriction-induced longevity of *C. elegans*. *Nature*, **2007**, *447*(7144), 550-555. Available from: <https://www.nature.com/articles/nature05837>
- [70] Lapierre, L.R.; Gelino, S.; Meléndez, A.; Hansen, M. Autophagy and lipid metabolism coordinately modulate life span in germlineless *C. elegans*. *Curr. Biol.*, **2011**, *21*(18), 1507-1514.
- [71] Salminen, A.; Kaamiranta, K. AMP-activated protein kinase (AMPK) controls the aging process via an integrated signaling network. *Ageing Res. Rev.*, **2012**, *11*(2), 230-241.
- [72] Inoki, K.; Zhu, T.; Guan, K.L. Guan, TSC2 mediates cellular energy response to control cell growth and survival. *Cell*, **2003**, *115*(5), 577-590.
- [73] Gwinn, D.M.; Shackelford, D.B.; Egan, D.F.; Mihaylova, M.M.; Mery, A.; Vasquez, D.S.; Turk, B.E.; Shaw, R.J. AMPK phosphorylation of raptor mediates a metabolic checkpoint. *Mol. Cell*, **2008**, *30*(2), 214-226.
- [74] Greer, E.L.; Oskoui, P.R.; Banko, M.R.; Maniar, J.M.; Gygi, M.P.; Gygi, S.P.; Brunet, A. The energy sensor AMP-activated protein kinase directly regulates the mammalian FOXO3 transcription factor. *J. Biol. Chem.*, **2007**, *282*(41), 30107-30119.
- [75] Greer, E.L.; Dowlatshahi, D.; Banko, M.R.; Villen, J.; Hoang, K.; Blanchard, D.; Gygi, S.P.; Brunet, A. An AMPK-FOXO pathway mediates longevity induced by a novel method of dietary restriction in *C. elegans*. *Curr. Biol.*, **2007**, *17*(19), 1646-1656.
- [76] Mihaylova, M.M.; Vasquez, D.S.; Ravnskaer, K.; Denechaud, P.D.; Yu, R.T.; Alvarez, J.G.; Downes, M.; Evans, R.M.; Montminy, M.; Shaw, R.J. Class IIa histone deacetylases are hormone-activated regulators of FOXO and mammalian glucose homeostasis. *Cell*, **2011**, *145*(4), 607-621.
- [77] Mair, W.; Morantte, I.; Rodrigues, A.P.; Manning, G.; Montminy, M.; Shaw, R.J.; Dillin, A. Lifespan extension induced by AMPK and calcineurin is mediated by CRTC-1 and CREB. *Nature*, **2011**, *470*(7334), 404-408. Available from: <https://www.nature.com/articles/nature09706>
- [78] Onken, B.; Driscoll, M. 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*, **2010**, *5*(1), e8758. Available from: <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0008758>

- [79] Joo, M.S.; Kim, W.D.; Lee, K.Y.; Kim, J.H.; Koo, J.H.; Kim, S.G. AMPK facilitates nuclear accumulation of Nrf2 by phosphorylating at serine 550. *Mol. Cell. Biol.*, **2016**, *36*(14), 1931-1942.
- [80] Salminen, A.; Hyttinen, J.M.; Kaarniranta, K. AMP-activated protein kinase inhibits NF- κ B signaling and inflammation: Impact on healthspan and lifespan. *J. Mol. Med.*, **2011**, *89*(7), 667-676.
- [81] Kaerberlein, M.; McVey, M.; Guarente, L. The SIR2/3/4 complex and SIR2 alone promote longevity in *Saccharomyces cerevisiae* by two different mechanisms. *Genes Dev.*, **1999**, *13*(19), 2570-2580.
- [82] Guarente, L. Calorie restriction and sirtuins revisited. *Genes Dev.*, **2013**, *27*(19), 2072-2085.
- [83] Burnett, C.; Valentini, S.; Cabreiro, F.; Goss, M.; Somogyvári, M.; Piper, M.D.; Hodginott, 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.; Kaerberlein, M.; Soti, C.; Partridge, L.; Gems, D. Absence of effects of Sir2 overexpression on lifespan in *C. elegans* and *Drosophila*. *Nature*, **2011**, *477*(7365), 482-485. Available from: <https://www.nature.com/articles/nature10296>
- [84] Kenyon, C. The plasticity of aging: Insights from long-lived mutants. *Cell*, **2005**, *120*(4), 449-460.
- [85] Kenyon, C.J. The genetics of ageing. *Nature*, **2010**, *464*(7288), 504-512. Available from: <https://www.nature.com/articles/nature08980>
- [86] Heidler, T.; Hartwig, K.; Daniel, H.; Wenzel, U. *Caenorhabditis elegans* lifespan extension caused by treatment with an orally active ROS-generator is dependent on DAF-16 and SIR-2.1. *Biogerontology*, **2010**, *11*(2), 183-195.
- [87] Luo, J.; Nikolaev, A.Y.; Imai, S.; Chen, D.; Su, F.; Shiloh, A.; Guarente, L.; Gu, W. Negative control of p53 by Sir2alpha promotes cell survival under stress. *Cell*, **2001**, *107*(2), 137-148.
- [88] van der Horst, A.; Tertoolen, L.G.; de Vries-Smits, L.M.; Frye, R.A.; Medema, R.H.; Burgering, B.M. FOXO4 is acetylated upon peroxide stress and deacetylated by the longevity protein hSir2(SIRT1). *J. Biol. Chem.*, **2004**, *279*(28), 28873-28879.
- [89] 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.; Greenberg, M.E. Stress-dependent regulation of FOXO transcription factors by the SIRT1 deacetylase. *Science*, **2004**, *303*(5666), 2011-2015. Available from: <http://science.sciencemag.org/content/early/2004/02/19/science.1094637>
- [90] Motta, M.C.; Divecha, N.; Lemieux, M.; Kamel, C.; Chen, D.; Gu, W.; Bultsma, Y.; McBurney, M.; Guarente, L. Mammalian SIRT1 represses forkhead transcription factors. *Cell*, **2004**, *116*(4), 551-563.
- [91] Cantó, C.; Auwerx, J. PGC-1alpha, SIRT1 and AMPK, an energy sensing network that controls energy expenditure. *Curr. Opin. Lipidol.*, **2009**, *20*(2), 98-105.
- [92] Lim, J.H.; Lee, Y.M.; Chun, Y.S.; Chen, J.; Kim, J.E.; Park, J.W. Sirtuin 1 modulates cellular responses to hypoxia by deacetylating hypoxia-inducible factor 1alpha. *Mol. Cell*, **2010**, *38*(6), 864-878.
- [93] Kauppinen, A.; Suuronen, T.; Ojala, J.; Kaarniranta, K.; Salminen, A. Antagonistic crosstalk between NF- κ B and SIRT1 in the regulation of inflammation and metabolic disorders. *Cell. Signal.*, **2013**, *25*(10), 1939-1948.
- [94] van de Ven, R.A.H.; Santos, D.; Haigis, M.C. Mitochondrial sirtuins and molecular mechanisms of aging. *Trends Mol. Med.*, **2017**, *23*(4), 320-331.
- [95] Tasselli, L.; Zheng, W.; Chua, K.F. SIRT6: Novel mechanisms and links to aging and disease. *Trends Endocrinol. Metab.*, **2017**, *28*(3), 168-185.
