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Review

Stress, epigenetics, and aging: Unraveling the intricate crosstalk

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SUMMARY

Aging, as a complex process involving multiple cellular and molecular pathways, is known to be exacerbated by various stresses. Because responses to these stresses, such as oxidative stress and genotoxic stress, are known to interplay with the epigenome and thereby contribute to the development of age-related diseases, investigations into how such epigenetic mechanisms alter gene expression and maintenance of cellular homeostasis is an active research area. In this review, we highlight recent studies investigating the intricate relationship between stress and aging, including its underlying epigenetic basis; describe different types of stresses that originate from both internal and external stimuli; and discuss potential interventions aimed at alleviating stress and restoring epigenetic patterns to combat aging or age-related diseases. Additionally, we address the challenges currently limiting advancement in this burgeoning field.

INTRODUCTION

Aging involves a gradual decline in physiological functions over years, and in humans, decades, increasing susceptibility to various chronic diseases.[1–4] Accumulating evidence suggests that aging is highly variable between individuals and can be induced by intrinsic and extrinsic stimuli through a combination of genetic and environmental factors.[5,6] Such stimuli, including oxidants, radiation, heat shock, chronic stress, and more, are well-known contributors to aging and related diseases[7–9] and known to activate intracellular stress responses, leading to cell biological changes and physiological adaptations. Because the cumulative impacts of excessive or persistent stresses exacerbate cellular damage, resulting in DNA damage and inflammation, such cascading intrinsic stimuli progressively accelerates cellular senescence and the consequent aging process, thereby heightening vulnerability to age-related disorders. Consequently, deciphering underlying causal effects and intricate regulatory mechanisms governing stress-accelerated aging becomes imperative in informing the formulation of innovative prognostications and interventions to alleviate aging and chronic diseases.[10–14]

Epigenetics refers to heritable changes in gene expression that occur without altering the DNA sequence.[15–17] Epigenetic modifications, such as DNA or RNA methylation, histone modifications, chromatin remodeling, and non-coding RNAs, are critical regulators of gene expression and play an essential role in the aging process.[10,12,13] Epigenetic changes can be influenced by stress and, in turn, affect the stress response, highlighting the importance of studying the interplay between epigenetics, stress, and aging. Seminal studies have provided valuable insights into the epigenetic mechanisms linking stress with aging through the induction of changes in gene expression and cellular function.[18–22] Nevertheless, an in-depth and comprehensive understanding of recent advances in this area is lacking.

In this review, we will summarize the current advancements in our knowledge of how various stresses trigger aging and age-related disorders via epigenetic mechanisms. We will discuss the interlinked impacts of different types of stresses, considering both intrinsic and extrinsic stimuli, on aging and related diseases. Furthermore, we will delve into how epigenetic regulation at multiple layers is involved in stress stimulation and responses. Additionally, we will review potential interventions aimed at alleviating aging and age-related diseases by reducing stress and restoring epigenetic homeostasis. Lastly, we will address the challenges in studying the epigenetic interplay between stress and aging and translating the aging interventions into clinical

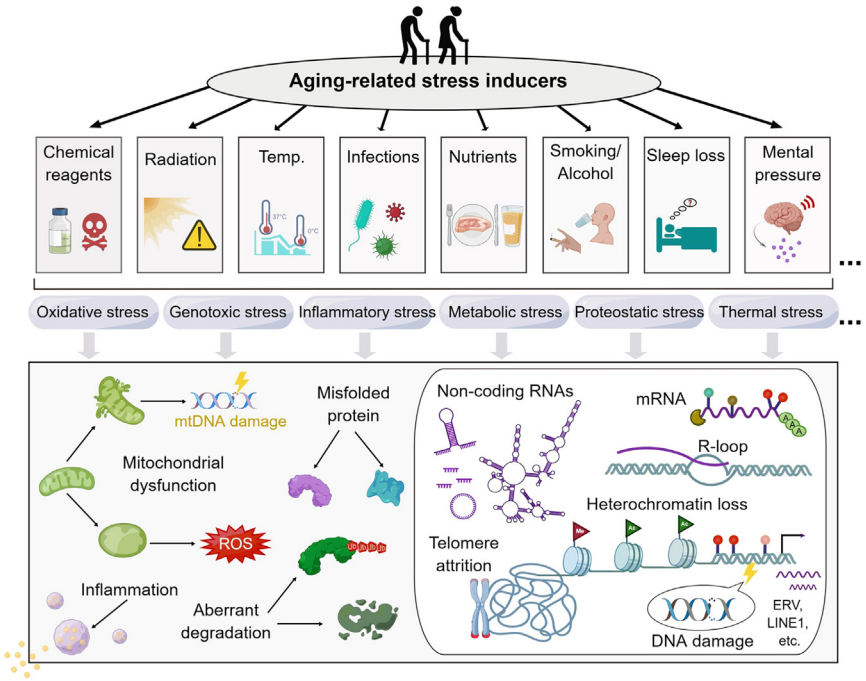

Figure 1. An overview of the interplay between aging-related stresses and epigenetic changes

Aging-related stressors, such as chemical reagents, radiation, abnormal temperatures (Temp.), infections, imbalanced nutrients, unhealthy habits (e.g., smoking and alcohol consumption), sleep deprivation, mental pressure, and spontaneous intracellular dysregulation, significantly impact aging progression and contribute to the development of age-related diseases. They act as inducers of oxidative stress, genotoxic stress, inflammatory stress, metabolic stress, proteostatic stress, and thermal stress, which have crosstalk with each other. Such crosstalk may lead to diverse cellular damages, including DNA damage, genetic mutation, telomere shortening, aberrant transcription, protein aggregation, mitochondrial dysfunction, and inflammation. These intracellular dysregulations can further stimulate cascading responses involving specific epigenetic changes. Such changes are occurring at distinct layers, which encompass higher-ordered genomic architecture, chromatin accessibility, histone modifications, DNA methylation, RNA modifications, and non-coding RNA expression.

applications. Although this review cannot cover all forms and manifestations of stresses associated with aging, we here focus on typical representatives, including oxidative stress, genotoxic stress, inflammatory stress, and metabolic stress.

DIFFERENT TYPES OF STRESSES RELATED TO AGING AND THE UNDERLYING EPIGENETIC REGULATION

Aging-related stresses induced by a range of internal and external stimuli can shape aging by triggering accumulation of cellular damages, ultimately contributing to age-related diseases.[8,9,23–25] Internal stimuli are predominantly produced by the cell itself, such as cellular-metabolism-derived reactive oxygen species (ROS), the deposition of which can contribute to cellular aging. Conversely, external stimuli, such as chemical reagents, radioactivity, ultraviolet (UV) irradiation, extreme temperatures, infections, etc., can elicit intrinsic stressors, which synergistically exacerbate the aging process. Stresses originating from both intrinsic and extrinsic sources are broadly associated with epigenetic alterations, encompassing dynamics in DNA and RNA methylations, histone modifications, and non-coding RNA expression. In this section, we will introduce aging-associated stresses induced by distinct stimuli, including oxidative stress, genotoxic stress, inflammatory stress, metabolic stress, etc. and discuss the epigenetic basis underlying the contribution of these stresses to aging (Figure 1).

