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Review

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

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Abstract: Aging is a gradual and irreversible 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 function 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 and Transposon element

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1. Introduction

Aging is a complex, multifaceted process leading to widespread functional decline that affects every organ, tissue, and cell. This also causes deterioration in their structure, function, adaptability, and resistance (Ferrucci *et al.*, 2020). 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 (Ogrodnik *et al.*, 2019). The cells, tissues, and organs face various barriers due to the accumulation of molecular damage. The accumulation of molecular damage leads to genome instability (Singh *et al.*, 2019), telomere dysfunction (Zhenshu Li *et al.*, 2022), loss of proteostasis (Bharath *et al.*, 2020), mitochondrial dysfunction (Tracy *et al.*, 2022), stem cell exhaustion (Lei *et al.*, 2022), and epigenetic alterations (Van Der Laan *et al.*, 2022), 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 (Kubben *et al.*, 2017). 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 (Herrmann *et al.*, 2018). When the telomeres become too short after numerous divisions, cell division becomes stops. Then the cell activates genetic programs, such as replicative senescence due to telomere shortening, and the accumulation of senescent cells can accelerate tissue and organism aging (Ovadya *et al.*, 2014). The telomere dysfunction also triggers a DNA damage response, which leads to the expression of proinflammatory factors, ultimately resulting in aging of the organism (Yukun Zhu *et al.*, 2019). Mitochondrial dysfunction is an imbalance mitochondria of network, leading to impaired function and disruption of the metabolic state, which also accelerates aging (Hood *et al.*, 2019). During mitochondrial dysfunction, there is usually a decrease in MMP, which is often accompanied by an increase in reactive oxygen species (ROS) production (Sun *et al.*, 2016). 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 (Mossad *et al.*, 2022). ROS, or reactive oxygen species, play a significant role in causing cellular damage due to their high reactivity (Yang *et al.*, 2010). 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 (Seung-Jae Lee *et al.*, 2010). 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 (Schriner *et al.*, 2005). The accumulation of cellular senescence is also another driving force of aging (López-Otín *et al.*, 2013), primarily caused by dysfunction of cellular activity and molecular damage from both internal and external factors (Hernandez-Segura *et al.*, 2018). 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 (Baker *et al.*, 2016).

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 (De Luca *et al.*, 2016, Di Ruocco *et al.*, 2018, Rodić *et al.*, 2014) and Alzheimer's disease (Gao *et al.*, 2018, Wenyan Sun *et al.*, 2018). The activation of these internal transposable elements affects the stability of the genome, resulting in insertional mutagenesis, DNA damage, and rearrangement of the genome (Burns *et al.*, 2012). 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 a multitude of exogenous and endogenous factors that encompass any changes in the chemical structure of DNA within cells and influence the process of aging (Curtin, 2012). DNA damage occurs thousands of times each day in every cell, with oxidative damage being a significant cause (Swenberg *et al.*, 2011). Mitochondrial respiration is a primary source of endogenous oxidative DNA damage (Maynard *et al.*, 2009). 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 (Vijg, 2021). 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 (Sirbu *et al.*, 2013). According to findings, DNA damage accumulation is a pillar of aging (Kennedy *et al.*, 2014) and has a range of molecular consequences such as genome instability, telomere dysfunction, mitochondrial dysfunction, epigenetic alterations, and proteostatic stress (Schumacher *et al.*, 2021). DNA damage is driving of aging, via activating signaling responses (Fagagna *et al.*, 2003), blocking transcription (Vermeij *et al.*, 2016), and mutagenesis (Vijg, 2014). 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 (López-Otín et al., 2013). 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 (Fitsiou *et al.*, 2021). 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 (Thompson, 2012). 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 (Yousefzadeh *et al.*, 2021). When lesions cannot be repaired, the DDR signaling continues, which then leads to either cell senescence or cell death (Fitsiou et al., 2021). However, dysfunction of p53 enables cells to proliferate under unfavourable conditions, thus promoting the growth of cancer cells (Kaiser *et al.*, 2018), disrupt tissue development, in mice exhibit growth retardation or minor developmental abnormalities (Rinon *et al.*, 2011, Tateossian *et al.*, 2015). 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 (Menck *et al.*, 2014, Richard D Wood, 2018). Hutchinson-Gilford progeria syndrome (HGPS) 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 (Arancio *et al.*, 2014). Thus are associated with genome instability and significantly accelerate aging (Burla *et al.*, 2018). 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 (Arancio et al., 2014, Burtner *et al.*, 2010). Nestor-Guillermo progeroid syndrome is also another progeroid syndrome, caused by mutations in the *BANF1* gene, which accelerating aging due to impaired chromatin organization (Loi *et al.*, 2016). 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 (Thompson, 2012, Valentin-Vega *et al.*, 2012). This is indicative of accelerated aging (Rothblum-Oviatt *et al.*, 2016). 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) (Kudlow *et al.*, 2007). Individuals with WS exhibit symptoms such as growth retardation, premature hair graying, lipodystrophy, and early onset of various age-related diseases (Sugimoto, 2014). 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 (Nguyen *et al.*, 2014). Individuals with BS have an average lifespan of 26 years and experience premature onset of numerous age-related diseases, including cancer, diabetes, and chronic obstructive pulmonary disease (De Renty *et al.*, 2017).