- [96] Kanfi, Y.; Naiman, S.; Amir, G.; Peshti, V.; Zinman, G.; Nahum, L.; Bar-Joseph, Z.; Cohen, H.Y. The sirtuin SIRT6 regulates lifespan in male mice. *Nature*, **2012**, *483*(7388), 218-221. Available from: <https://www.nature.com/articles/nature10815>
- [97] Flatt, T.; Min, K.J.; D'Alterio, C.; Villa-Cuesta, E.; Cumbers, J.; Lehmann, R.; Jones, D.L.; Tatar, M. *Drosophila* germ-line modulation of insulin signaling and lifespan. *Proc. Natl. Acad. Sci. U.S.A.*, **2008**, *105*(17), 6368-6373.
- [98] Hsin, H.; Kenyon, C. Signals from the reproductive system regulate the lifespan of *C. elegans*. *Nature*, **1999**, *399*(6734), 362-366. Available from: <https://www.nature.com/articles/20694>
- [99] Arantes-Oliveira, N.; Apfeld, J.; Dillin, A.; Kenyon, C. Regulation of life-span by germ-line stem cells in *Caenorhabditis elegans*. *Science*, **2002**, *295*(5554), 502-505. Available from: <http://science.sciencemag.org/content/295/5554/502>
- [100] Mason, J.B.; Cargill, S.L.; Anderson, G.B.; Carey, J.R. Transplantation of young ovaries to old mice increased life span in transplant recipients. *J. Gerontol. A Biol. Sci. Med. Sci.*, **2009**, *64*(12), 1207-1211.
- [101] Austin, J.; Kimble, J. glp-1 is required in the germ line for regulation of the decision between mitosis and meiosis in *C. elegans*. *Cell*, **1987**, *51*(4), 589-599.
- [102] Antebi, A. Regulation of longevity by the reproductive system. *Exp. Gerontol.*, **2013**, *48*(7), 596-602.
- [103] Yamawaki, T.M.; Berman, J.R.; Suchanek-Kavipurapu, M.; McCormick, M.; Gaglia, M.M.; Lee, S.J.; Kenyon, C. The somatic reproductive tissues of *C. elegans* promote longevity through steroid hormone signaling. *PLoS Biol.*, **2010**, *8*(8), e1000468. Available from: <http://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1000468>
- [104] Libina, N.; Berman, J.R.; Kenyon, C. Tissue-specific activities of *C. elegans* DAF-16 in the regulation of lifespan. *Cell*, **2003**, *115*(4), 489-502.
- [105] Amrit, F.R.; Steenkiste, E.M.; Ratnappan, R.; Chen, S.W.; McClendon, T.B.; Kostka, D.; Yanowitz, J.; Olsen, C.P.; Ghazi, A.F. DAF-16 and TCER-1 facilitate adaptation to germline loss by restoring lipid homeostasis and repressing reproductive physiology in *C. elegans*. *PLoS Genet.*, **2016**, *12*(2), e1005788. Available from: <http://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1005788>
- [106] Fielenbach, N.; Antebi, A. *C. elegans* dauer formation and the molecular basis of plasticity. *Genes Dev.*, **2008**, *22*(16), 2149-2165.
- [107] Gerisch, B.; Rottiers, V.; Li, D.; Motola, D.L.; Cummins, C.L.; Lehrach, H.; Mangelsdorf, D.J.; Antebi, A. A bile acid-like steroid modulates *Caenorhabditis elegans* lifespan through nuclear receptor signaling. *Proc. Natl. Acad. Sci. U.S.A.*, **2007**, *104*(12), 5014-5019.
- [108] Wollam, J.; Magner, D.B.; Magomedova, L.; Rass, E.; Shen, Y.; Rottiers, V.; Habermann, B.; Cummins, C.L.; Antebi, A. A novel 3-hydroxysteroid dehydrogenase that regulates reproductive development and longevity. *PLoS Biol.*, **2012**, *10*(4), e1001305. Available from: <http://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1001305>
- [109] Berman, J.R.; Kenyon, C. Germ-cell loss extends *C. elegans* life span through regulation of DAF-16 by kri-1 and lipophilic-hormone signaling. *Cell*, **2006**, *124*(5), 1055-1068.
- [110] López-Otin, C.; Blasco, M.A.; Partridge, L.; Serrano, M.; Kroemer, G. The hallmarks of aging. *Cell*, **2013**, *153*(6), 1194-1217.
- [111] Weir, H.J.; Yao, P.; Huynh, F.K.; Escoubas, C.C.; Goncalves, R.L.; Burkewitz, K.; Laboy, R.; Hirschey, M.D.; Mair, W.B. Dietary restriction and AMPK increase lifespan via mitochondrial network and peroxisome remodeling. *Cell Metab.*, **2017**, *26*(6), 884-896.
- [112] Puigserver, P.; Wu, Z.; Park, C.W.; Graves, R.; Wright, M.; Spiegelman, B.M. A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. *Cell*, **1998**, *92*(6), 829-839.
- [113] Wu, Z.; Puigserver, P.; Andersson, U.; Zhang, C.; Adelmant, G.; Mootha, V.; Troy, A.; Cinti, S.; Lowell, B.; Scarpulla, R.C.; Spiegelman, B.M. Mechanisms controlling mitochondrial biogenesis and respiration through the thermogenic coactivator PGC-1. *Cell*, **1999**, *98*(1), 115-124.
- [114] Virbasius, J.V.; Scarpulla, R.C. Activation of the human mitochondrial transcription factor A gene by nuclear respiratory factors: A potential regulatory link between nuclear and mitochondrial gene expression in organelle biogenesis. *Proc. Natl. Acad. Sci. U.S.A.*, **1994**, *91*(4), 1309-1313.
- [115] Fernandez-Marcos, P.J.; Auwerx, J. Regulation of PGC-1 α , a nodal regulator of mitochondrial biogenesis. *Am. J. Clin. Nutr.*, **2011**, *93*(4), 884S-890S.
- [116] Hock, M.B.; Kralli, A. Transcriptional control of mitochondrial biogenesis and function. *Annu. Rev. Physiol.*, **2009**, *71*, 177-203.
- [117] Handschin, C.; Rhee, J.; Lin, J.; Tarr, P.T.; Spiegelman, B.M. An autoregulatory loop controls peroxisome proliferator-activated receptor gamma coactivator 1 alpha expression in muscle. *Proc. Natl. Acad. Sci. U.S.A.*, **2003**, *100*(12), 7111-7116.
- [118] Wu, H.; Kanatous, S.B.; Thurmond, F.A.; Gallardo, T.; Isotani, E.; Bassel-Duby, R.; Williams, R.S. Regulation of mitochondrial biogenesis in skeletal muscle by CaMK. *Science*, **2002**, *296*(5566), 349-352. Available from: <http://science.sciencemag.org/content/296/5566/349>
- [119] Bergeron, R.; Ren, J.M.; Cadman, K.S.; Moore, I.K.; Perret, P.;

- Pypaert, M.; Young, L.H.; Semenkovich, C.F.; Shulman, G.I. Chronic activation of AMP kinase results in NRF-1 activation and mitochondrial biogenesis. *Am. J. Physiol. Endocrinol. Metab.*, **2001**, *281*(6), E1340-E1346.
- [120] Zong, H.; Ren, J.M.; Young, L.H.; Pypaert, M.; Mu, J.; Birnbaum, M.J.; Shulman, G.I. AMP kinase is required for mitochondrial biogenesis in skeletal muscle in response to chronic energy deprivation. *Proc. Natl. Acad. Sci. U.S.A.*, **2002**, *99*(25), 15983-15987.