Oxidative stress

ROS, such as hydrogen peroxide (H_2O_2), are primarily generated in the mitochondria as natural by-products of cellular metabolism but can also be induced in response to environmental factors, such as radiation and chemicals.[26] Accumulation of ROS triggers the activation of signaling pathways, including the nuclear-factor-erythroid-2-related factor 2 (NRF2) pathway, and the expression of antioxidant enzymes, such as superoxide dismutases (SODs), which aim to eliminate harmful effects of ROS. However, excessive ROS production or impaired antioxidant defense can lead to oxidative stress, causing damage to cellular macromolecules and ultimately contributing to cellular dysfunction and aging-related processes.[27–30] Interestingly, recent studies have shown a close relationship between oxidative-stress-related aging and its underlying epigenetic regulation.

On the one hand, epigenetic regulation is implicated in endogenous oxidative-stress-related aging processes due to the hyperactive production of intracellular ROS and the impairment of antioxidant systems. For instance, glyceraldehyde 3-phosphate dehydrogenase (NADPH) oxidase 4 (NOX4), one of the major endogenous ROS-generating enzymes, displays increased expression that is consistently coupled with excessive ROS accumulation in various aging models of rodents and human cells.[31–33] Enrichment of the active histone mark H4K16ac at the promoter region contributes to the epigenetic activation of the *NOX4* gene and release of H_2O_2 in cellular aging,[34] indicating NOX4 as a potential aging biomarker and driver with possible involvement of epigenetics. Multiple layers of epigenetic alterations are also associated with dysregulation of antioxidant systems during aging. For example, dysregulation of microRNA (miRNA) processing contributes to DNA methyltransferase 3A (DNMT3A)-mediated hypermethylation and repressed expression of SOD2, a mitochondrial SOD, which, in turn, results in high ROS levels and accelerates aging in human mesenchymal stem cells (MSCs).[35] Moreover, in fibroblasts from aged mice, decreased expression of SOD3, an extracellular SOD, along with elevated levels of ROS, coincides with changes in a variety

of histone marks at the *SOD3* promoter region, such as the decrease in H3K9ac and the increase in H3K27me3.[36] Furthermore, the antioxidant activity of NRF2, which declines with human MSC aging, can also be regulated by DNA methylation and histone modifications.[37,38] For example, deficiency of SIRT6, one of the seven mammalian sirtuins, results in failed deacetylation of H3K56 and impeded transcription of NRF2 target genes, such as the gene encoding heme oxygenase 1 (*HMOX-1*), increasing ROS accumulation and accelerating human MSC aging.[39] Additionally, SIRT3 and SIRT7, two other sirtuin members, also participate in maintaining intracellular redox homeostasis and counteracting stem cell aging at least partially by stabilizing the nuclear lamina and heterochromatin.[40,41] Overall, these findings suggest that the epigenetic regulation of ROS-generating enzymes and antioxidant factors contributes to intrinsic oxidative stress and the aging process.

On the other hand, oxidative stress induced by exogenous stimuli can also cause epigenetic alterations and contribute to aging and age-related diseases. Beyond directly inducing the oxidation of methylated cytosines (5-methylcytosine, abbreviated as 5mC in DNA) to 5-hydroxymethylcytosine (5hmC), ROS are also able to regulate the activity of epigenetic enzymes modifying DNA, RNA, and histone modifications. For instance, in human neuroblastoma cells, H_2O_2 treatment upregulates the expression of amyloid precursor protein (APP) and beta-site APP cleaving enzyme 1 (BACE1) via the induction of DNA hypomethylation due to the repression of DNMT1 and DNMT3A. This stress response is associated with increasing β-amyloid (Aβ) deposition, a mechanism known to play a pivotal role in Alzheimer's disease (AD), an aging-related neurodegenerative disorder.[42] Moreover, alterations in DNA methylation may also be involved in ROS-related aging regulation induced by UV, high glucose, and psychosocial stress.[43–48] Apart from DNA methylation, RNA methylation and histone modification are also implicated in the regulation of oxidative-stress-related aging triggered by exogenous inducers. For example, in H_2O_2-treated human colon carcinoma cells, the enhancement of RNA methyltransferases METTL3/METTL14-mediated N^6-methyladenosine (abbreviated as m^6A in RNA) and NSUN2-mediated 5-methylcytidine (abbreviated as m^5C in RNA) modifications facilitates translation of the senescence marker p21, which exacerbates oxidative-stress-induced cellular aging.[49] Upregulation of p21 can also be triggered by the elevation of H4K16ac due to the reduced binding of histone deacetylase 2 (HDAC2) at its promoter region in H_2O_2-induced neuronal degeneration.[50] Similarly, smoking-associated ROS induction directly triggers downregulation of HDAC2 and subsequent upregulation of p21, contributing to cellular aging in patients with chronic obstructive pulmonary disease, another age-related disorder.[51]

Despite numerous studies suggesting that oxidative stress reduces longevity and promotes aging, there is countering evidence showing beneficial roles of ROS in extending lifespan.[26] For example, in yeast, mitochondrial ROS can increase the deposition of H3K36me3 by downregulating the expression of its demethylase, resulting in Sir3p-mediated transcriptional silence of subtelomeric regions and longevity.[52] In addition, in *C. elegans*, early-life exposure to H_2O_2 can increase stress resistance and lifespan via the global reduction of H3K4me3.[53] These findings suggest that ROS in aging regulation is both pleiotropic and context dependent.

Genotoxic stress

Genotoxic stress refers to any disturbance in genomic stability caused by internal or external factors, including oxidative damage, radiation, and chemical agents, as well as errors in DNA replication, repair, and transcription.[9,28,54–56] In response to genotoxic stress, signaling pathways are activated to safeguard genomic integrity, such as the DNA damage response (DDR) pathways, which encompass ataxia telangiectasia mutated (ATM), ataxia telangiectasia and Rad3-related protein (ATR), and p53, and can result in either of two outcomes: successful DNA repair or genomic instability. Genomic instability, characterized by DNA damage and genetic mutations, is a critical hallmark and major contributor to aging and age-related diseases.[10,57] In recent years, significant progress has been made toward understanding the regulatory mechanisms responsible for epigenetic changes during aging within the context of genotoxic stress.

A variety of genetic disorders that show premature aging defects,[9,55] such as Werner syndrome (WS) and Hutchinson-Gilford progeria syndrome (HGPS), are usually identified by detecting accumulation of DNA damage and disruption of the epigenome. For example, accumulation of phosphorylated H2AX (γH2AX), a surrogate marker of genotoxic stress detecting double-strand breaks (DSBs), and increased nuclear foci of 53BP1, evidence for the activation of DDR, are observed in cellular models of WS and HGPS.[58,59] Extensive epigenetic abnormalities at the genomic and transcriptomic levels are also detected in these cellular aging models at multiple levels, including lamina-chromatin interactions, higher-ordered genomic organization covering compartments, topologically associating domains (TADs) and loops, chromatin accessibility, multiple histone modifications, as well as DNA and RNA methylation.[60–62] Beyond WS and HGPS, other progeroid disorders caused by mutations in DNA repair genes, such as Xeroderma pigmentosa and Cockayne syndrome, also display genotoxic stress-related features, including defective DNA repair and accelerated cellular senescence.[63,64] Additionally, genetic mutations in epigenetic modifying enzymes, such as SIRT6, can also lead to genomic instability, epigenetic dysregulation, and premature aging.[56] Finally, it is worth noting that recent research suggests that even non-mutagenic DSBs can disrupt the epigenetic landscape and contribute to accelerated aging.[65]

