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Review Article

DNA Damage, Transposable Element Expression and Their Associated Factors in Aging

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Abstract

Aging is a spontaneous and permanent physiological process that leads to declines in tissue and cell functions, along with an increased risk of developing various age-related diseases. The primary driving force associated with aging is the accumulation of damaged genetic material in the cell, such as DNA. DNA damage can be caused by endogenous and exogenous factors, which leads to genome instability, mitochondrial dysfunction, epigenetic modifications, and proteostatic disturb. Another driving force associated with aging is the disruption of cellular metabolism. This disruption is closely linked to alterations in the role of metabolic pathways, including insulin/IGF-1 and mTOR, which regulate crucial cellular processes like cell growth, cell proliferation, and apoptosis. The activation of the insulin/IGF-1 signaling pathway highly promotes cell growth and proliferation, while also inhibits autophagy and increasing ROS production. This ultimately leads to accelerated aging. Another crucial signaling pathway is the mTOR signaling pathway. It is responsible for detecting nutrient availability and controlling cell growth and metabolism. The dysregulation of mTOR function can lead to the development of neurodegenerative diseases, which are characterized by the aggregation of protein. Activation of transposable elements is the other driving force of aging, caused by changes in DNA methylation and the loss of heterochromatin. As a result, this leads to DNA damage, genomic instability, and inflammation. The aim of this review is to elucidate the consequence of DNA damage and other associated factors drive aging.

Keywords

Aging, Genome Instability, Molecular Damage, Transposon Element

1. Introduction

Aging is a complex and multifaceted process that results in widespread functional decline, impacting every organ, tissue, and cell in the body. This also causes deterioration in their structure, function, adaptability, and resistance [1]. Molecular damage is the primary factor that affects aging and alterations an essential biomolecules in cell. Additionally, molecular damage initiates cellular senescence, which further accelerates the accumulation of intracellular damage [2]. The cells, tissues, and organs face various barriers due to the accumulation of molecular damage. The accumulation of molecular

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damage leads to genome instability [3], telomere dysfunction [4], loss of proteostasis [5], mitochondrial dysfunction [6], stem cell exhaustion [7], and epigenetic alterations [8], these factors are the main drivers of the aging. DNA damage and the accumulation of damaged DNA disturbs the stability of cells and lead to genome instability [9]. Telomere is repetitive sequences located at the ends of chromosomes and it became critically short during cell division, reaching to the Hayflick limit, finally leads to DNA damage and cellular senescence [10]. When the telomeres become too short after numerous divisions, cell division becomes stops. The cell then activates genetic programs, including replicative senescence resulting from telomere shortening. The buildup of senescent cells can speed up aging in both tissues and in the entire organism [11]. The telomere dysfunction also triggers a DNA break reply, which leads to the expression of proinflammatory factors, ultimately resulting in aging of the organism [12]. Mitochondrial dysfunction is an imbalance mitochondria of network, leading to impaired function and disruption of the metabolic state, which also accelerates aging [13]. During mitochondrial dysfunction, there is usually a decrease in MMP, which is often accompanied by an increase ROS production [14]. The increase in ROS levels within cells leads to chronic oxidative stress, which in turn disrupts crucial pathways and has an impact on the aging process [15]. ROS, or reactive oxygen species, play a significant role in causing cellular damage due to their high reactivity [16]. According to the Seung-Jae study, small amounts of ROS can promote longevity in C. elegans, whereas high doses have the opposite effect and reduce their lifespan [17]. Antioxidant enzymes play a crucial role in neutralizing reactive oxygen species (ROS) and protecting against oxidative stress. When the activity of mitochondrial antioxidant enzymes is impaired, it can lead to an increase in oxidative stress. This was observed by Schriner, in mice lacking dependent superoxide dismutase (SOD) or catalase, which resulted in premature death due to severe mitochondrial dysfunction and neuro-degeneration. On the other hand, mice with a transgene of SOD or catalase showed increased longevity [18]. The accumulation of cellular senescence is also another driving force of aging [19], primarily caused by dysfunction of cellular activity and molecular damage from both internal and external factors [20]. The cellular senescence affects tissue regeneration by causing an excessive accumulation of senescent cells. Additionally, these cells secrete a large number of inflammatory factors and exhibit the senescence-associated secretory phenotype (SASP), which has detrimental effects on the surrounding environment [21].