- [121] Reznick, R.M.; Zong, H.; Li, J.; Morino, K.; Moore, I.K.; Yu, H.J.; Liu, Z.X.; Dong, J.; Mustard, K.J.; Hawley, S.A.; Befroy, D.; Pypaert, M.; Hardie, D.G.; Young, L.H.; Shulman, G.I. Aging-associated reductions in AMP-activated protein kinase activity and mitochondrial biogenesis. *Cell Metab.*, **2007**, *5*(2), 151-156.
- [122] Palikaras, K.; Lionaki, E.; Tavernarakis, N. Coordination of mitophagy and mitochondrial biogenesis during ageing in *C. elegans*. *Nature*, **2015**, *521*(7553), 525-528. Available from: <https://www.nature.com/articles/nature14300>
- [123] Fang, E.F.; Scheibye-Knudsen, M.; Brace, L.E.; Kassahun, H.; SenGupta, T.; Nilsen, H.; Mitchell, J.R.; Croteau, D.L.; Bohr, V.A. Defective mitophagy in XPA via PARP-1 hyperactivation and NAD(+)/SIRT1 reduction. *Cell*, **2014**, *157*(4), 882-896.
- [124] Labbadia, J.; Morimoto, R.I. The biology of proteostasis in aging and disease. *Annu. Rev. Biochem.*, **2015**, *84*, 435-464.
- [125] Lindquist, S. The heat-shock response. *Annu. Rev. Biochem.*, **1986**, *55*, 1151-1191.
- [126] Richter, K.; Haslbeck, M.; Buchner, J. The heat shock response: Life on the verge of death. *Mol. Cell*, **2010**, *40*(2), 253-266.
- [127] Anckar, J.; Sistonen, L. Regulation of HSF1 function in the heat stress response: Implications in aging and disease. *Annu. Rev. Biochem.*, **2011**, *80*, 1089-1115.
- [128] Ali, A.; Bharadwaj, S.; O'Carroll, R.; Ovsenek, N. HSP90 interacts with and regulates the activity of heat shock factor 1 in *Xenopus* oocytes. *Mol. Cell Biol.*, **1998**, *18*(9), 4949-4960.
- [129] Douglas, P.M.; Baird, N.A.; Simic, M.S.; Uhlein, S.; McCormick, M.A.; Wolff, S.C.; Kennedy, B.K.; Dillin, A. Heterotypic signals from neural HSF-1 separate thermotolerance from longevity. *Cell Rep.*, **2015**, *12*(7), 1196-1204.
- [130] Brunquell, J.; Morris, S.; Lu, Y.; Cheng, F.; Westerheide, S.D. The genome-wide role of HSF-1 in the regulation of gene expression in *Caenorhabditis elegans*. *BMC Genomics*, **2016**, *17*, 559. Available from: <https://bmegenomics.biomedcentral.com/articles/10.1186/s12864-016-2837-5>
- [131] Tullet, J.M. DAF-16 target identification in *C. elegans*: Past, present and future. *Biogerontology*, **2015**, *16*(2), 221-234.
- [132] Li, J.; Labbadia, J.; Morimoto, R.I. Rethinking HSF1 in stress, development, and organismal health. *Trends Cell Biol.*, **2017**, *27*(12), 895-905.
- [133] Ding, W.X.; Yin, X.M. Sorting, recognition and activation of the misfolded protein degradation pathways through macroautophagy and the proteasome. *Autophagy*, **2008**, *4*(2), 141-150.
- [134] Feng, Y.; He, D.; Yao, Z.; Klionsky, D.J. The machinery of macroautophagy. *Cell Res.*, **2014**, *24*(1), 24-41.
- [135] Levine, B.; Kroemer, G. Autophagy in the pathogenesis of disease. *Cell*, **2008**, *132*(1), 27-42.
- [136] Simonsen, A.; Cumming, R.C.; Brech, A.; Isakson, P.; Schubert, D.R.; Finley, K.D. Promoting basal levels of autophagy in the nervous system enhances longevity and oxidant resistance in adult *Drosophila*. *Autophagy*, **2008**, *4*(2), 176-184.
- [137] Pyo, J.O.; Yoo, S.M.; Ahn, H.H.; Nah, J.; Hong, S.H.; Kam, T.I.; Jung, S.; Jung, Y.K. Overexpression of Atg5 in mice activates autophagy and extends lifespan. *Nat. Commun.*, **2013**, *4*, 2300. Available from: <https://www.nature.com/articles/ncomms3300>
- [138] Lapierre, L.R.; Kumsta, C.; Sandri, M.; Ballabio, A.; Hansen, M. Transcriptional and epigenetic regulation of autophagy in aging. *Autophagy*, **2015**, *11*(6), 867-880.
- [139] Rubinsztein, D.C.; Mariño, G.; Kroemer, G. Autophagy and aging. *Cell*, **2011**, *146*(5), 682-695.
- [140] Settembre, C.; Di Malta, C.; Polito, V.A.; Arencibia, M.G.; Vetrini, F.; Erdin, S.; Erdin, S.U.; Huynh, T.; Medina, D.; Colella, P.; Sardiello, M.; Rubinsztein, D.C.; Ballabio, A. TFEB links autophagy to lysosomal biogenesis. *Science*, **2011**, *332*(6036), 1429-1433. Available from: <http://science.sciencemag.org/content/332/6036/1429>
- [141] Settembre, C.; Ballabio, A. TFEB regulates autophagy: An integrated coordination of cellular degradation and recycling processes. *Autophagy*, **2011**, *7*(11), 1379-1381.
- [142] Lapierre, L.R.; De Magalhaes Filho, C.D.; McQuary, P.R.; Chu, C.C.; Visvikis, O.; Chang, J.T.; Gelino, S.; Ong, B.; Davis, A.E.; Irazoqui, J.E.; Dillin, A.; Hansen, M. The TFEB orthologue HLLH-30 regulates autophagy and modulates longevity in *Caenorhabditis elegans*. *Nat. Commun.*, **2013**, *4*, 2267. Available from: <https://www.nature.com/articles/ncomms3267>
- [143] Kumsta, C.; Chang, J.T.; Schmalz, J.; Hansen, M. Hormetic heat stress and HSF-1 induce autophagy to improve survival and proteostasis in *C. elegans*. *Nat. Commun.*, **2017**, *8*, 14337. Available from: <https://www.nature.com/articles/ncomms14337>
- [144] Schatz, G. The protein import machinery of mitochondria. *Protein Sci.*, **1993**, *2*, 141-146. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2142353/pdf/8443595.pdf>
- [145] Martinus, R.D.; Garth, G.P.; Webster, T.L.; Cartwright, P.; Naylor, D.J.; Hoogenraad, N.J. Selective induction of mitochondrial chaperones in response to loss of the mitochondrial genome. *Eur. J. Biochem.*, **1996**, *240*(1), 98-103.
- [146] Feng, J.; Bussi re, F.; Hekimi, S. Mitochondrial electron transport is a key determinant of life span in *Caenorhabditis elegans*. *Dev. Cell*, **2001**, *1*(5), 633-644.
- [147] Lee, S.S.; Lee, R.Y.; Fraser, A.G.; Kamath, R.S.; Ahringer, J.; Ruvkun, G. A systematic RNAi screen identifies a critical role for mitochondria in *C. elegans* longevity. *Nat. Genet.*, **2003**, *33*(1), 40-48.