2.2. Telomer Shorting

Telomeres are repeating, noncoding DNA sequences located at the ends of eukaryotic chromosomes, primarily composed of telomeric DNA and telomere-binding proteins (Maciejowski *et al.*, 2017). 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 (De Lange, 2018). 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 (Yukun Zhu et al., 2019). The length of telomeres is regulated by telomerase, when telomerase activity is increased and the chromosomes remain intact, the lifespan of an organism is extended (Yukun Zhu et al., 2019). 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 (Ishikawa, 2013). During replicative senescence, irreparable DNA damage is accumulated, leading to permanent cell-cycle arrest and is considered one of the main factors driving aging (Günes *et al.*, 2013). 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 (Herrmann et al., 2018, Jiang-Yi Wang *et al.*, 2017). 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 (Fumagalli *et al.*, 2012). One mechanism currently being studied as a significant contributor to telomeres length attrition is cellular oxidative stress (Monaghan *et al.*, 2018). This occurs when the concentration of pro-oxidant molecules in the body is higher compared to that of antioxidant substances (Halliwell *et al.*, 2015). 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 (Von Zglinicki, 2002). Increased levels of glucocorticoid hormones (GC) can also cause telomeres to attrition in vertebrates, including humans (Angelier *et al.*, 2018, Haussmann *et al.*, 2015). This occurs because GC hormones increase cellular oxidative stress by reducing natural antioxidant defences (Angelier et al., 2018, Costantini *et al.*, 2011) and suppressing telomerase expression (Choi *et al.*, 2008). 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 (Fang *et al.*, 2014, Gibson *et al.*, 2012). SIRT1 has been revealed to increase mitochondrial function and biogenesis through the transcription factor PGC-1α. Loss of SIRT1 activity therefore leads to mitochondrial dysfunction (Fang et al., 2014) lead to increase ROS production. ROS is also other main cause of telomere attrition (Gonzales-Ebsen *et al.*, 2017). ROS can generate approximately 100 different types of oxidatively damaged bases (Cadet *et al.*, 2013). 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 (Pfeiffer *et al.*, 2012). 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 (Arnoult *et al.*, 2012)). 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 (Pfeiffer et al., 2012).