Intracellular oxidation and replication stress are also internal sources of genotoxic stress that are associated with epigenetic regulation and contributing to aging-related processes. For instance, oxidative DNA modifications induced by cellular ROS, such as 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG), which increases during aging and age-related diseases, erodes genomic stability but also serves as an epigenetic marker connected to DNA and histone methylation remodeling and for control of downstream gene transcription.[66,67] Similarly, 5hmC, an oxidized form of 5mC, appears to be localized at DNA damage sites and acts as a substrate for base excision repair, as well as an epigenetic mark involved in regulating gene expression related to neurodegenerative disorders.[68,69] Replication stress caused by disturbances in DNA polymerase progression is another factor contributing to genomic instability and cellular aging.[54,70] Additionally, epigenomic reorganization, including changes in histone modifications and nucleosome assembly, has been implicated in replication stress.[54]

Telomere shortening is another critical aspect of aging-associated genomic instability. It is considered one of the key hallmarks of aging, triggering DNA damage at chromosome ends and exacerbating the progression of aging and related diseases.[10,71–73] Notably, progressive telomere attrition is associated with epigenetic alterations at multiple layers such as DNA and RNA methylation and histone modifications. For instance, a positive correlation has been reported between lower DNA methylation levels and shorter telomere lengths, which may contribute to increased genomic instability and susceptibility to diseases and aging.[74] The DNA-damage-inducible protein GADD45α also links DNA methylation status to the regulation of telomere integrity in the aging-related process.[73] Similarly, RNA methylation plays a significant role in telomere stability as well. For example, the RNA-binding protein HuR enhances telomerase activity through m^5C modification on *TERC* RNA, a mechanism which counters cellular senescence.[75] Moreover, METTL3-mediated RNA m^6A modification has also been implicated in maintaining telomere integrity by stabilizing *TERRA*.[76] In addition, a variety of histone modifications, including both repressive and active marks, regulate the integrity of telomeric and subtelomeric regions, such as H3K9me3, H4K20me3, and various acetylated forms of H3 and H4.[77] In addition to telomeres are various other specialized nucleic acid structures that show high susceptibility to genotoxic stresses. These include the G-quadruplex (G4),[78] a non-canonical four-stranded DNA structure formed by G-rich sequences, and the R-loop,[79] a three-stranded structure containing a DNA:RNA hybrid and a displaced single-stranded DNA. These structures can also interact with multiple histone marks, participating in the regulation of stem cell pluripotency and differentiation, as well as aging-related processes.[80–84]

Extranuclear nucleic acid structures, including mitochondrial DNA (mtDNA) and micronuclei (MN), can also function as genotoxic stress sentinels. Due to the lack of a refined DNA repair system and proximity to the major source of ROS, mtDNA is more prone to damage or mutation. As a result, mtDNA mutations accumulate with age, leading to mitochondrial dysfunction and the progression of aging-associated disorders, such as cancer and age-related infertility.[85–88] Epigenetic regulation of mtDNA involves inherent DNA methylation and non-coding RNA within mitochondria, impacting gene expression and subsequent mitochondrial homeostasis and aging.[89,90] On the other hand, mitochondria also indirectly influence the nuclear epigenome, including DNA and histone methylation, through metabolic intermediates and by-products, such as α-ketoglutarate.[91,92] In addition, copy-number variation of mtDNA is also associated with aging-related epigenetic regulation, as demonstrated by studies on human tissues supporting a positive correlation between mtDNA copy number and epigenetic aging.[93,94] Unlike mtDNA, MN represent non-canonical structures formed from mis-segregation of chromosome and in response to extensive DNA damage.[79,95] Aberrant MN are associated with altered histone modifications and chromatin accessibility, suggesting a connection to abnormal transcription, genomic instability, and potentially aging.[96,97]

A variety of exogenous factors such as UV radiation, γ rays, and genotoxic chemicals are also linked to genomic instability and epigenomic remodeling during aging. For instance, UV-induced DNA damage is associated with shifts in DNA and RNA methylation patterns, which further contribute to the progression of cellular and tissue aging.[62,98–100] Likewise, γ irradiation can induce DNA damage and accelerate skin aging through a miRNA-mediated regulatory axis.[101] Bleomycin-induced cellular senescence also involves accumulation of DNA damage and reorganization of the epigenome, characterized by KDM4-mediated demethylation of H3K9 and H3K36.[102] Moreover, in exogenous oncogene-induced cellular aging models, a possible interplay between DDR and higher-ordered chromatin organization has been described.[103–105] In addition, lifestyle risk factors, such as alcohol,[106–108] smoking,[109–111] and sleep disturbance,[112–115] also contribute to genotoxic stress and are associated with aging-related epigenetic variations. Taken together, these findings provide a concise overview of endogenous and exogenous sources of genotoxic stresses and their complex interplay with epigenetic alterations in the regulation of aging.

Inflammatory stress

Inflammation is a vital response that maintains tissue balance, aids immune responses, and supports tissue repair. However, excessive inflammation (inflammatory stress) harms physiological functions and contributes to age-related diseases.[116–118] Aging itself is associated with a chronic low-grade inflammation state known as inflammaging, in which immune responses and tissue regeneration are disrupted.[116,119] A deep-learning method, based on inflammatory patterns and applied as an aging clock,[120] emphasized the critical link between inflammation and aging. Various stimuli such as DNA damage and foreign infections can induce inflammatory stress, triggering downstream signaling pathways, such as nuclear factor-κB (NF-κB), to promote the transcription of pro-inflammatory cytokines. Specific for aging-associated inflammation is the senescence-associated secretory phenotype (SASP), a common feature of cellular senescence, where secreted pro-inflammatory factors exacerbate inflammation to further drive development of age-related conditions.[119] Epigenetic modifications play a crucial role in regulating gene expression during aging-related inflammation. Understanding the intricate interplay between epigenetics and inflammation is therefore essential for uncovering the molecular basis of aging and identifying potential therapies.

Among multifaceted internal causes of inflammatory stress, genomic instability represents a critical one which can uniquely drive sterile inflammation related to aging and associates with many aspects of epigenetics. For example, DNA damage itself acts as an inducer of inflammation and prompts post-translational modifications of involved modulators in DDR. Damage-susceptible R-loops or MN also contribute to aseptic inflammation and are implicated in aging-related pathways.[79] Moreover, mutations in genes encoding epigenetic modifying enzymes (e.g., *DNMT3A*) also intersect with the regulation of chronic inflammation linked to aging.[121,122] Remarkably, genomic-instability-induced derepression of retrotransposable elements (REs), which can activate the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) innate immunity pathway (Figure 2), has been inextricably intertwined with aging-associated inflammation.[123] For example, knockout of SIRT7 in human MSCs results in heterochromatin loss, disrupted lamina-chromatin interaction, increased chromatin accessibility, and derepression of long-interspersed element-1 (LINE1) retrotransposons. These