Transposable elements are found in the genomes of hosts and can impact different aspects of the aging process and various age-related diseases, such as cancer [22-24] and Alzheimer's disease [25, 26]. The activation of these internal transposable elements affects the stability of the genome, resulting in insertional mutagenesis, DNA damage, and rearrangement of the genome [27]. This review primarily focuses on exploring the causes and effects of molecular damage and cellular dysfunction associated with the process of aging. Specifically, it explores DNA damage, telomere shortening, mitochondrial dysfunction, autophagy dysfunction and cellular senescence. Additionally, it explores the pathways that are affecting the aging process directly. These pathways include the insulin/IGF-1 signaling pathway, the mTOR pathway, Sirtuin 1 (SIRT1), and the AMPK pathway.

Methodology

This review was carried out by a comprehensive electronic literature search using Google Scholar, PubMed, Science Direct and Google search. The following key words and their combination: “aging and DNA damage, hallmark of aging, molecular mechanism of aging”. All works meeting the subject matter were considered, including; original articles, meta-analyses and reviews.

2. Molecular Damages and Associated Factors Driving Aging

This review cannot cover all forms and manifestations of molecular damage, but I note the importance of DNA damage and its molecular consequences, such as genome instability, telomere dysfunction, mitochondrial dysfunction, epigenetic alterations, autophagy dysfunction, and cellular senescence.

2.1. DNA Damage and Genome Instability

DNA is highly susceptible to damage from both external and internal factors, which can alter its chemical structure within cells and influence the aging process [28]. DNA damage occurs thousands of times each day in every cell, with oxidative damage being a significant cause [29]. Mitochondrial respiration is a primary source of endogenous oxidative DNA damage [30]. It’s the driving force behind aging in humans and mammals, through its direct effects of the lesions on DNA replication or transcription, cell elimination or cessation of cell replication, and DNA mutations [31]. The decline in repair capacity of damaged DNA leads to the accumulation of DNA damage. This accumulation, in turn, contributes to cellular senescence and mutations in both nuclear and mitochondrial genes [32]. According to findings, DNA damage accumulation is a pillar of aging [33] and has a range of molecular consequences such as genome instability, telomere dysfunction, mitochondrial dysfunction, epigenetic alterations, and proteostatic stress [34]. DNA damage is driving of aging, via activating signaling responses [35], blocking transcription [36], and mutagenesis [37]. The DNA strand can broke-down by endogenous (from internal biological processes) and exogenous (from the environment). This, in turn, triggers the activation of the DNA damage response (DDR) pathway [19]. The DNA damage response (DDR) involves distinct and universally conserved repair and signaling pathways. These pathways are responsible for detecting specific changes in the DNA, halting the cell cycle,

and repairing the damage. When the damage is effectively repaired, the signaling in the DDR is stopped and the cells return to their original, pre-damaged state [38]. To do that DDR starts with the MRN complex (MRE11-RAD50-NBS1) activating the PIKKs, including ataxia-telangiectasia mutated, ATM-related kinase (ATR), and other related PIKKs [39]. The continuous signaling of DNA damage, which involves the activation of p53 and other response pathways, has both positive and negative consequences. It impacts various aspects of cellular function and plays a crucial role in determining cell fate [40]. When lesions cannot be repaired, the DDR signaling continues, which then leads to either cell senescence or cell death [38]. However, dysfunction of p53 enables cells to proliferate under unfavourable conditions, thus promoting the growth of cancer cells [41], disrupt tissue development, in mice exhibit growth retardation or minor developmental abnormalities [42, 43]. Defects in DNA repair pathways are associated with specific genome instability syndromes, which are characterized by developmental defects, an increased risk of cancer, and signs of accelerated aging [44, 45]. Hutchinson-Gilford progeria syndrome and Werner syndrome are rare genetic disorders in humans that cause premature aging and a shortened lifespan. HGPS and Werner syndrome are caused by mutations in genes that control DNA repair and the *A-type lamin*, which results in disorganized chromatin structures [46]. Thus are associated with genome instability and significantly accelerate aging [47]. Understanding the molecular pathology of these premature aging diseases also provides insights into the complex aging process. However, individuals with HGPS do not exhibit all the typical signs of aging, as the syndrome primarily affects multiple tissues. Nonetheless, these models allow us to replicate some of the molecular and cellular changes associated with natural aging, giving us a unique opportunity to study the aging process in a human context [46, 48]. Nestor-Guillermo progeroid syndrome is also another progeroid syndrome, caused by mutations in the *BANF1* gene, which accelerating aging due to impaired chromatin organization [49]. Mutations in the ATM gene, which produces a serine/threonine kinase that becomes active when DNA is damaged, are responsible for causing ataxia telangiectasia (AT), which also exhibits premature aging of the hair and skin [39, 50]. This is indicative of accelerated aging [51]. The helicase encoded by the *WRN* gene is responsible for managing replication stress and maintaining telomere stability, and mutations of this gene also lead Werner syndrome (WS) [52]. Individuals with WS exhibit symptoms such as growth retardation, premature hair graying, lipodystrophy, and early onset of various age-related diseases [53]. Furthermore, Bloom syndrome (BS) is also caused by mutations in the *BLM* gene, which encodes a RecQ helicase that plays a crucial role in suppressing recombination and maintaining genome stability [54]. Individuals with BS have an average lifespan of 26 years and frequently face the early onset of various age-related diseases, including cancer, diabetes, and chronic obstructive pulmonary disease [55].