- [148] Durieux, J.; Wolff, S.; Dillin, A. The cell-non-autonomous nature of electron transport chain-mediated longevity. *Cell*, **2011**, *144*(1), 79-91.
- [149] Larsen, P.L.; Clarke, C.F. Extension of life-span in *Caenorhabditis elegans* by a diet lacking coenzyme Q. *Science*, **2002**, *295*(5552), 120-123. Available from: <http://science.sciencemag.org/content/295/5552/120.full>
- [150] Haynes, C.M.; Yang, Y.; Blais, S.P.; Neubert, T.A.; Ron, D. The matrix peptide exporter HAF-1 signals a mitochondrial UPR by activating the transcription factor ZC376.7 in *C. elegans*. *Mol. Cell*, **2010**, *37*(4), 529-540.
- [151] Nargund, A.M.; Pellegrino, M.W.; Fiorese, C.J.; Baker, B.M.; Haynes, C.M. Mitochondrial import efficiency of ATFS-1 regulates mitochondrial UPR activation. *Science*, **2012**, *337*(6094), 587-590. Available from: <http://science.sciencemag.org/content/337/6094/587>
- [152] Bennett, C.F.; Wende, H.V.; Simko, M.; Klum, S.; Barfield, S.; Choi, H.; Pineda, V.V.; Kaerberlein, M. Activation of the mitochondrial unfolded protein response does not predict longevity in *Caenorhabditis elegans*. *Nat. Commun.*, **2014**, *5*, 3483. Available from: <https://www.nature.com/articles/ncomms4483>
- [153] Lee, S.J.; Hwang, A.B.; Kenyon, C. Inhibition of respiration extends *C. elegans* life span via reactive oxygen species that increase HIF-1 activity. *Curr. Biol.*, **2010**, *20*(23), 2131-2136.
- [154] Nakai, D.; Shimizu, T.; Nojiri, H.; Uchiyama, S.; Koike, H.; Takahashi, M.; Hirokawa, K.; Shirasawa, T. coq7/clk-1 regulates mitochondrial respiration and the generation of reactive oxygen species via coenzyme Q. *Aging Cell*, **2004**, *3*(5), 273-281.
- [155] Yoshida, H.; Matsui, T.; Yamamoto, A.; Okada, T.; Mori, K. XBP1 mRNA is induced by ATF6 and spliced by IRE1 in response to ER stress to produce a highly active transcription factor. *Cell*, **2001**, *107*(7), 881-891.
- [156] Hollien, J.; Weissman, J.S. Decay of endoplasmic reticulum-localized mRNAs during the unfolded protein response. *Science*, **2006**, *313*(5783), 104-107. Available from: <http://www.sciencemag.org/lookup/doi/10.1126/science.1129631>
- [157] Lee, J.; Ozcan, U. Unfolded protein response signaling and metabolic diseases. *J. Biol. Chem.*, **2014**, *289*(3), 1203-1211.
- [158] Harding, H.P.; Zhang, Y.; Bertolotti, A.; Zeng, H.; Ron, D. Perk is essential for translational regulation and cell survival during the unfolded protein response. *Mol. Cell*, **2000**, *5*(5), 897-904.
- [159] Harding, H.P.; Novoa, I.; Zhang, Y.; Zeng, H.; Wek, R.; Schapira, M.; Ron, D. Regulated translation initiation controls stress-induced gene expression in mammalian cells. *Mol. Cell*, **2000**, *6*(5), 1099-1108.
- [160] Yoshida, H.; Haze, K.; Yanagi, H.; Yura, T.; Mori, K. Identification of the cis-acting endoplasmic reticulum stress response element responsible for transcriptional induction of mammalian glucose-regulated proteins. Involvement of basic leucine zipper transcription factors. *J. Biol. Chem.*, **1998**, *273*(50), 33741-33749.
- [161] Brown, M.K.; Naidoo, N. The endoplasmic reticulum stress response in aging and age-related diseases. *Front. Physiol.*, **2012**, *3*,

263. Available from: <https://www.frontiersin.org/articles/10.3389/fphys.2012.00263/full>
- [162] Hennis-Korenblit, S.; Zhang, P.; Hansen, M.; McCormick, M.; Lee, S.J.; Cary, M.; Kenyon, C. Insulin/IGF-1 signaling mutants reprogram ER stress response regulators to promote longevity. *Proc. Natl. Acad. Sci. U.S.A.*, **2010**, *107*(21), 9730-9735.
- [163] Luis, N.M.; Wang, L.; Ortega, M.; Deng, H.; Katewa, S.D.; Li, P.W.; Karpac, J.; Jasper, H.; Kapahi, P. Intestinal IRE1 Is required for increased triglyceride metabolism and longer lifespan under dietary restriction. *Cell Rep.*, **2016**, *17*(5), 1207-1216.
- [164] Taylor, R.C.; Dillin, A. XBP-1 is a cell-nonautonomous regulator of stress resistance and longevity. *Cell*, **2013**, *153*(7), 1435-1447.
- [165] Franceschi, C.; Bonafè, M.; Valensin, S.; Olivieri, F.; De Luca, M.; Ottaviani, E.; De Benedictis, G. Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann. N.Y. Acad. Sci.*, **2000**, *908*, 244-254.
- [166] Franceschi, C.; Campisi, J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J. Gerontol. A Biol. Sci. Med. Sci.*, **2014**, *69*(Suppl 1), S4-S9.
- [167] Lawrence, T. The nuclear factor NF-kappaB pathway in inflammation. *Cold Spring Harb. Perspect. Biol.*, **2009**, *1*(6), a001651.
- [168] Oeckinghaus, A.; Ghosh, S. The NF-kappaB family of transcription factors and its regulation. *Cold Spring Harb. Perspect. Biol.*, **2009**, *1*(4), a000034.
- [169] Kriete, A.; Mayo, K.L.; Yalamanchili, N.; Beggs, W.; Bender, P.; Kari, C.; Rodeck, U. Cell autonomous expression of inflammatory genes in biologically aged fibroblasts associated with elevated NF-kappaB activity. *Immun. Ageing*, **2008**, *5*, 5.
- [170] Korhonen, P.; Helenius, M.; Salminen, A. Age-related changes in the regulation of transcription factor NF-kappa B in rat brain. *Neurosci. Lett.*, **1997**, *225*(1), 61-64.
- [171] Helenius, M.; Hänninen, M.; Lehtinen, S.K.; Salminen, A. Aging-induced up-regulation of nuclear binding activities of oxidative stress responsive NF-kB transcription factor in mouse cardiac muscle. *J. Mol. Cell. Cardiol.*, **1996**, *28*(3), 487-498.
- [172] Adler, A.S.; Sinha, S.; Kawahara, T.L.; Zhang, J.Y.; Segal, E.; Chang, H.Y. Motif module map reveals enforcement of aging by continual NF- κ B activity. *Genes Dev.*, **2007**, *21*(24), 3244-3257.
- [173] Kawahara, T.L.; Michishita, E.; Adler, A.S.; Damian, M.; Berber, E.; Lin, M.; McCord, R.A.; Ongaiqui, K.C.; Boxer, L.D.; Chang, H.Y.; Chua, K.F. SIRT6 links histone H3 lysine 9 deacetylation to NF-kappaB-dependent gene expression and organismal life span. *Cell*, **2009**, *136*(1), 62-74.