2.3. Epigenetic Alterations

Epigenetic mechanisms encompass various processes, such as DNA methylation, histone modifications, chromatin remodeling, and transcriptional alteration through noncoding RNAs (ncRNAs) (Sen *et al.*, 2016). 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 (Nikolac Perkovic *et al.*, 2021). DNA methylation has various functions, including the alternative splicing, and the regulation of gene expression (Moore *et al.*, 2013). The DNA methyltransferases (DNMTs) are enzymes that play a role in DNA methylation, to transfer a methyl group at the fifth position of cytosine (5mC) from S-adenosyl-methionine (SAM) to the carbon-5 position of the cytosine residues in the CpG region (Hervouet *et al.*, 2018, Jeltsch *et al.*, 2017). 5-Hydroxymethylcytosine (5hmC) is a modification of DNA base that is derived from 5-methylcytosine through the actions of the ten-eleven translocation protein family (Zarakowska *et al.*, 2018). A recent study has found that the deamination of 5mC and oxidative damage are significant factors in somatic mutagenesis (Cagan *et al.*, 2022). These mutations also lead to the development of cancer (Stratton *et al.*, 2009), leads to premature aging, specifically Werner's syndrome and Hutchinson-Gilford Progeria syndrome (Horvath, 2013) and those are highly contribute to ageing (Vijg *et al.*, 2020). Histone modifications are a type of epigenetic alteration, including acetylation, methylation, phosphorylation, ubiquitination, and glycosylation. Among these, acetylation and methylation are the most characteristic modifications associated with senescence (Paluvai *et al.*, 2020). When histone methyltransferases or histone demethylases are present, they can alter the levels of histone methylation, which can then participate in either transcriptional activation or repression. Generally, methylation at lysine 4 of histone 3 (H3K4), H3K36, and H3K79 promotes transcriptional activation, while methylation at H3K27 and H4K20 causes transcriptional repression (Yi *et al.*, 2020). 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 (Yuan Wang *et al.*, 2018). These enzymes are crucial for longevity, as demonstrated by studies on yeast (Kirfel *et al.*, 2020). In particular, when the histone acetyltransferase gene GCN5 is deleted, it leads to a decrease in the replicative lifespan of yeast (Yuan Wang et al., 2018). H3K36me3 and H3K9me3 also have important roles in the aging process. In both S. cerevisiae and C. elegans, a deficiency in H3K36me3 is associated with a shorter lifespan. Consistently, the lifespan of S. cerevisiae is extended when there is a loss of H3K36me3 demethylase (Sen *et al.*, 2015). Similarly, the loss of H3K9me3 in the adult Drosophila midgut leads to aging of intestinal stem cells (Jeon *et al.*, 2018). Interestingly, in aged somatic tissues of C. elegans, there is an increase in global H3K9me3 levels at heterochromatic regions in the distal arms of chromosomes, but a decrease in euchromatic central regions of autosomes (Cheng-Lin Li *et al.*, 2021). 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 (Jason G Wood *et al.*, 2010). Furthermore, diminished levels of H3K9me3 and HP1 in mesenchymal stem cells (MSCs) carrying pathogenic mutations of HGPS or Werner Syndrome (WS), which also accelerate aging (Zunpeng Liu *et al.*, 2022, Wu *et al.*, 2018, Weiqi Zhang *et al.*, 2015). 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 Switch/sucrose non-fermentable (SWI2/SNF2) complex's core structural domain connects to each other through two induced Brace helices. This anchors chromatin remodelers to specific nucleosome positions and initiates substrate for remodelling reactions (Xiaoyu Liu *et al.*, 2017). 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 homeobox protein dve-1 in the nucleus, causing a decrease in histone acetylation and chromatin reorganization in C. elegans. On the other hand, the addition of nutrients that enhance acetyl-CoA production is enough to delay the lifespan of C. elegans following mitochondrial stress (Di Zhu *et al.*, 2020).

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 (Kauppila *et al.*, 2017). During mitochondrial dysfunction, the mitochondrial membrane potential (MMP) decreases and is associated with increased production of reactive oxygen species (ROS) (Sun et al., 2016) and indicate ETC dysfunction (Nacarelli *et al.*, 2019). 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 mitochondrial DNA, proteins, and lipids. This damage, in turn, reduces mitochondrial dynamics and hinders mitophagy, ultimately leading to mitochondrial dysfunction (Bakula *et al.*, 2020). Mitochondrial dysfunction has been also associated to aging and various age-related diseases, such as cancer, neurodegenerative, kidney diseases (Sun et al., 2016, Zhunina *et al.*, 2021). During mitochondrial dysfunction, MMP is reduced (Bagkos *et al.*, 2014) and increased production of reactive oxygen species (ROS) are also stress-induced senescence (Passos *et al.*, 2010), replicative senescence, oncogene-induced senescence (Nelson *et al.*, 2018), and senescence triggered by genetic telomere uncapping (Passos et al., 2010). The defective of proofreading activity of mtDNA polymerase contributes to mtDNA mutations, which in turn cause significant mitochondrial dysfunction and premature aging (Trifunovic *et al.*, 2005). 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 (Ryzhkova *et al.*, 2018). According to Vermulst et al., findings, the deletions of mtDNA are drivers of premature aging in mice (Vermulst *et al.*, 2008) and also induce cellular senescence (Kolesar *et al.*, 2014). Moreover, mitochondrial dysfunction also associated with chronic inflammation in different diseases, such as myocardial infarction (MI), sickle cell disease, and neurodegenerative disorders (De Oliveira *et al.*, 2021, Marchi *et al.*, 2023) and it also caused dysregulated nutrient sensing pathways, such as insulin/IGF-1, mTOR, AMPK, and sirtuins (Bartolomé *et al.*, 2017).