2.2. Telomer Shorting

Telomeres are repeating noncoding DNA sequences located at the ends of eukaryotic chromosomes. They are primarily composed of telomeric DNA and associated telomere-binding proteins [56]. In mammals, it's made up of thousands of TTAGGG repeats. These repeats are covered by sheltering complex, which helps create a T-loop structure that hides the end of the telomere. This hiding mechanism prevents the activation of DDR sensors [57]. Telomeric DNA becomes shorter as cells divide more, and when it reaches the Hayflick limit, dysfunction of the telomeres triggers the response DNA damage. As a result, cells stop dividing and start expressing proinflammatory factors, leading to aging in the organism [12]. Telomere length is controlled by telomerase. When telomerase activity increases and chromosomes remain intact, the lifespan of an organism is extended [12]. However, telomerase becomes inactive, the length of telomeric ends is blocked in somatic human cells, and telomeres become shorter with each successful cell division, leading to restricted cell proliferation. This process is known as replicative senescence [58]. During replicative senescence, irreparable DNA damage is accumulated, leading to permanent cell-cycle arrest and is considered one of the main factors driving aging [59]. Herrmann's and Jiang‐Yi findings confirmed that mice without telomerase have shorter telomeres and experience premature aging. Conversely, mice that are resistant to cancer and have high levels of telomerase expression have longer telomeres and age at a slower rate [10, 60]. The telomere without protection appears similar to a DNA double-strand break (DSB), causing the continuous activation of DDR, which ultimately results in replicative senescence [61]. One mechanism currently being studied as a significant contributor to telomeres length attrition is cellular oxidative stress [62]. This occurs when the concentration of pro-oxidant molecules in the body is higher compared to that of antioxidant substances [63]. Telomere is highly susceptible to oxidative damage due to the presence of numerous guanine triplet sequences. These sequences are more prone to oxidation when compared to other bases [64]. Increased levels of glucocorticoid hormones (GC) can also cause telomeres to attrition in vertebrates, including humans [65, 66]. This occurs because GC hormones increase cellular oxidative stress by reducing natural antioxidant defences [66, 67] and suppressing telomerase expression [68]. Another important signaling pathway that causes telomere attrition is NAD^+-SIRT1-PGC-1α axis. In this axis, short telomeres are recognized as double-strand breaks by NAD^+ dependent peroxisome proliferator-activated receptors (PARP1), which can initiate DNA repair signals, a process that requires the consumption of NAD^+. Hyper-activation of peroxisome proliferator-activated receptors 1 (PARP1) leads to NAD^+ consumption, hence limiting NAD^+-dependent deacetylase sirtuin-1 (SIRT1) activity [69, 70]. SIRT1 has been revealed to increase mitochondrial function and biogenesis through the transcription factor PGC-1α. Loss of SIRT1 activity therefore leads to mitochondrial dys-

function [69] lead to increase ROS production. ROS is also other main cause of telomere attrition [71]. ROS can generate approximately 100 different types of oxidatively damaged bases [72]. The length of telomeres is also attributed by Ku-proteins, which are regulated by TOR through two pathways. First, when Ku-proteins are present, they directly interact with telomeric repeats to increase telomerase expression. This, in turn, promotes telomere length (TL) maintenance [73]. Conversely, inhibiting TOR leads to a decrease in Ku-protein expression, resulting in reduced telomerase expression and TL attrition. Second, Ku-proteins can also bind to telomeric RNA repeats called TERRA (Telomeric Repeats containing RNA with repetitive UUAGGG sequences [74]). When Ku-proteins bind to TERRA, they can induce TL shortening by promoting the expression of the enzyme Exonuclease I. This enzyme cleaves nucleotides from telomeric DNA [73].