- [174] Jing, H.; Lee, S. NF- κ B in cellular senescence and cancer treatment. *Mol. Cells*, **2014**, *37*(3), 189-195.
- [175] Salminen, A.; Huuskonen, J.; Ojala, J.; Kauppinen, A.; Kaarniranta, K.; Suuronen, T. Activation of innate immunity system during aging: NF-kB signaling is the molecular culprit of inflamm-aging. *Ageing Res. Rev.*, **2008**, *7*(2), 83-105.
- [176] Yeung, F.; Hoberg, J.E.; Ramsey, C.S.; Keller, M.D.; Jones, D.R.; Frye, R.A.; Mayo, M.W. Modulation of NF- κ B-dependent transcription and cell survival by the SIRT1 deacetylase. *EMBO J.*, **2004**, *23*(12), 2369-2380.
- [177] Salminen, A.; Kaarniranta, K. Insulin/IGF-1 paradox of aging: Regulation via AKT/IKK/NF-kappaB signaling. *Cell Signal.*, **2010**, *22*(4), 573-577.
- [178] Dan, H.C.; Cooper, M.J.; Cogswell, P.C.; Duncan, J.A.; Ting, J.P.; Baldwin, A.S. Akt-dependent regulation of NF- κ B is controlled by mTOR and Raptor in association with IKK. *Genes Dev.*, **2008**, *22*(11), 1490-1500.
- [179] Lee, D.F.; Kuo, H.P.; Chen, C.T.; Hsu, J.M.; Chou, C.K.; Wei, Y.; Sun, H.L.; Li, L.Y.; Ping, B.; Huang, W.C.; He, X.; Hung, J.Y.; Lai, C.C.; Ding, Q.; Su, J.L.; Yang, J.Y.; Sahin, A.A.; Hortobagyi, G.N.; Tsai, F.J.; Tsai, C.H.; Hung, M.C. IKK β suppression of TSC1 links inflammation and tumor angiogenesis via the mTOR pathway. *Cell*, **2007**, *130*(3), 440-455.
- [180] Tilstra, J.S.; Clauson, C.L.; Niedernhofer, L.J.; Robbins, P.D. NF- κ B in aging and disease. *Ageing Dis.*, **2011**, *2*(6), 449-465.
- [181] Kornberg, R.D. Chromatin structure: A repeating unit of histones and DNA. *Science*, **1974**, *184*(4139), 868-871. Available from: <http://science.sciencemag.org/content/184/4139/868>
- [182] Thoma, F.; Koller, T.; Klug, A. Involvement of histone H1 in the organization of the nucleosome and of the salt-dependent superstructures of chromatin. *J. Cell Biol.*, **1979**, *83*(2 Pt 1), 403-427.
- [183] Venkatesh, S.; Workman, J.L.; Venkatesh, J. Histone exchange, chromatin structure and the regulation of transcription. *Nat. Rev. Mol. Cell. Biol.*, **2015**, *16*(3), 178-189.
- [184] Lapasset, L.; Milhavel, O.; Prieur, A.; Besnard, E.; Babled, A.; Ait-Hamou, N.; Leschik, J.; Pellestor, F.; Ramirez, J.M.; De Vos, J.; Lehmann, S.; Lemaitre, J.M. Rejuvenating senescent and centenarian human cells by reprogramming through the pluripotent state. *Genes Dev.*, **2011**, *25*(21), 2248-2253. Available from: <http://genesdev.cshlp.org/content/25/21/2248>
- [185] Ocampo, A.; Reddy, P.; Martinez-Redondo, P.; Platero-Luengo, A.; Hatanaka, F.; Hishida, T.; Li, M.; Lam, D.; Kurita, M.; Beyret, E.; Araoka, T.; Vazquez-Ferrer, E.; Donoso, D.; Roman, J.L.; Xu, J.; Esteban, C.R.; Nuñez, G.; Delicado, E.N.; Campistol, J.M.; Guillen, I.; Guillen, P.; Belmonte, J.C.I. *In vivo* amelioration of age-associated hallmarks by partial reprogramming. *Cell*, **2016**, *167*(7), 1719.e12-1733.e12.
- [186] Wu, H.; Zhang, Y. Reversing DNA methylation: Mechanisms, genomics, and biological functions. *Cell*, **2014**, *156*(1-2), 45-68.
- [187] Deaton, A.M.; Bird, A. CpG islands and the regulation of transcription. *Genes Dev.*, **2011**, *25*(10), 1010-1022.
- [188] Hermann, A.; Goyal, R.; Jeltsch, A. The Dnmt1 DNA-(cytosine-C5)-methyltransferase methylates DNA processively with high preference for hemimethylated target sites. *J. Biol. Chem.*, **2004**, *279*(46), 48350-48359.
- [189] Okano, M.; Bell, D.W.; Haber, D.A.; Li, E. DNA methyltransferases Dnmt3a and Dnmt3b are essential for *de novo* methylation and mammalian development. *Cell*, **1999**, *99*(3), 247-257.
- [190] Kim, M.; Costello, J. DNA methylation: An epigenetic mark of cellular memory. *Exp. Mol. Med.*, **2017**, *49*(4), e322. Available from: <https://www.nature.com/articles/emm201710>
- [191] Choy, M.K.; Movassagh, M.; Goh, H.G.; Bennett, M.R.; Down, T.A.; Foo, R.S. Genome-wide conserved consensus transcription factor binding motifs are hyper-methylated. *BMC Genomics*, **2010**, *11*, 519. Available from: <https://bmcgenomics.biomedcentral.com/articles/10.1186/1471-2164-11-519>
- [192] Hendrich, B.; Tweedie, S. The methyl-CpG binding domain and the evolving role of DNA methylation in animals. *Trends Genet.*, **2003**, *19*(5), 269-277.
- [193] Zhu, H.; Wang, G.; Qian, J. Transcription factors as readers and effectors of DNA methylation. *Nat. Rev. Genet.*, **2016**, *17*(9), 551-565.
- [194] Shah, S.; McRae, A.F.; Marioni, R.E.; Harris, S.E.; Gibson, J.; Henders, A.K.; Redmond, P.; Cox, S.R.; Pattie, A.; Corley, J.; Murphy, L.; Martin, N.G.; Montgomery, G.W.; Starr, J.M.; Wray, N.R.; Deary, I.J.; Visscher, P.M. Genetic and environmental exposures constrain epigenetic drift over the human life course. *Genome Res.*, **2014**, *24*(11), 1725-1733.
- [195] Yuan, T.; Jiao, Y.; de Jong, S.; Ophoff, R.A.; Beck, S.; Teschendorff, A.E. An integrative multi-scale analysis of the dynamic DNA methylation landscape in aging. *PLoS Genet.*, **2015**, *11*(2), e1004996. Available from: <http://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1004996>
- [196] Li, Y.; Daniel, M.; Tollefsbol, T.O. Epigenetic regulation of caloric restriction in aging. *BMC Med.*, **2011**, *9*, 98. Available from: <https://bmcmedicine.biomedcentral.com/articles/10.1186/1741-7015-9-98>
- [197] Avrahami, D.; Li, C.; Zhang, J.; Schug, J.; Avrahami, R.; Rao, S.; Stadler, M.B.; Burger, L.; Schübeler, D.; Glaser, B.; Kaestner, K.H. Aging-dependent demethylation of regulatory elements correlates with chromatin state and improved β cell function. *Cell Metab.*, **2015**, *22*(4), 619-632.