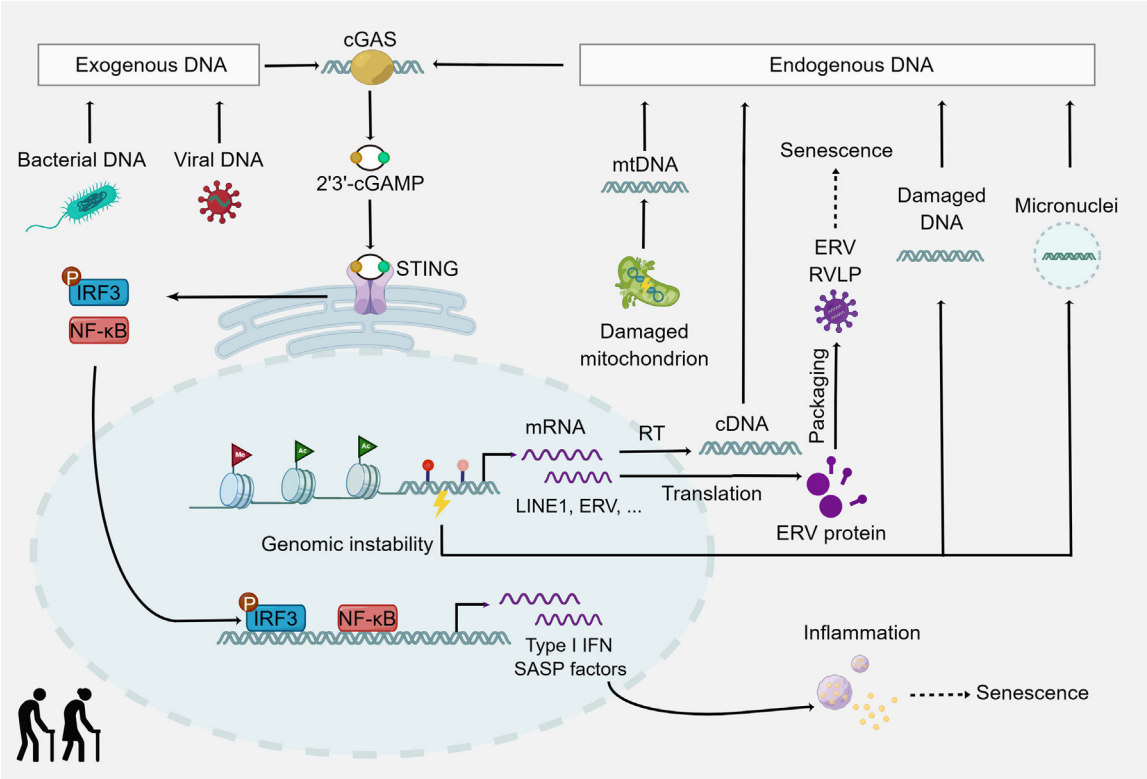

Figure 2. The cGAS-STING signaling in aging-related inflammation

The cGAS-STING pathway is induced by exogenous or endogenous DNA and then promotes the synthesis of 2′3′-cyclic GMP-AMP (cGAMP), phosphorylation of interferon regulatory factor 3 (IRF3), and nuclear translocation of NF-κB. This mechanism triggers activation of interferon (IFN)-I and SASP signaling, which further contributes to aging-related inflammation. Notably, exogenous DNA comes mainly from bacterial or viral infections. In contrast, endogenous DNA is primarily derived from genomic instability that produces damaged DNA fragments or micronuclei, cDNA of REs, such as LINE1 and ERV, and DNA leakage from damaged mitochondrion. Abbreviations are as follows: RT, reverse transcription; cDNA, complementary DNA; RVLP, retrovirus-like particles.

cellular dysfunctions activate the cGAS-STING pathway, upregulating inflammatory factors and further exacerbating stem cell aging.[41] Similar observations are seen in prematurely aged human MSCs with deficiency of the circadian regulators CLOCK and BMAL1.[124,125] Consistent with the findings at the cellular level, LINE1 activation also induces inflammatory responses in SIRT6-deficient progeroid mice, as well as in physiologically aged human and mouse tissues.[126,127] Additionally, endogenous retroviruses (ERVs), another type of RE, whose activation involves the remodeling of DNA methylation and histone modifications, can also stimulate the cGAS-STING pathway and upregulate inflammation to amplify aging, potentially via a paracrine mechanism.[128,129] RNA m^6A decoration is also implicated in the regulation of REs and SASP factors.[100,130–132] However, direct evidence is still lacking to address whether m^6A regulates the aging-related inflammatory responses via modulation of RE activity. Similar to REs, released mtDNA can elicit the cGAS-STING activity as well, driving inflammation, neurotoxicity, and brain aging, although it is unknown whether the epigenome is involved.[133]

Non-coding RNA and three-dimensional (3D) genomic organization are also involved in the regulatory network of aging-related inflammation. For example, non-coding RNAs derived from the pericentromeric region impair the DNA-binding capacity of CCCTC-binding factor (CTCF), a key player in chromatin organization, accounting for increased chromatin accessibility and activated transcription of SASP genes.[134] Moreover, genomic remodeling of H3K27ac-enriched enhancers within TADs modulates the expression dynamics of adjacent SASP genes in replicatively senescent cells.[135] Additionally, METTL3 and METTL14 facilitate the formation of promoter-enhancer loops to regulate SASP gene expression independently of m^6A.[136] These findings reflect the intricate regulation of aging-associated inflammation from distinct epigenetic layers.

Inflammatory stress related to aging may also originate from extrinsic stimuli, such as viral or bacterial infections, which usually trigger acute inflammation. For instance, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which has received great attentions in recent years, has been coupled to accumulated DNA damage, hyperactivated inflammation, and accelerated aging in host cells.[137–141] Multiple epigenetic regulation is involved in this process. For example, the SARS-CoV-2 protein ORF8 functions as a histone H3 mimic to affect the host epigenome, thus widely disrupting the landscape of histone modifications, as featured by increased H3K9me3 and H3K27me3 and decreased H3K9ac.[142] Furthermore, SARS-CoV-2 induces widespread nuclear reorganization in host cells, especially at the compartment scale, which potentially contributes to the altered gene expression profile covering inflammatory

genes.[143,144] Besides, the SARS-CoV-2 N-protein disrupts 53BP1 recruitment by competitively binding damage-induced long non-coding RNA, leading to impaired DNA repair, which, in turn, exacerbates inflammation and cellular senescence.[145] To be noted, increasing evidence support that the high susceptibility to SARS-CoV-2 infection in the elderly and the lethal "cytokine storm" may be related to the high expression of SARS-CoV-2 receptor genes during aging, whereas the specific epigenetic mechanisms remain elusive.[146–148] Inflammation induced by poly(I:C) treatment or bacterial infection can promote epigenetic aging as well.[117] Additionally, psychological stress and sleep-deprivation-induced chronic inflammation have been linked to epigenetic dysregulation and accelerated aging.[22,113,114,149–153] However, further research is needed to uncover the precise molecular mechanisms involved.

Metabolic stress

Nutrition and metabolism intricately regulate a variety of biological processes. Imbalanced nutrient and metabolic signals profoundly impact cellular functions, accelerating aging and age-related diseases.[154,155] Nutrient affects biological functions through signaling pathways, such as insulin/insulin-like growth factor 1 (IGF-1), mammalian target of rapamycin (mTOR), sirtuins, and AMP-activated protein kinase (AMPK), which regulate cellular growth, autophagy, and metabolism. Dysregulation of these pathways, often associated with metabolic disorders, such as obesity and diabetes, accelerates aging.[9] Metabolic stress, induced by various causes, such as excessive caloric intake, nutrient deprivation, impaired nutrient sensing, and accumulation of toxic metabolites, leads to oxidative damage and mitochondrial dysfunction, promoting cellular senescence and accelerated aging.[156] Epigenetic modifications can mediate the effects of metabolic stress on aging by altering distinct marks and influencing metabolic gene expression. Understanding these connections will provide novel insights into the development of strategies for maintaining metabolic balance and promoting healthy aging.