2.3. Epigenetic Alterations

Epigenetic mechanisms encompass various processes, including DNA methylation, histone modifications, chromatin remodeling, and transcriptional changes regulated by noncoding RNAs (ncRNAs) [75]. The first epigenetic alteration is DNA methylation, which occurs directly at the DNA level. It regulates gene expression by interacting with the proteins involved in gene silencing or inhibiting the interaction between DNA and transcription factors [76]. DNA methylation has various functions, including the alternative splicing, and the regulation of gene expression [77]. The DNA methyltransferases (DNMTs) are enzymes that play a role in DNA methylation, to transfer a methyl group at the fifth position of cytosine (5 mC) from S-adenosyl-methionine (SAM) to the carbon-5 position of the cytosine residues in the CpG region [78, 79]. 5 hmC is a DNA base modification that arises from 5-methylcytosine, catalyzed by the ten-eleven translocation protein family [80]. A recent study revealed that both the deamination of 5 mC and oxidative damage play significant roles in somatic mutagenesis [81]. These mutations also lead to the development of cancer [82], leads to premature aging, specifically Werner's syndrome and Hutchinson-Gilford Progeria syndrome [83] and those are highly contribute to ageing [84]. Histone modifications are a type of epigenetic alteration, including acetylation, methylation, phosphorylation, ubiquitination, and glycosylation. Among these modifications, acetylation and methylation are the most notable changes linked to senescence [85]. Histone methyltransferases and demethylases modify histone methylation levels, which in turn affect transcriptional activation or repression. Generally, methylation of lysine 4 on histone 3 (H3K4), along with H3K36 and H3K79, promotes transcriptional activation. In contrast, methylation at H3K27 and H4K20 is associated with transcriptional repression [86]. Histone acetyltransferases (HATs) and histone deacetylases (HDACs) are enzymes that catalyse histone acetylation or deacetylation reactions. HATs are typically involved in activating transcription, while HDACs exert repressive [87]. These enzymes are crucial for longevity, as demonstrated by studies on yeast [88]. In particular, when the histone acetyltransferase gene GCN5 is deleted, it leads to a decrease in the replicative lifespan of yeast [87]. H3K36me3 and H3K9me3 are important factors in the aging process. In both S. cerevisiae and C. elegans, a lack of H3K36me3 is associated with a reduced lifespan. In contrast, the lifespan of S. cerevisiae increases when the demethylase responsible for H3K36me3 is absent [89]. Likewise, the loss of H3K9me3 in the adult Drosophila midgut results in the aging of intestinal stem cells [90]. In the aged somatic tissues of C. elegans, global levels of H3K9me3 increase in the heterochromatic regions located at the distal arms of chromosomes, while they decrease in the euchromatic central regions of the autosomes [91]. According to Jason's findings, in Drosophila, the signals for H3K9me3 and Heterochromatin protein 1 (HP1) on chromosomes are significantly higher in young flies but not in aged flies. Additionally, overexpression of HP1 reduces premature aging and extends lifespan [92]. Additionally, mesenchymal stem cells (MSCs) with pathogenic mutations linked to Hutchinson-Gilford Progeria Syndrome (HGPS) or Werner Syndrome (WS) show reduced levels of H3K9me3 and HP1, both of which contribute to accelerated aging [93-95]. The third epigenetic alteration is chromatin remodelling, which modifies chromatin structure and the position of nucleosomes using ATP-dependent enzyme similar to helicase. This allows regulatory proteins to interact with DNA. Liu et al. discovered that the core structural domain of the Switch/Sucrose Non-Fermentable (SWI2/SNF2) complex connects via two induced brace helices. This connection anchors chromatin remodelers to specific nucleosome positions, initiating the substrate for remodeling reactions [96]. During senescence-induced mitochondrial stress, a malfunction in the tricarboxylic acid cycle results in reduced production of acetyl coenzyme (acetyl-CoA). This reduction leads to the accumulation of histone deacetylase and the homeobox protein dve-1 in the nucleus. As a result, histone acetylation decreases, disrupting chromatin organization in C. elegans. In contrast, supplying nutrients that enhance acetyl-CoA production can effectively extend the lifespan of C. elegans under mitochondrial stress [97].