- [198] Sun, D.; Luo, M.; Jeong, M.; Rodriguez, B.; Xia, Z.; Hannah, R.; Wang, H.; Le, T.; Faull, K.F.; Chen, R.; Gu, H.; Bock, C.; Meissner, A.; Göttgens, B.; Darlington, G.J.; Li, W.; Goodell, M.A. Epigenomic profiling of young and aged HSCs reveals concerted changes during aging that reinforce self-renewal. *Cell Stem Cell*, **2014**, *14*(5), 673-688.
- [199] Domcke, S.; Bardet, A.F.; Ginno, P.A.; Hartl, D.; Burger, L.; Schübeler, D. Competition between DNA methylation and transcription factors determines binding of NRF1. *Nature*, **2015**, *528*(7583), 575-579. Available from: <https://www.nature.com/articles/nature16462>
- [200] Steegenga, W.T.; Boekschoten, M.V.; Lute, C.; Hooiveld, G.J.; de Groot, P.J.; Morris, T.J.; Teschendorff, A.E.; Butcher, L.M.; Beck, S.; Müller, M. Genome-wide age-related changes in DNA methylation and gene expression in human PBMCs. *Age*, **2014**, *36*(3), 9648.
- [201] Reddington, J.P.; Perricone, S.M.; Nestor, C.E.; Reichmann, J.;

- Youngson, N.A.; Suzuki, M.; Reinhardt, D.; Dunican, D.S.; Prendergast, J.G.; Mjoseng, H.; Ramsahoye, B.H.; Whitelaw, E.; Greally, J.M.; Adams, I.R.; Bickmore, W.A.; Meehan, R.R. Redistribution of H3K27me3 upon DNA hypomethylation results in de-repression of Polycomb target genes. *Genome Biol.*, **2013**, *14*(3), R25. Available from: <https://genomebiology.biomedcentral.com/articles/10.1186/gb-2013-14-3-r25>
- [202] Stubbs, T.M.; Bonder, M.J.; Stark, A.K.; Krueger, F.B.; Ageing Clock Team; von Meyenn, F.; Stegle, O.; Reik, W. Multi-tissue DNA methylation age predictor in mouse. *Genome Biol.*, **2017**, *18*(1), 68. Available from: <https://genomebiology.biomedcentral.com/articles/10.1186/s13059-017-1203-5>
- [203] Hannum, G.; Guinney, J.; Zhao, L.; Zhang, L.; Hughes, G.; Sada, S.; Klotzle, B.; Bibikova, M.; Fan, J.B.; Gao, Y.; Deconde, R.; Chen, M.; Rajapakse, I.; Frieder, S.; Ideker, T.; Zhang, K. Genome-wide methylation profiles reveal quantitative views of human aging rates. *Mol. Cell.*, **2013**, *49*(2), 359-367.
- [204] Horvath, S. DNA methylation age of human tissues and cell types. *Genome Biol.*, **2013**, *14*(10), R115. Available from: <https://genomebiology.biomedcentral.com/articles/10.1186/gb-2013-14-10-r115/comments>
- [205] Bocklandt, S.; Lin, W.; Sehl, M.E.; Sánchez, F.J.; Sinsheimer, J.S.; Horvath, S.; Vilain, E. Epigenetic predictor of age. *PLoS One*, **2011**, *6*(6), e14821. Available from: <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0014821>
- [206] Horvath, S.; Langfelder, P.; Kwak, S.; Aaronson, J.; Rosinski, J.; Vogt, T.F.; Eszes, M.; Faul, R.L.; Curtis, M.A.; Waldvogel, H.J.; Choi, O.W.; Tung, S.; Vinters, H.V.; Coppola, G.; Yang, X.W. Huntington's disease accelerates epigenetic aging of human brain and disrupts DNA methylation levels. *Aging*, **2016**, *8*(7), 1485-1512.
- [207] Bannister, A.J.; Kouzarides, T. Regulation of chromatin by histone modifications. *Cell Res.*, **2011**, *21*(3), 381-395.
- [208] Eberharter, A.; Becker, P.B. Histone acetylation: A switch between repressive and permissive chromatin. Second in review series on chromatin dynamics. *EMBO Rep.*, **2002**, *3*(3), 224-229.
- [209] Zhang, Y.; Reinberg, D. Transcription regulation by histone methylation: Interplay between different covalent modifications of the core histone tails. *Genes Dev.*, **2001**, *15*(18), 2343-2360.
- [210] Weber, C.M.; Henikoff, S. Histone variants: Dynamic punctuation in transcription. *Genes Dev.*, **2014**, *28*(7), 672-682.
- [211] Kouzarides, T. Chromatin modifications and their function. *Cell*, **2007**, *128*(4), 693-705.
- [212] Labbadia, J.; Morimoto, R.I. Repression of the heat shock response is a programmed event at the onset of reproduction. *Mol. Cell*, **2015**, *59*(4), 639-650.
- [213] Eijkelenboom, A.; Mokry, M.; Smits, L.M.; Nieuwenhuis, E.E.; Burgering, B.M. FOXO3 selectively amplifies enhancer activity to establish target gene regulation. *Cell Rep.*, **2013**, *5*(6), 1664-1678.
- [214] Merkwirth, C.; Jovaisaite, V.; Durieux, J.; Matilainen, O.; Jordan, S.D.; Quiros, P.M.; Steffen, K.K.; Williams, E.G.; Mouchiroud, L.; Tronnes, S.U.; Murillo, V.; Wolff, S.C.; Shaw, R.J.; Auwerx, J.; Dillin, A. Two conserved histone demethylases regulate mitochondrial stress-induced longevity. *Cell*, **2016**, *165*(5), 1209-1223.
- [215] Tian, Y.; Garcia, G.; Bian, Q.; Steffen, K.K.; Joe, L.; Wolff, S.; Meyer, B.J.; Dillin, A. Mitochondrial stress induces chromatin reorganization to promote longevity and UPR(mt). *Cell*, **2016**, *165*(5), 1197-1208.
- [216] Maures, T.J.; Greer, E.L.; Hauswirth, A.G.; Brunet, A. The H3K27 demethylase UTX-1 regulates *C. elegans* lifespan in a germline-independent, insulin-dependent manner. *Aging Cell*, **2011**, *10*(6), 980-990.
- [217] Greer, E.L.; Maures, T.J.; Hauswirth, A.G.; Green, E.M.; Leeman, D.S.; Maro, G.S.; Han, S.; Banko, M.R.; Gozani, O.; Brunet, A. Members of the H3K4 trimethylation complex regulate lifespan in a germline-dependent manner in *C. elegans*. *Nature*, **2010**, *466*(7304), 383-387. Available from: <https://www.nature.com/articles/nature09195>
- [218] Greer, E.L.; Maures, T.J.; Ucar, D.; Hauswirth, A.G.; Mancini, E.; Lim, J.P.; Benayoun, B.A.; Shi, Y.; Brunet, A. Transgenerational epigenetic inheritance of longevity in *Caenorhabditis elegans*. *Nature*, **2011**, *479*(7373), 365-371. Available from: <https://www.nature.com/articles/nature10572>
- [219] Han, S.; Schroeder, E.A.; Silva-García, C.G.; Hebestreit, K.; Mair, W.B.; Brunet, A. Mono-unsaturated fatty acids link H3K4me3 modifiers to *C. elegans* lifespan. *Nature*, **2017**, *544*(7649), 185-190. Available from: <https://www.nature.com/articles/nature21686>
- [220] Zhang, M.; Poplawski, M.; Yen, K.; Cheng, H.; Bloss, E.; Zhu, X.; Patel, H.; Mobbs, C.V. Role of CBP and SATB-1 in aging, dietary restriction, and insulin-like signaling. *PLoS Biol.*, **2009**, *7*(11), e1000245. Available from: <http://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1000245>
- [221] Yuan, L.W.; Gambee, J.E. Histone acetylation by p300 is involved in CREB-mediated transcription on chromatin. *Biochim. Biophys. Acta*, **2001**, *1541*(3), 161-169.