Metabolic pathways utilize nutrients such as glucose, fatty acids, and amino acids to generate metabolites that regulate life activities. Disruptions in nutrient uptake and metabolism can cause epigenetic changes, impacting gene expression patterns associated with aging. For example, glucose metabolism involves the non-oxidative pentose phosphate pathway (PPP) and transketolase, an essential enzyme. Defects in transketolase impair glucose metabolism, increase oxidative stress, trigger mitochondrial dysfunction, global DNA hypermethylation, repression of functional genes in immune cells, and potentially contribute to immunosenescence.[157,158] During stem cell aging-related processes, reduced glucose uptake may contribute to decreased histone acetylation (including H4K16ac),[159] which potentially associates with increased CDC42, a Rho family GTPase involved in aging regulation.[160] Lipid metabolism affects aging and longevity by interacting with DNA methylation and histone modifications. As an example, the gene encoding a fatty acid elongase known as elongation of very long chain fatty acids-like 2 (*ELOVL2*), a master regulator controlling the synthesis of polyunsaturated fatty acid, is hypermethylated, concomitated with a downregulated expression level during biological aging. Deficiency of ELOVL2 leads to dysregulated lipid metabolism, indicated by accumulation of short fatty acids, glucose intolerance, insulin resistance, and premature aging in mice.[161] Metabolic dysregulation of specific fatty acids inhibits HDAC, resulting in alterations in histone acylation and crotonylation, and subsequent gene expression dynamics.[162,163] Besides, the epitranscriptomic machinery, including the RNA m^6A demethylase fat mass- and obesity-associated protein (FTO), also affects lipid metabolism. For instance, FTO genetic variants associate with obesity risk, whereas its deficiency reduces adipose tissue.[164,165] Similarly, knockout of FTO in human MSCs causes impaired lipid synthesis, along with accelerated senescence phenotypes encompassing nuclear abnormalities, heterochromatin loss, and telomere attrition.[166] Amino acid metabolism and its interconnections with epigenetics also play a role in aging regulation. For example, vascular endothelial cell (VEC) aging involves downregulation of intracellular serine and phosphoglycerate dehydrogenase (PHGDH), a key enzyme in serine synthesis. Knockdown of PHGDH decreases serine levels and accelerates VEC aging. Mechanistically, PHGDH facilitates nuclear translocation of pyruvate kinase M2 (PKM2) via p300-catalyzed acetylation, leading to histone H3T11 phosphorylation and expression of aging-associated factors, such as SIRT1.[167] In addition, branched-chain amino acids modulate aging or longevity potentially through altering the neuronal histone acetylome covering H3K9ac.[168,169]

Non-coding RNAs, an integral layer of epigenomics, are connected to aging-related metabolic regulation as well. One example is miRNA, which plays a pivotal role in regulating metabolic balance during aging and age-related disorders. miRNAs are believed to target nutrient sensing pathways, such as insulin and mTOR signaling, affecting glucose and lipid metabolism.[170] For instance, miR-143, downregulated during aging, promotes myogenesis as an alternative mechanism. However, overexpression of miR-143 interferes with insulin-related regulation and disrupts liver glucose metabolism in mouse models of obesity.[171] Another important player is *Altre*, a long non-coding RNA found in regulatory T cells that increases with aging. *Altre* is involved in regulating mitochondrial dynamics to maintain immune-metabolic homeostasis in the liver during aging. Consequently, depletion of *Altre* leads to dysregulated lipid metabolism, hyperactive ROS accumulation, and inflammatory liver microenvironment in aged mice.[172]

Other types of phytochemicals from diets or general metabolic intermediates and by-products from host cells or gut microbes also interplay with aging-related epigenetics (Figure 3). For example, dihydrocaffeic acid (DHCA), present in grapes and other plants and a microbial metabolite with antioxidant capacity, can decrease DNMT1 expression in mice, leading to intronic DNA hypomethylation and downregulated expression of interleukin (IL)-6, a common SASP factor.[173] S-adenosyl-methionine (SAM), an important metabolite involved in one-carbon metabolism, enhances the trimethylation of H3K36 and production of IL-1β, another well-known SASP factor, thus contributing to aging-related defects.[174,175] NAD^+, a cofactor of sirtuins, links epigenetic regulation to aging-related gene expression dynamics such that declining NAD^+ levels during aging are associated with alterations in histone acetylation patterns.[176] For instance, reduced NAD^+ levels concomitant with impaired SIRT2 activity contribute to aging-induced demyelination through failed inhibition of H3K18

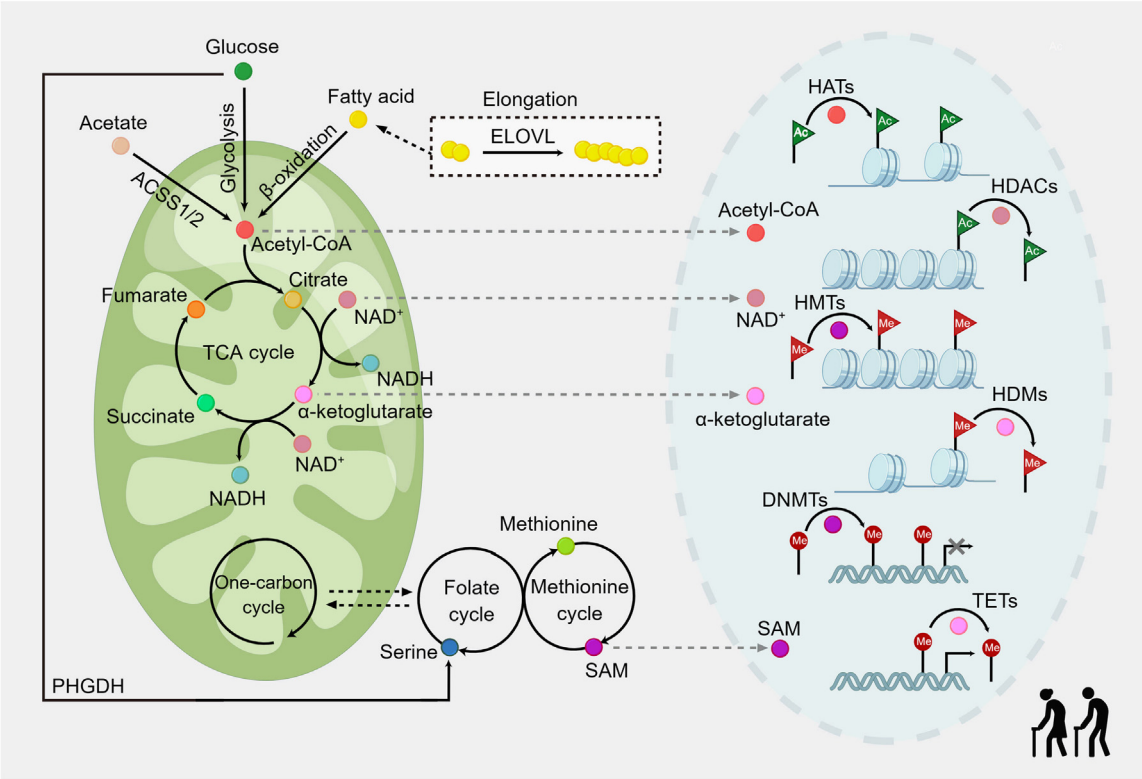

Figure 3. The interplay between metabolism and epigenetics

Mitochondria provide essential metabolic intermediates or by-products implicated in aging regulation, for example, acetyl-CoA, NAD^+, α-ketoglutarate, and SAM, which function as cofactors to remodel epigenetic marks, such as histone acetylation and methylation, and DNA methylation.