2.4. Mitochondrial Dysfunction

The main factor behind mitochondrial dysfunction is often attributed to damage induced by reactive oxygen species (ROS) to the mitochondrial genome [98]. During mitochondrial dysfunction, the mitochondrial membrane potential (MMP) decreases and is associated with increased production of reactive oxygen species (ROS) [14] and indicate ETC dysfunction [99]. About 90% of ROS is produced in mitochondria from a leakage of electrons in the electron transport chain (Gruber et al., 2013). Increased production of reactive oxygen species (ROS) can cause oxidative damage to mito-

chondrial DNA, proteins, and lipids. This damage, in turn, reduces mitochondrial dynamics and hinders mitophagy, ultimately leading to mitochondrial dysfunction [100]. Mitochondrial dysfunction has been also associated to aging and various age-related diseases, such as cancer, neurodegenerative, kidney diseases [14, 101]. During mitochondrial dysfunction, MMP is reduced [102] and increased production of reactive oxygen species (ROS) are also stress-induced senescence [103], replicative senescence, oncogene-induced senescence [104], and senescence triggered by genetic telomere uncapping [103]. The defective of proofreading activity of mtDNA polymerase contributes to mtDNA mutations, which in turn cause significant mitochondrial dysfunction and premature aging [105]. High levels of reactive oxygen species (ROS) and mutations or deletions in mitochondrial DNA (mtDNA) can result in a defective proofreading activity of mtDNA polymerase. This, in turn, leads to damage in the replication system and/or repair mechanisms of mtDNA [106]. According to Vermulst et al., findings, the deletions of mtDNA are drivers of premature aging in mice [107] and also induce cellular senescence [108]. Moreover, mitochondrial dysfunction also associated with chronic inflammation in different diseases, such as myocardial infarction (MI), sickle cell disease, and neurodegenerative disorders [109, 110] and it also caused dysregulated nutrient sensing pathways, such as insulin/IGF-1, mTOR, AMPK, and sirtuins [111].

2.5. Autophagy Alterations

Autophagy is a highly conserved process that breaks down cellular components, such as damaged organelles and misfolded protein aggregates [112], within lysosomes. Under normal conditions, autophagy is regulated by reactive oxygen species (ROS). However, when ROS levels become excessive, they can damage organelles and cause protein modification and aggregation. On the other hand, autophagy plays a crucial role in mitigating oxidative damage [113]. During starvation, ROS-induced activation of AMPK induced autophagy. In cells deficient in ETC, O_2^- production is halted under starvation conditions, which decreases AMPK activation and increases activation of the mTOR pathway. Consequently, starvation-induced autophagy is reduced [114]. Downstream of AMPK, peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC-1α) is essential for modulating antioxidant genes in response to oxidative stress. The AMPK-PGC-1α signaling pathway controls mitochondrial ROS levels. Cells with decreased AMPK activity experience elevated mitochondrial ROS and undergo premature aging [115]. Dysfunction of autophagy via various factors significantly speeds up the aging process in different species [116]. However, increase the autophagy activity can slow down aging [117]. According to Aman et al., study the increased expression of autophagy genes ATG-1, ATG-7, and ATG-18 in C. elegans leads to an extended lifespan [116]. Autophagy also has a crucial role in clearing damaged mitochondria, which means that when autophagy is compromised, it leads to mitochondrial dysfunction, abnormal mitochondrial accumulation, and oxidative stress [113, 118]. The decline in repair capacity of DNA due to various factor leads to the accumulation of DNA damage. This accumulation, in turn, contributes to cellular senescence and mutations in both nuclear and mitochondrial genes, which have been associated with aging [32]. One of the main causes of impaired DNA repair mechanism is that the defect in autophagy [119]. According to the findings of Yanan and his colleagues, the accumulation of p62 has been observed in rats when autophagy is dysfunction, which in turn disturbs DNA damage responses (DDR) [120]. However, inhibiting p62 accumulation also reduces defective autophagy-induced genome damage [121]. Usually p62 is involved in regulating the balance between NHEJ and HR [122]. In the absence of autophagy (specifically in Atg3 knockout), the recruitment of DNA repair proteins, including BRCA1, RAP80, and Rad51, to double-strand breaks is impaired in a manner dependent on p62 [120]. Autophagy-deficient cells exhibit impaired activation of checkpoint kinase-1 (Chk1), a key player in DNA repair via homologous recombination (HR). When Chk1 fails to respond to DNA damage, the recruitment of Rad51 to the damaged sites is diminished [123]. In Atg5-deficient embryonic fibroblast cells, the lack of autophagy results in an inability to detect damaged DNA by the XP group C (XPC) and DNA damage-binding protein 2 (DDB2) [124]. Impaired autophagy leads to DNA damage, increased mutation rates, and chromosomal instability in various cell types, including mouse embryonic fibroblasts (MEFs) [125].