- [222] Kobayashi, Y.; Furukawa-Hibi, Y.; Chen, C.; Horio, Y.; Isobe, K.; Ikeda, K.; Motoyama, N. SIRT1 is critical regulator of FOXO-mediated transcription in response to oxidative stress. *Int. J. Mol. Med.*, **2005**, *16*(2), 237-243.
- [223] Islam, M.M.; Zhang, C.L. TLX: A master regulator for neural stem cell maintenance and neurogenesis. *Biochim. Biophys. Acta*, **2015**, *1849*(2), 210-216.
- [224] Zhang, R.; Poustovoitov, M.V.; Ye, X.; Santos, H.A.; Chen, W.; Zhang, S.M.; Erzberger, J.P.; Serebriiskii, I.G.; Canutescu, A.A.; Dunbrack, R.L.; Pehrson, J.R.; Berger, J.M.; Kaufman, P.D.; Adams, P.D. Formation of MacroH2A-containing senescence-associated heterochromatin foci and senescence driven by ASF1a and HIRA. *Dev. Cell*, **2005**, *8*(1), 19-30.
- [225] Piazzesi, A.; Papić, D.; Bertan, F.; Salomoni, P.; Nicotera, P.; Bano, D. Replication-independent histone variant H3.3 controls animal lifespan through the regulation of pro-longevity transcriptional programs. *Cell Rep*, **2016**, *17*(4), 987-996.
- [226] Maze, I.; Wenderski, W.; Noh, K.M.; Bagot, R.C.; Tzavaras, N.; Purushothaman, I.; Elsässer, S.J.; Guo, Y.; Ionete, C.; Hurd, Y.L.; Tamminga, C.A.; Halene, T.; Farrelly, L.; Soshnev, A.A.; Wen, D.; Rafii, S.; Birtwistle, M.R.; Akbarian, S.; Buchholz, B.A.; Blitzer, R.D.; Nestler, E.J.; Yuan, Z.F.; Garcia, B.A.; Shen, L.; Molina, H.; Allis, C.D. Critical role of histone turnover in neuronal transcription and plasticity. *Neuron*, **2015**, *87*(1), 77-94.
- [227] Duarte, L.F.; Young, A.R.; Wang, Z.; Wu, H.A.; Panda, T.; Kou, Y.; Kapoor, A.; Hasson, D.; Mills, N.R.; Ma'ayan, A.; Narita, M.; Bernstein, E. Histone H3.3 and its proteolytically processed form drive a cellular senescence programme. *Nat. Commun.*, **2014**, *5*, 5210. Available from: <https://www.nature.com/articles/ncomms6210>
- [228] Längst, G.; Manelyte, L. Chromatin remodelers: From function to dysfunction. *Genes*, **2015**, *6*(2), 299-324.
- [229] Zaret, K.S.; Carroll, J.S. Pioneer transcription factors: Establishing competence for gene expression. *Genes Dev.*, **2011**, *25*(21), 2227-2241.
- [230] Sherwood, R.I.; Hashimoto, T.; O'Donnell, C.W.; Lewis, S.; Barkal, A.A.; van Hoff, J.P.; Karun, V.; Jaakkola, T.; Gifford, D.K. Discovery of directional and nondirectional pioneer transcription factors by modeling DNase profile magnitude and shape. *Nat. Biotechnol.*, **2014**, *32*(2), 171-178.
- [231] Bochkis, I.M.; Przybylski, D.; Chen, J.; Regev, A. Changes in nucleosome occupancy associated with metabolic alterations in aged mammalian liver. *Cell Rep.*, **2014**, *9*(3), 996-1006.
- [232] Singh, A.; Kumar, N.; Matai, L.; Jain, V.; Garg, A.; Mukhopadhyay, A. A chromatin modifier integrates insulin/IGF-1 signaling and dietary restriction to regulate longevity. *Aging Cell*, **2016**, *15*(4), 694-705.
- [233] Zhang, J.; Ohta, T.; Maruyama, A.; Hosoya, T.; Nishikawa, K.; Maher, J.M.; Shibahara, S.; Itoh, K.; Yamamoto, M. BRG1 interacts with Nrf2 to selectively mediate HO-1 induction in response to oxidative stress. *Mol. Cell Biol.*, **2006**, *26*(21), 7942-7952.
- [234] Plath, K.; Mlynarczyk-Evans, S.; Nusinow, D.A.; Panning, B. Panning, Xist RNA and the mechanism of X chromosome inactivation. *Annu. Rev. Genet.*, **2002**, *36*, 233-278.
- [235] Lee, J.T.; Bartolomei, M.S. X-inactivation, imprinting, and long noncoding RNAs in health and disease. *Cell*, **2013**, *152*(6), 1308-1323.
- [236] Sánchez, Y.; Segura, V.; Marín-Béjar, O.; Athie, A.; Marchese, F.P.; González, J.; Bujanda, L.; Guo, S.; Matheu, A.; Huarte, M. Genome-wide analysis of the human p53 transcriptional network unveils a lncRNA tumour suppressor signature. *Nat. Commun.*, **2014**, *5*, 5812. Available from: <https://www.nature.com/articles/ncomms6812>
- [237] Grossi, E.; Sánchez, Y.; Huarte, M.E. Expanding the p53 regulatory network: LncRNAs take up the challenge. *Biochim. Biophys. Acta*, **2016**, *1859*(1), 200-208.
- [238] Marín-Béjar, O.; Marchese, F.P.; Athie, A.; Sánchez, Y.; González,

- J.; Segura, V.; Huang, L.; Moreno, I.; Navarro, A.; Monzó, M.; Garcia-Foncillas, J.; Rinn, J.L.; Guo, S.; Huarte, M. Pint lincRNA connects the p53 pathway with epigenetic silencing by the Polycomb repressive complex 2. *Genome Biol.*, **2013**, *14*(9), R104. Available from: <https://genomebiology.biomedcentral.com/articles/10.1186/gb-2013-14-9-r104>
- [239] Lazorthes, S.; Vallot, C.; Briois, S.; Aguirrebengoa, M.; Thuret, J.Y.; St. Laurent, G.; Rougeulle, C.; Kapranov, P.; Mann, C.; Trouche, D.; Nicolas, E. A vlincRNA participates in senescence maintenance by relieving H2AZ-mediated repression at the INK4 locus. *Nat. Commun.*, **2015**, *6*, 5971. Available from: <https://www.nature.com/articles/ncomms6971>
- [240] Haithecock, E.; Dayani, Y.; Neufeld, E.; Zahand, A.J.; Feinstein, N.; Mattout, A.; Gruenbaum, Y.; Liu, J. Age-related changes of nuclear architecture in *Caenorhabditis elegans*. *Proc. Natl. Acad. Sci. U.S.A.*, **2005**, *102*(46), 16690-16695.