2.5. Autophagy Alterations

Autophagy is a well-conserved process that breaks down cellular components, such as damaged organelles and misfolded protein aggregates (Dikic *et al.*, 2018), within lysosomes. Under normal conditions, autophagy is regulates by ROS, but excessive ROS can damage organelles and cause protein modification and aggregation. On the other hand, autophagy can mitigate oxidative damage (Jisun Lee *et al.*, 2012). 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 (Lin Li *et al.*, 2013). 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 (Rabinovitch *et al.*, 2017). Dysfunction of autophagy via various factors significantly speeds up the aging process in different species (Aman *et al.*, 2021). However, increase the autophagy activity can slow down aging (Leidal *et al.*, 2018). 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 (Aman et al., 2021). 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 (Hansen *et al.*, 2018, Jisun Lee et al., 2012). 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 (Sirbu et al., 2013). One of the main causes of impaired DNA repair mechanism is that the defect in autophagy (Hewitt *et al.*, 2017). 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) (Yanan Wang *et al.*, 2016). However, inhibiting p62 accumulation also reduces defective autophagy-induced genome damage (Mathew *et al.*, 2009). Usually p62 is involved in regulating the balance between NHEJ and HR (Hewitt *et al.*, 2016). Under autophagic deficiency (Atg3 knockout), the recruitment of DNA repair proteins such as BRCA1, RAP80, and Rad51 to double strand breaks is compromised in a p62-dependent manner (Yanan Wang et al., 2016). Autophagy-deficient cells have defective activation of checkpoint kinase-1 (Chk1), which is important for DNA repair through HR. The failure of Chk1 in response to DNA damage results in reduced recruitment of Rad51 to the damaged sites (Gillespie *et al.*, 2016). In Atg5-deficient embryonic fibroblast cells, the deficiency in autophagy leads to the failure to sense damaged DNA by XP group C (XPC) and DNA damaging-binding protein 2 (DDB2) (Qiang *et al.*, 2016). Moreover, impaired autophagy results in DNA damage, increased mutation rates, and chromosomal instability in different cell (MEFs) (Mathew *et al.*, 2007).

3. Cellular Senescence

Cellular senescence is a state of irreversible cell cycle arrest (Morsli *et al.*, 2022). Aging results in both biological and functional changes, affecting not only organism but also cellular level (Hansen et al., 2018). 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 (Ohtani, 2022). Immune cells can aggravate the progression of aging-related diseases by triggering the production of more proinflammatory cytokines (Zhou *et al.*, 2021). Additionally, T-cell senescence is considered a key aspect of immune senescence. Premature T-cell accelerate aging in various organs and systems, with thymic degeneration, mitochondrial dysfunction, genetic and epigenetic changes, and protein homeostasis imbalance being the primary indicators of T-cell senescence (Mittelbrunn *et al.*, 2021). Desdín-Micó G et al. discovered that mice lacking mitochondrial transcription factor A (TFAM) experienced a range of aging-related symptoms, due to T cells senescence with mitochondrial dysfunction and ultimately, led to accelerating aging and premature death in the mice (Desdín-Micó *et al.*, 2020). 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 (Henriques *et al.*, 2012, Yu Sun *et al.*, 2018). 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 (Indo *et al.*, 2015). The main antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), peroxidase (GPX), and glutathione (GSH), work to reduce excessive ROS, however, their effectiveness is reduced by cellular aging and leads to rise ROS level (Balaban *et al.*, 2005). The senescent state is regulated by the p53/p21 and p16/pRB pathways (Abbas *et al.*, 2017, Campisi, 2013, Muñoz-Espín *et al.*, 2014). 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 (Lanigan *et al.*, 2011, Muñoz-Espín et al., 2014). 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 (Lanigan et al., 2011). Cellular senescence mainly triggered by DNA damaging (Di Micco *et al.*, 2021). If DNA damage cannot be repaired and continues, results in prolonged DDR signaling and long-term proliferation arrest in the form of cellular senescence (Fumagalli *et al.*, 2014). Based on various findings, another primary causes of cellular senescence are telomere shortening (Bernadotte *et al.*, 2016), mitochondrial dysfunction (Wiley *et al.*, 2016, Yue *et al.*, 2016) and the dysfunction of autophagy pathways (Gewirtz, 2013). The p53 function loss promotes chromosomal instability and causes cellular senescence or apoptosis (Qianqian He *et al.*, 2018). Cellular senescence is crucial in preventing the formation of tumors, aiding in tissue repair and wound healing, promoting insulin secretion, and supporting mammalian development (Demaria *et al.*, 2014, Helman *et al.*, 2016, Storer *et al.*, 2013). However, the accumulation of senescent in the cells over time, likely due to decreased immune-clearance in almost all vertebrates (Yan Liu *et al.*, 2009) and has been proven to actively contribute to the process of aging (Roos *et al.*, 2016). Senescent cells also play a role in age-related diseases like atherosclerosis (Roos et al., 2016), osteoporosis (Chandra *et al.*, 2020), non-alcoholic fatty liver disease (Ogrodnik *et al.*, 2017), cancer (Alimirah *et al.*, 2020), neurodegenerative diseases (Chinta *et al.*, 2018, Peisu Zhang *et al.*, 2019), and other conditions associated with aging (Kirkland *et al.*, 2020).