3. Cellular Senescence

Cellular senescence is a state of irreversible cell cycle arrest [126]. Aging results in both biological and functional changes, affecting not only organism but also cellular level [118]. The senescent cells constantly secrete SASP factors, including proinflammatory cytokines, chemokines, growth factors, and proteases, which alter the local tissue environment and contribute to aging and aging-related disorders [127]. Immune cells can aggravate the progression of aging-related diseases by triggering the production of more proinflammatory cytokines [128]. Additionally, T-cell senescence is a crucial component of immune aging. Premature T-cells contribute to aging in various organs and systems, with key indicators of T-cell senescence including thymic degeneration, mitochondrial dysfunction, genetic and epigenetic changes, and imbalances in protein homeostasis [129]. Desdín-Micó G et al. discovered that mice lacking mitochondrial transcription factor A (TFAM) displayed several aging-related symptoms. These symptoms were linked to T cell senescence and mitochondrial dysfunction, which ultimately accelerated the aging process and led to premature death in the mice [130]. In other cause, DNA repair systems fail, cellular damage occurs, contributing to the cellular and organism aging. Several factors,

such as oxidative stress, DNA damage, telomere shortening, and the senescence-associated secretory phenotype (SASP) of inflammation, may play key roles in trigger aging [131, 132]. Oxidative stress is primarily caused by reactive oxygen species (ROS) such as superoxide, hydrogen peroxide, and hydroxyl radicals. This stress can lead to DNA, lipid, and protein damage, ultimately resulting in cellular aging [133]. The primary antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), peroxidase (GPX), and glutathione (GSH), help to reduce excessive reactive oxygen species (ROS). However, their effectiveness decreases with cellular aging, resulting in an increase in ROS levels [134]. The senescent state is regulated by the p53/p21 and p16/pRB pathways [135-137]. When there is DNA damage, the p53 pathway is activated, leading to the expression of p21, which is an inhibitor of cyclin-dependent kinase (CDK), as a result the retinoblastoma protein (pRB) becomes activated [137, 138]. Hence, pRB also plays a crucial role in senescence by binding and deactivating the E2F family of transcription factors, which are responsible for inducing cell cycle proteins and DNA replication factors. This establishes a reciprocal regulation between the p53/p21 and p16/pRB signalling pathways. However, these pathways can independently induce senescence [138]. Cellular senescence mainly triggered by DNA damaging [139]. If DNA damage is irreparable and persists, it triggers prolonged DNA damage response (DDR) signaling and leads to long-term proliferation arrest, ultimately resulting in cellular senescence [140]. Based on various findings, another primary causes of cellular senescence are telomere shortening [141], mitochondrial dysfunction [142, 143] and the dysfunction of autophagy pathways [144]. The p53 function loss promotes chromosomal instability and causes cellular senescence or apoptosis [145]. Cellular senescence is crucial for preventing tumor formation, aiding tissue repair and wound healing, enhancing insulin secretion, and supporting mammalian development [146-148]. However, the accumulation of senescent in the cells over time, likely due to decreased immune-clearance in almost all vertebrates [149] and has been proven to actively contribute to the process of aging [150]. Senescent cells also play a role in age-related diseases like atherosclerosis [150], osteoporosis [151], non-alcoholic fatty liver disease [152], cancer [153], neurodegenerative diseases [154, 155], and other conditions associated with aging [156].