Abbreviations are as follows: HATs, histone acetyltransferases; HDACs, histone deacetylases; HMTs, histone methyltransferases; HDMs, histone demethylases; DNMTs, DNA methyltransferases; TETs, ten-eleven translocation DNA demethylases.

acetylation and ID4 transcription.[177] Moreover, decreased SIRT2 activity also disrupts deacetylation but facilitates phosphorylation of $p66^{Shc}$, a mitochondrial adaptor protein, resulting in aberrant mitochondrial ROS and exacerbated vascular aging.[178] Likewise, acetyl-coenzyme A (CoA), a metabolite that can be derivedfrom glucose, fatty acids, and amino acids, also participates in aging regulation by remodeling histone acetylation. For example, the acetyl-CoA synthetase Acs2 in yeast, or its human ortholog ACSS2, can promote H4K16ac enrichment at the subtelomeric region, compromising telomere silencing and accelerating aging.[179] Similarly, reduced acetyl-CoA production sensed by the nucleosome remodeling and deacetylase (NuRD) complex leads to decreased histone acetylation and chromatin remodeling, which furthers aging progression.[180] Besides, as mentioned earlier, α-ketoglutarate, an intermediate of the tricarboxylic acid (TCA) cycle, acts as a cofactor for both DNA and histone demethylases, exerting extensive effects on gene regulation in aging-related epigenetic modulation.[91,92] Taken together, these findings reveal a complex interplay between multi-dimensional epigenetic regulation, nutrient sensing, and metabolic pathways in aging-related processes.

Other types of stresses

Beyond oxidation, inflammation, genotoxicity, and metabolic imbalance, other types of stresses such as proteostatic stress and thermal stress play significant roles in the aging process (Figure 1). Proteostatic stress, a disruption of the protein quality control system leading to accumulation of toxic proteins and cellular dysfunction, comprises abnormal protein synthesis and degradation or the accumulation of misfolded or damaged proteins within cells. It can be induced by oxidative damage, endoplasmic reticulum (ER) stress, and heat shock, and involves signaling pathways associated with unfolded protein response (UPR) and autophagy. Thermal stress, on the other hand, occurs when cells or organisms experience temperature conditions outside their optimal range. Extremely high or low temperatures can provoke heat or cold shock response and even disrupt the thermoregulation system, which further exacerbate oxidative stress, protein misfolding, and cellular damage. Both proteostatic stress and thermal stress play important roles in regulating aging, and investigating such roles stand to offer additional insights into underlying mechanisms, including the interactive role of epigenetics.

Proteostatic stress

Loss of proteostasis is regarded as a hallmark and driver of aging and age-related diseases.[10,181,182] Throughout the entire cycle of protein synthesis, folding, and degradation, epigenetic modifications play important regulatory roles. During protein synthesis, disruption of ribosome-associated quality control compromises translation, resulting in proteostasis collapse and age-dependent

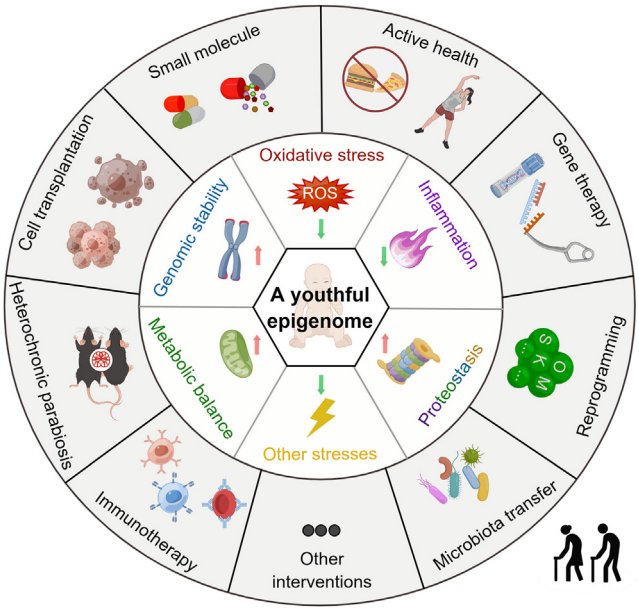

Figure 4. Aging interventions related to stress relief and epigenomic stabilization

A diverse range of interventions, including active health approaches, small molecule-based strategies, gene therapy, cell transplantation, heterochronic parabiosis, reprogramming, fecal microbiota transplantation, immunotherapy, etc., are explored to alleviate harmful stresses and rejuvenate the aging epigenome. These intervention strategies demonstrate varying degrees of effectiveness in attenuating aging and age-related degenerations across cellular, tissue, or organismal levels.

protein aggregation.[183] Ribosomal mutations causing translation errors drive premature aging in mice, reflected as shortened lifespan along with weight loss, ROS accumulation, telomere attrition, and accelerated epigenetic aging.[184] RNA epigenetics and post-translational modifications are also involved in the regulation of aging-related proteostasis. As mentioned earlier, m^6A and m^5C modifications coordinately regulate the translation efficiency of p21, impacting cellular aging.[49] tRNA m^7G methylation and mRNA ac4C modification are also implicated in translational homeostasis regulation,[185,186] potentially influencing the aging process. Moreover, decreased H3K27me3 is associated with downregulation of the eukaryotic translation initiation factor 4A2 (eIF4A2), which acts as both a translation activator and a repressor.[187] METTL13-catalyzed dimethylation at lysine 55 enhances the intrinsic GTPase activity of eukaryotic translation elongation factor 1A (eEF1A), another critical player in protein synthesis, leading to increased translational output.[188] These observations point to a diversity of epigenetic regulation in protein translation potentially associated with aging progression.

Misfolding and abnormal aggregation of proteins are connected to epigenetic regulation in aging-related processes. For example, misfolding and aggregation of the Aβ peptide, which is linked with the onset and progression of AD, can be exacerbated by genome-wide increase in H3K27ac and H3K9ac levels.[189] Furthermore, aberrant accumulation of the microtubule-binding protein tau causes neurotoxic effects that promote neurodegeneration, wherein phosphorylation and ubiquitination modifications play an important role.[190–192] Aging-interfered protein degradation likewise involves epigenetic dysregulation. For example, global loss of ubiquitination in *C. elegans* during aging led to dysregulated proteasomal degradation and a shortened lifespan.[193] Additionally, aging-induced accumulation of apolipoprotein E (APOE) facilitated degradation of the nuclear lamina and heterochromatin-associated proteins via the autophagy-lysosomal pathway.[194] This process is accompanied by heterochromatin loss, dissociation of lamina-chromatin interaction, gain of chromatin accessibility, and reactivation of repetitive elements. Taken together, these findings highlight the involvement of epigenetics in aging-related loss of proteostasis and provide valuable insights into aging mechanisms.