- [241] Criscione, S.W.; Teo, Y.V.; Neretti, N. The chromatin landscape of cellular senescence. *Trends Genet.*, **2016**, *32*(11), 751-761.
- [242] Pegoraro, G.; Misteli, T. The central role of chromatin maintenance in aging. *Aging*, **2009**, *1*(12), 1017-1022.
- [243] Mounkes, L.C.; Stewart, C.L. Aging and nuclear organization: Lamins and progeria. *Curr. Opin. Cell Biol.*, **2004**, *16*(3), 322-327.
- [244] Blagosklonny, M.V. Progeria, rapamycin and normal aging: Recent breakthrough. *Aging*, **2011**, *3*(7), 685-691.
- [245] Cao, K.; Blair, C.D.; Faddah, D.A.; Kieckhafer, J.E.; Olive, M.; Erdos, M.R.; Nabel, E.G.; Collins, F.S. Progerin and telomere dysfunction collaborate to trigger cellular senescence in normal human fibroblasts. *J. Clin. Invest.*, **2011**, *121*(7), 2833-2844.
- [246] McClintock, D.; Ratner, D.; Lokuge, M.; Owens, D.M.; Gordon, L.B.; Collins, F.S.; Djabali, K. The mutant form of lamin A that causes Hutchinson-Gilford progeria is a biomarker of cellular aging in human skin. *PLoS One*, **2007**, *2*(12), e1269. Available from: <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0001269>
- [247] Kubben, N.; Zhang, W.; Wang, L.; Voss, T.C.; Yang, J.; Qu, J.; Liu, G.H.; Misteli, T. Repression of the antioxidant NRF2 pathway in premature aging. *Cell*, **2016**, *165*(6), 1361-1374.
- [248] Cabanillas, R.; Cadiñanos, J.; Villameyide, J.A.; Pérez, M.; Longo, J.; Richard, J.M.; Alvarez, R.; Durán, N.S.; Illán, R.; González, D.J.; López-Otín, C. Néstor-Guillermo progeria syndrome: A novel premature aging condition with early onset and chronic development caused by BANF1 mutations. *Am. J. Med. Genet. A*, **2011**, *155A*(11), 2617-2625.
- [249] Montes de Oca, R.; Lee, K.K.; Wilson, K.L. Binding of barrier to autointegration factor (BAF) to histone H3 and selected linker histones including H1.1. *J. Biol. Chem.*, **2005**, *280*(51), 42252-42262.
- [250] Zheng, R.; Ghirlando, R.; Lee, M.S.; Mizuuchi, K.; Krause, M.; Craigie, R. Barrier-to-autointegration factor (BAF) bridges DNA in a discrete, higher-order nucleoprotein complex. *Proc. Natl. Acad. Sci. U.S.A.*, **2000**, *97*(16), 8997-9002.
- [251] Samwer, M.; Schneider, M.W.G.; Hoefler, R.; Schmalhorst, P.S.; Jude, J.G.; Zuber, J.; Gerlich, D.W. DNA cross-bridging shapes a single nucleus from a set of mitotic chromosomes. *Cell*, **2017**, *170*(5), 956.e23-972.e23.
- [252] Freund, A.; Laberge, R.M.; Demaria, M.; Campisi, J. Lamin B1 loss is a senescence-associated biomarker. *Mol. Biol. Cell*, **2012**, *23*(11), 2066-2075.
- [253] Shah, P.P.; Donahue, G.; Otte, G.L.; Capell, B.C.; Nelson, D.M.; Cao, K.; Aggarwala, V.; Cruickshanks, H.A.; Rai, T.S.; McBryan, T.; Gregory, B.D.; Adams, P.D.; Berger, S.L. Lamin B1 depletion in senescent cells triggers large-scale changes in gene expression and the chromatin landscape. *Genes Dev.*, **2013**, *27*(16), 1787-1799.
- [254] Muñoz-Najar, U.; Sedivy, J.M. Epigenetic control of aging. *Anti-oxid. Redox Signal.*, **2011**, *14*(2), 241-259.
- [255] Mersfelder, E.L.; Parthun, M.R. The tale beyond the tail: Histone core domain modifications and the regulation of chromatin structure. *Nucleic Acids Res.*, **2006**, *34*(9), 2653-2662.
- [256] Wu, T.P.; Wang, T.; Seetin, M.G.; Lai, Y.; Zhu, S.; Lin, K.; Liu, Y.; Byrum, S.D.; Mackintosh, S.G.; Zhong, M.; Tackett, A.; Wang, G.; Hon, L.S.; Fang, G.; Swenberg, J.A.; Xiao, A.Z. DNA methylation on N(6)-adenine in mammalian embryonic stem cells. *Nature*, **2016**, *532*(7599), 329-333. Available from: <https://www.nature.com/articles/nature17640>
- [257] Lu, C.; Thompson, C.B. Metabolic regulation of epigenetics. *Cell Metab.*, **2012**, *16*(1), 9-17.
- [258] Kornblihtt, A.R.; de la Mata, M.; Fededa, J.P.; Muñoz, M.J.; Nogueas, G. Multiple links between transcription and splicing. *RNA*, **2004**, *10*(10), 1489-1498.
- [259] Naftelberg, S.; Schor, I.E.; Ast, G.; Kornblihtt, A.R. Regulation of alternative splicing through coupling with transcription and chromatin structure. *Annu. Rev. Biochem.*, **2015**, *84*, 165-198.
- [260] Luco, R.F.; Allo, M.; Schor, I.E.; Kornblihtt, A.R.; Misteli, T. Epigenetics in alternative pre-mRNA splicing. *Cell*, **2011**, *144*(1), 16-26.
- [261] Zhou, H.L.; Luo, G.; Wise, J.A.; Lou, H. Regulation of alternative splicing by local histone modifications: Potential roles for RNA-guided mechanisms. *Nucleic Acids Res.*, **2014**, *42*(2), 701-713.
- [262] Braunschweig, U.; Guerousov, S.; Plocik, A.M.; Graveley, B.R.; Blencowe, B.J. Dynamic integration of splicing within gene regulatory pathways. *Cell*, **2013**, *152*(6), 1252-1269.
- [263] Li, Y.I.; van de Geijn, B.; Raj, A.; Knowles, D.A.; Petti, A.A.; Golan, D.; Gilad, Y.; Pritchard, J.K. RNA splicing is a primary link between genetic variation and disease. *Science*, **2016**, *352*(6285), 600-604. Available from: <http://science.sciencemag.org/content/352/6285/600>
- [264] Heintz, C.; Doktor, T.K.; Lanjuin, A.; Escoubas, C.; Zhang, Y.; Weir, H.J.; Dutta, S.; Silva-García, C.G.; Bruun, G.H.; Morantte, I.; Hoxhaj, G.; Manning, B.D.; Andresen, B.S.; Mair, W.B. Splicing factor 1 modulates dietary restriction and TORC1 pathway longevity in *C. elegans*. *Nature*, **2017**, *541*(7635), 102-106. Available from: <https://www.nature.com/articles/nature20789>
- [265] Tabrez, S.S.; Sharma, R.D.; Jain, V.; Siddiqui, A.A.; Mukhopadhyay, A. Differential alternative splicing coupled to nonsense-mediated decay of mRNA ensures dietary restriction-induced longevity. *Nat. Commun.*, **2017**, *8*(1), 306. Available from: <https://www.nature.com/articles/s41467-017-00370-5>