4. Conserved Genetic Pathways

The aging process, along with the frequency and severity of age-related diseases, is influenced by several conserved genetic pathways. Key pathways involved in this process include the insulin/IGF-1 signaling pathway, the mTOR pathway, and the AMPK pathway [19]. When cellular nutrients are abundant, the insulin/IGF-1 and mTOR pathways are activated, leading to the promotion of anabolic processes and the inhibition of autophagy [157]. In mammals, insulin/IGF-1 signaling plays a crucial role in aligning nutrient availability with energy balance and metabolic processes. This signaling pathway is activated by insulin-like peptide ligands in response to nutrient levels. One way insulin/IGF-1 signaling conveys its signals is through the PI3K/Akt pathway, which phosphorylates several targets, including the tuberous sclerosis complex (TSC1/2) [158]. The insulin/IGF-1 signaling (IIS) pathway is a crucial mechanism that controls ageing in eukaryotes. Extensive evidence supports the idea that reducing IIS promotes longevity and enhances overall health in various species, such as nematodes, flies, and mice [159]. Insulin/IGF-1 also controls protein synthesis, energy metabolism, and the proliferation and differentiation of insulin/IGF-1 sensitive cells. According to Bartke finding, the defects of insulin/IGF-1 signaling pathway extend longevity's, however over activating of pathway accelerates the aging [160]. Ock's study found that removing IGF-1R from mouse cardiomyocytes reduced age-related myocardial inflammation, hypertrophy, and interstitial fibrosis in the heart. This indicates that insulin/IGF-1 signaling has opposing effects that significantly influence the overall health and lifespan of mammals [161]. mTOR is a serine/threonine kinase belonging to the phosphoinositide kinase-related family. It comprises two complexes: mTORC1 and mTORC2. The activation of mTORC1 is stimulated by signaling pathways that involve the phosphoinositide-3-kinase-related kinase family and AKT kinase, along with nutrients such as amino acids and phosphates [162]. Activated TORC1 promotes anabolic processes, such as protein, lipid, and nucleotide synthesis, while inhibiting catabolic processes like autophagy [163]. The frequent alteration of mTOR plays an important role during tumorigenesis, metastasis, and drug resistance in human malignancies [164, 165]. In senescence, mTOR is persistently activated [166], possibly due to increased levels of reactive oxygen species (ROS) produced by dysfunctional mitochondria [167]. Dysregulation of mTOR function can contribute to the development of neurodegenerative diseases, which are marked by protein aggregation [168]. The AMPK pathway, which is the third important pathway discussed in this review, its activated when cellular energy levels decrease and when there are high ratios of AMP/ATP and ADP/ATP [169]. AMPK is responsible for regulating homeostasis, metabolism, stress resistance, cell survival and growth, cell death, and autophagy. These factors play a crucial role in determining the aging process and lifespan [170]. The activation of AMPK encourages the formation of new mitochondria and regulates their dynamics and mitophagy [171]. According to recent findings, the activation of AMPK increases the lifespan of D. melanogaster by 30%, extending it from six weeks to eight weeks [172]. Conversely, caloric restriction-induced activation of AMPK protects rats from senescence by enhancing autophagic activity and reducing oxidative damage [173]. AMPK also plays a crucial role in autophagy [170], which is a cellular degradation pathway that breaks down and reuses components to maintain cellular balance [174]. Dysfunction of autophagy is

strongly associated with ageing and organ dysfunction [175]. The dysregulation of AMPK is associated with accelerated aging due to promoting inflammation, cancer, and metabolic pathologies such as diabetes and obesity [176]. Another important pathway is Sirtuins play a crucial role in regulating a wide range of cellular processes, including metabolism, mitochondrial homeostasis, autophagy, DNA repair, apoptosis, oxidative/antioxidative balance, and senescence. The main mechanisms by which Sirtuin suppresses cellular senescence involve delaying age-related telomere attrition, maintaining genome integrity, and promoting DNA damage repair. SIRT1 also enhances the ability to induce cell cycle arrest and oxidative stress resistance, while inhibiting cell death [177] and apoptotic pathways [178]. Similarly, SIRT1 is implicated in a range of age-related processes and disorders, including neurodegenerative diseases and cardiovascular diseases [179]. Subsequent studies have shown that sirtuins can regulate longevity in various lower organisms, particularly yeast Sir2 and its homologues, which extend lifespan in budding yeast S. cerevisiae, worms, C. elegans, fruit flies, D. melanogaster, and mice [180, 181]. The pro-longevity effect of Sir2 also confirmed in higher organisms, although the mechanisms of its pro-longevity effects differ from those in yeast. These mechanisms include changes in mitochondrial function and biogenesis, suppression of inflammation, and regulation of genomic stability [182]. The dysregulation of insulin/IGF-1, mTOR, AMPK, and other conserved signaling pathways is closely associated with human aging and age-related diseases, often due to insufficient nutrient supply [157, 183].