Thermal stress

Increasing evidence suggest a complex interaction between aging and thermoregulation. For instance, rodents and humans experience age-related declines in body temperature, indicating reduced heat tolerance and abnormal thermoregulatory responses.[195,196] Conversely, impaired thermoregulation due to age or extreme environmental exposure can exacerbate molecular and cellular damage, accelerating aging and aging-related disorders.[197–199] As an example, rodents exposed to hot ambient temperatures acquired elevated body temperature, decreased metabolic rate, and shortened lifespan.[200] In contrast, moderate cold exposure improves proteostasis and prolongs the lifespan of *C. elegans*.[201] Recent studies reveal how such epigenetic mechanisms regulate thermal stress-related aging. For example, aging-induced downregulation of SIRT1 is responsible for the weakened DNA-binding capacity of the heat shock factor (HSF)-1, potentially due to failed deacetylation and contributing to the impaired heat tolerance.[197,202–204] Interestingly, however, mild heat exposure can also promote longevity via remodeling DNA and histone modifications. For instance, heat stress in worms induces heritable longevity, which is mediated by DNA methyltransferase DAMT-1-catalyzed N^6-methyladenosine (abbreviated as 6mA in DNA) modification and histone methyltransferase SET-25 and SET-32-catalyzed H3K9me3 deposition. Meanwhile, transcription factors like the abnormal dauer formation protein (DAF)-16/forkhead box protein O (FOXO), HSF-1, and the nuclear receptor DAF-12/farnesoid X receptor (FXR) are also required for the transgenerational inheritance of heat stress-induced longevity.[205] Likewise, early-life exposure to moderate heat stress in *C. elegans* promotes longevity and long-lasting stress resistance but through establishing an epigenetic memory mediated by histone acetyltransferase CREB-binding protein (CBP)-1 and the chromatin remodeling complex switch/sucrose nonfermentable (SWI/SNF).[206] These findings demonstrate the critical role of epigenetics in heat-stress-related aging regulation and provide potential targets to enhance stress resistance and outfight aging.

AGING INTERVENTIONS FOR STRESS ALLEVIATION AND EPIGENETIC REJUVENATION

On the basis of mechanisms underlying the interconnection between stress and aging, various intervention strategies have been proposed to combat aging and age-related disorders. These include adopting a healthy lifestyle and therapeutic treatments, including small molecules, gene therapies, and cell

transplantation. Additionally, promising interventions for slowing down aging also include heterochronic parabiosis, reprogramming, gut microbial transfer, and immunotherapy. This section will briefly discuss representative aging interventions and their associated stress alleviation and epigenetic regulation (Figure 4).

Active-health-based interventions

Achieving active health involves maintaining a state of well-being through regular physical activity and adopting a healthy lifestyle that encompasses various factors such as diet, exercise, sleep, mood, and environment. Calorie restriction (CR) is an effective approach for combating aging by reducing calorie intake without sacrificing essential nutrients. It has shown wide-ranging effects on extending health span or lifespan through the improvement of stress resistance in a species-conserved manner from yeast to human,[207–210] with the involvement of epigenetic mechanisms, including DNA methylation shifting and histone modification remodeling.[211–213] In addition to CR, other dietary control strategies, such as amino acid or protein restriction and intermittent or periodic fasting, also present beneficial influences on energy metabolism, health span, and longevity, mostly in animal models.[207] Exercise, similar to CR, triggers geroprotective effects and mitigates age-related hazards at least partially by alleviating inflammatory and metabolic stresses.[214,215] Epigenetic regulation, possibly through alterations in DNA methylation and histone modifications, plays an important role in the geroprotective effects of exercise. For example, late-life exercise mitigated DNA-methylation-indicated epigenetic aging in skeletal muscle in mice.[216] Exercise also influences H3K9 methylation profiles in the rat hippocampus with an age-dependent manner.[217] Additionally, emotional stability, regular sleep patterns, and effective smoking cessation also present beneficial results to decelerate epigenetic aging in humans.[218–221]

Small-molecule-based interventions

Extensive efforts have been dedicated toward development of small-molecule-based aging interventions that can be broadly categorized into two classes. The first class, geroprotective or rejuvenating compounds, enhances metabolic homeostasis, bolsters antioxidant capacity, reduces inflammatory stress, and promotes (epi)genomic stability. For example, metformin, an anti-diabetic drug widely applied to promote longevity and healthspan in model organisms,[222–224] has been approved in a clinical trial named Targeting Aging with Metformin (TAME) for its potential aging-targeting effects.[225] Metformin exhibits the ability to reverse a range of aging hallmarks in multiple cellular and animal models, leading to improved nutrient signaling, enhanced intercellular communications, ameliorated proteostasis, attenuated genomic instability, and remodeled epigenetic landscape with increased DNA methylation and H3K27me3 deposition.[225] Resveratrol, an activator of SIRT1, retards aging-related deterioration in mice and prolongs health span or lifespan with metabolic benefits mimicking dietary restriction,[226–228] potentially by affecting DNA methylation and histone acetylation.[229,230] NAD^+, as mentioned earlier, can regulate the activity of sirtuins as well and participate in aging regulation potentially via histone deacetylation. Supplementation with its precursors, such as nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN), effectively prevented the decline of NAD^+ and triggered geroprotective effects at least in rodents.[224,231] Vitamin C, also known as ascorbic acid, has a geroprotective role in prematurely senescent stem cells via restoration of heterochromatin and nuclear lamina.[232] Nucleoside reverse transcriptase inhibitors, such as lamivudine (3TC) and abacavir, alleviate aging-related inflammation via inhibition of LINE1 and ERV.[126–129] Additionally, other small molecules, such as rapamycin,[233] aspirin,[234] uridine,[235] taurine,[236] quercetin,[237] chloroquine,[238] gallic acid,[239] lycorine hydrochloride,[240] oltipraz,[241] etc., have also demonstrated rejuvenating effects.

The second class, known as senolytics, involves agents capable of targeting elimination of senescent cells by inducing apoptosis.[242] For instance, the pan-tyrosine kinase inhibitor dasatinib and the flavonoid quercetin were the first senolytic agents identified to induce apoptosis of senescent cells and alleviate age-related impairments in various tissues,[243–245] which may be associated with changes in DNA and histone methylation profiles.[246,247] Other senolytics, including BCL-2 inhibitors, such as Navitoclax (ABT-263), ABT-737, A1331852, and A1155463,[248–252] heat shock protein 90 (HSP90) inhibitors,[253] cardiac glycosides,[254] and FOXO4 peptide,[255] also function by inducing senescent cell apoptosis to ameliorate tissue damage, yet their association with epigenetic regulation remains largely unknown.

Gene-therapy-based interventions

Gene therapy interventions hold promise in counteracting human stem cell aging and age-related degenerations. For instance, rejuvenating factors, such as DGCR8, CLOCK, CBX4, and SOX5, counteract human stem cell aging by stabilizing heterochromatin and, when delivered via lentiviral injection, have been reported to promote cartilage regeneration and attenuate osteoarthritis in mice.[124,256–258] Similarly, administration of lentiviral vectors encoding YAP or FOXD1 also alleviate mouse osteoarthritis.[259] Overexpression of SIRT2 is capable of alleviating cardiac aging in mice.[260] In addition, adeno-associated virus (AAV)-mediated delivery of vascular endothelial growth factor (VEGF) triggers amelioration of aging-associated pathologies, such as osteoporosis and inflammaging, rejuvenation of metabolism, and extension of lifespan in mice.[261] Conversely, genetic inhibition of aging acceleration factors, such as ERV and KAT7, also result in beneficial effects on alleviating human stem cell aging and extends mouse health span or lifespan. For example, lentiviral CRISPR-mediated inhibition of ERV rejuvenated senescent human stem cells and induced structural and functional improvements in the joints of aged mice.[128] Similarly, inactivation of KAT7, a histone acetyltransferase, attenuated human stem cell aging by decreasing H3K14ac deposition and p15 expression and extended lifespan in both physiologically and prematurely aged mice.[262] In addition, knockout of APOE stabilized the nuclear lamina and heterochromatin, alleviating stem cell aging and presenting a potential target for novel gene therapies.[194] Furthermore, targeting progerin transcripts with antisense technology increased the lifespan of progeroid mice, highlighting another avenue for potential development of genetic therapeutic strategies.[263] However, most of these genetic intervention approaches have not yet been tested in clinical trials.

Interestingly, learning from long-lived animals also holds great promise for developing new genetic intervention strategies to combat aging. The naked mole-rat (NMR), for example, is known for its outstanding resistance to aging-related diseases, including cancer and exceptional longevity.[264–266] This may be attributed to its stable genome and epigenome because NMR cells are characterized by the unusual stabilization of p53 protein, high deposition of H3K27 methylation, and low deposition of H3K27 acetylation, alongside a more closed chromatin state at the promoter region.[266–268] Most recently, a study reported a mouse model overexpressing NMR hyaluronic acid synthase 2, which showed a higher level of hyaluronan. More intriguingly, these genetically modified mice displayed resistance to inflammation, oxidative stress, and cancer, as well as an extended health span and lifespan.[269] These findings suggest that the NMR longevity mechanism can be extended to other species, paving a potential way for gene-based strategies against aging-related disorders in humans.

Cell-transplantation-based interventions

Cell transplantation-based strategies have been developed in both laboratory and clinical studies to combat aging and age-related disorders. For example, transplantation of glial progenitor cells into aged mice achieves long-term integration as well as improved neurological function.[270] Moreover, administration of stem cells or vascular cells, expressing genetically enhanced NRF2 or FOXO3, conferred resistance to both aging and tumorigenesis and successfully promoted vascular or cardiac regeneration in mice.[37,271–273] In general, MSCs represent a powerful source for cell transplantation approaches and have been applied in clinical studies toward antagonizing age-related disorders.[274] For instance, transfusion of human umbilical cord-derived MSCs in patients with liver cirrhosis yielded safe and effective improvements in liver function.[275] Furthermore, the therapeutic safety and efficacy of MSCs in treatment of osteoarthritis lend clinical validation toward broad applicability of stem cell transplantation strategies in mitigating aging-related disorders.[276] Interestingly, stem cell-derived extracellular vesicles also show rejuvenation effects both *in vitro* and *in vivo*. For instance, exosomes derived from antler stem cells alleviate human MSC aging and mouse osteoarthritis.[277] Similarly, extracellular vesicles from umbilical-cord-derived MSCs also rejuvenate senescent MSCs and mitigate bone and kidney degeneration in aged mice.[278] In addition, MSC-derived extracellular vesicles have also been reported to reverse epigenetic aging and improve health span in mice, potentially mediated through miRNA-dependent regulation.[279,280]

Other intervention strategies

Many other geroprotective strategies, including heterochronic parabiosis, reprogramming, fecal microbiota transplantation, and immunotherapy, offer promising effects on combating aging-related conditions (Figure 4). Heterochronic parabiosis, where young and aged mice are surgically joined together to share a common circulatory system, rejuvenates tissue and organ functions in the aged organism through exposure to factors present in young blood.[281–284] Such rejuvenation may be achieved in part by DNA methylation remodeling.[285] Reprogramming refers to a rejuvenation strategy via the global remodeling to revert somatic cells to a pluripotent state by overexpression of Yamanaka transcription factors (OCT4, SOX2, KLF4, and MYC, also known as OSKM) or induction with chemicals.[286–289] This approach restores a youthful epigenetic status via resetting H3K9me3, H4K20me3, and DNA methylation levels.[286,290–292] Another promising strategy for restoring healthy aging is fecal microbiota transplantation, which can reshape the host gut microbiota and alleviate aging in multiple tissues.[293–295] In this process, microbiota-derived metabolites may act as epigenetic players to remodel the host's DNA and histone modifications.[296,297] Additionally, and similar to senolytics, aging-delaying immunotherapies aim to eliminate senescent cells by stimulating the organism's immune system rather than inducing apoptosis. In principle, by identifying antigens specifically enriched in senescent cells (also known as seno-antigens), such as the glycoprotein nonmetastatic melanoma protein B (GPNMB) and urokinase-type plasminogen activator receptor (uPAR), vaccines or chimeric antigen receptor (CAR) T cells recognizing these seno-antigens achieve targeted removal of senescent cells, ultimately enabling the treatment of aging-related disorders, such as atherosclerosis, liver fibrosis and cancers, as well as the extension of health span or lifespan in mice.[298,299] However, the possible epigenetic involvement in these immunotherapy-based interventions remains unexplored.

CONCLUSION AND PERSPECTIVES

In conclusion, we here provide an extensive exploration of current advances in understanding the intricate relationship between stress, aging, and the involved epigenetics. We discuss a wide range of epigenetic modifications at different layers and the various, although not all, stresses associated with aging. Of note, these stresses are interdependent and have crosstalk with each other to form a complex network of aging mechanisms. Furthermore, we also review intervention strategies aimed at mitigating aging by alleviating stress and stabilizing epigenetic processes. These strategies hold great promise for guiding the development of innovative therapeutic approaches to combat age-related disorders.

However, it is imperative to acknowledge that most of the current evidence on the relationship between epigenetic inheritance and stress-related aging provides correlation, not causation, highlighting the need for deeper mechanistic insights to develop safe and effective aging interventions. On the other hand, although some aging interventions have progressed to clinical trials, many more remain at the laboratory stage, reflecting a significant gap between basic research and practical application.[12] However, findings from model organisms and cellular models may not directly apply to humans in clinical settings, necessitating species, tissue, and cell-type-specific investigations and cautious interpretation of results. Fortunately, such validation approaches become increasingly feasible due to advancements in high-resolution, spatial, single-cell and multi-omics sequencing technologies,[300] which will help deepen our understanding of the systemic, heterogeneous, and programmed nature of aging, especially from the perspective of stress and epigenetic interactions. Besides, to avoid disparities that may emerge in different research models and settings, establishing uniform standards or guidelines for

model design, mechanism validation, and evaluation approaches of intervention effectiveness and safety would be advantageous. Specifically, for example, preclinical investigations using large animal models, particularly non-human primates,[301,302] can prove valuable in validating molecular targets and assessing the safety and efficacy of aging interventions, facilitating their translation to clinical trials. Moreover, the identification and utilization of increasingly sensitive and specific aging biomarkers will be instrumental in precisely evaluating the detrimental effects of stresses and the efficacy of interventions.[242,303] As an example, large-scale studies involving robust cohorts might be of great significance.[304] Additionally, the development of user-friendly and efficient technical equipment, such as artificial-intelligence-assisted wearable devices, holds significant promise for advancing data collection and analysis in this field.[305] These technological advancements may also facilitate real-time monitoring of molecular changes, enabling timely interventions and personalized treatment approaches. Taken together, continued research that focuses on addressing the existing limitations and challenges in this field carries immense potential for enhancing our understanding of the epigenetic crosstalk between stress and aging. Combined, such efforts will drive the development of novel intervention strategies for effective clinical translation, ultimately leading to the successful mitigation of age-associated diseases.

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AUTHOR CONTRIBUTIONS

G.-H.L., W.Z., and J.Q. designed the review. Z.W. drafted the manuscript. All authors performed manuscript reviewing and editing and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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