5. Transposable Elements

TEs are DNA sequences that can move within genomes without the help of host cell DNA. TEs constitute about 50% of the human genome [184] and 85% of plants genome [185]. Reducing DNA methylation and loss of heterochromatin are highly contributed to the rapid increase of TE expression and transposition [186]. The activation of endogenous transposable elements greatly causes to genome instability [27], telomere dysfunction, mitochondrial dysfunction, epigenetic alterations, and proteostatic stress [34]. Several studies have indicated that overexpression of TE is associated with an increase in immune response and inflammation [187, 188] because transposable elements have the ability to be translated into proteins and peptides. When these peptides are present in the cell membrane, they are recognized as foreign elements, triggering an innate immune response. As a result, the induction of innate immunity leads to an increased expression of pro-inflammatory factors such as IFN and cytokines, which in turn further promotes TE expression. This positive feedback loop of TE overexpression consequently leads to an enhanced expression of inflammatory factors [189, 190]. Additionally, the expression and translation of transposable elements can also result in the formation of toxic products. These products, for instance, can contribute to the development of autoimmune diseases. Furthermore, the activity and replication of TEs within an increased genomic TE content may indirectly impose metabolic costs on the host [191, 192]. Altered activity of specific transposable elements is also associated with multiple age-associated pathologies, including cancer [23] and Alzheimer's disease (AD) [26]. The activation of TEs and its connection to aging is supported by a study conducted in termites. This study reveals that reproducing queens and kings can live for decades without a substantial rise in TE expression levels. On the other hand, major workers, with a lifespan of only a few weeks, exhibit an up-regulation of TEs as they age [193]. Recent studies have shown that both calorie restriction (CR) and anti-aging drugs like rapamycin can decrease TE transcript levels, while aging and age-accelerating interventions can also increase TE expression [194]. In addition to using anti-aging agents, the lifespan of mutant flies or mice with overexpression of TEs can be extended through the use of nucleoside reverse transcriptase inhibitors (NRTIs), which suppress TE reverse transcriptase [195].

6. Conclusion

Understanding the molecular mechanisms and signaling pathways involved in aging is crucial for elucidating the intricate process of aging and identifying potential intervention targets. Molecular damage and cellular dysfunction such as oxidative stress, inflammation, DNA damage, telomere shortening, and cellular senescence affect the aging process both directly and indirectly. The insulin/insulin-like growth factor 1 (IGF-1) signaling pathway plays a key role in regulating metabolism, growth, and longevity in organisms. Reduced signaling through this pathway has been associated with increased lifespan across various species. Additionally, the sirtuin pathway, which regulates cellular metabolism, stress responses, and longevity, has also been implicated in the aging process. Activation of sirtuins has been shown to promote longevity and delay aging in multiple model organisms. Another significant pathway is the mTOR (mechanistic target of rapamycin) pathway, which integrates signals from nutrient availability, energy status, and stress to regulate cellular metabolism, growth, and senescence. Dysregulation of the mTOR pathway has been linked to age-related diseases, and interventions targeting mTOR signaling have demonstrated promise in extending lifespan and improving healthspan in various model organisms. Transposable elements (TEs) are mobile genetic elements that can move within the genome, potentially disrupting gene function or regulation. They have garnered attention for their role in aging, as their activity can lead to genomic instability—a hallmark of aging. Numerous studies suggest that TEs become more active with age, contributing to genomic instability and cellular dysfunction. Furthermore, TEs can induce inflammation and alter gene expression patterns, further exacerbating the aging process. In conclusion, aging is a complex process characterized by multiple molecular mechanisms and signaling pathways.

Abbreviations

BS	Bloom Syndrome
ncRNAs	Noncoding RNAs
5hmC	5-Hydroxymethylcytosine
ROS	Reactive Oxygen Species
MEFs	Mouse Embryonic Fibroblasts
TEs	Transposable Elements
SASP	Senescence-Associated Secretory Phenotype
AT	Ataxia Telangiectasia
DDR	DNA Damage Response
ATR	ATM-Related Kinase

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