4. Conserved Genetic Pathways

The process of aging and the frequency and severity of age-related diseases are affected by different conserved genetic pathways. These important pathways include the insulin/IGF-1 signaling pathway, the mTOR pathway, and the AMPK pathway (López-Otín et al., 2013). 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 (Johnson, 2018). In mammals, insulin/IGF-1 signaling plays a crucial role in coordinating nutrient availability with energy balance and metabolic processes. This signaling pathway is activated by insulin-like peptide ligands in response to nutrient availability. One way that insulin/IGF-1 signaling transmits signals is through the PI3K/Akt pathway, which phosphorylates various targets, including tuberous sclerosis complex (TSC1/2) (Templeman *et al.*, 2018). 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 (Johnson *et al.*, 2013). 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 (Bartke *et al.*, 2013). Furthermore, Ock's study also revealed that removing IGF-1R in mouse cardiomyocytes reduced age-related myocardial inflammation, hypertrophy, and interstitial fibrosis in the heart. This suggests that the opposing effects of insulin/IGF-1 signaling have significant impacts on the overall health and lifespan of mammals (Ock *et al.*, 2016). mTOR is a serine/threonine kinase that belongs to the phosphoinositide kinase-related family, and has mTOR 1 and mTOR 2 complex. Activation of mTORC1 occurs through phosphoinositide-3-(PI3)-kinase-related kinase family and AKT kinase signaling, as well as by nutrients like amino acids and phosphates (Laplante *et al.*, 2012). Activated TORC1 promotes anabolic processes, such as protein, lipid, and nucleotide synthesis, while inhibiting catabolic processes like autophagy (González *et al.*, 2017). The frequent alteration of mTOR plays an important role during tumorigenesis, metastasis, and drug resistance in human malignancies (Yundong He *et al.*, 2022, Kirtonia *et al.*, 2022). In senescence, mTOR is persistently activated (Carroll *et al.*, 2017), possibly due to increased levels of reactive oxygen species (ROS) produced by dysfunctional mitochondria (Nacarelli *et al.*, 2016). The dysregulation of mTOR function can lead to the development of neurodegenerative diseases, which are characterized by the aggregation of proteins (Perluigi *et al.*, 2015). 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 (Lin *et al.*, 2018). 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 (Salminen *et al.*, 2012). The activation of AMPK encourages the formation of new mitochondria and regulates their dynamics and mitophagy (Toyama *et al.*, 2016). According to recent findings, the activation of AMPK increases the lifespan of D. melanogaster by 30%, extending it from six weeks to eight weeks (Moqrich, 2014). On the other hand, AMPK activation is induced by caloric restriction protects rats against senescence by enhancing autophagic activity and reducing oxidative damage (Ning *et al.*, 2013). AMPK also plays a crucial role in autophagy (Salminen et al., 2012), which is a cellular degradation pathway that breaks down and reuses components to maintain cellular balance (Ma *et al.*, 2018). Dysfunction of autophagy is strongly associated with ageing and organ dysfunction (García-Prat *et al.*, 2016). The dysregulation of AMPK is associated with accelerated aging due to promoting inflammation, cancer, and metabolic pathologies such as diabetes and obesity (Garcia *et al.*, 2017). 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 (Brunet *et al.*, 2004) and apoptotic pathways (Yanfei Liu *et al.*, 2019). Similarly, SIRT1 is implicated in a range of age-related processes and disorders, including neurodegenerative diseases and cardiovascular diseases (Zhao *et al.*, 2020). 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 (Kanfi *et al.*, 2012, Kapahi *et al.*, 2017). 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 (Wątroba *et al.*, 2016). The dysregulation of insulin/IGF-1, mTOR, AMPK, and other conserved signaling pathways closely associated with human aging and age-related diseases resulting from inadequate nutrient supply (Fernandes *et al.*, 2021, Johnson, 2018).

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 (Jönsson *et al.*, 2020) and 85% of plants genome (Wicker *et al.*, 2018). Reducing DNA methylation and loss of heterochromatin are highly contributed to the rapid increase of TE expression and transposition (Sedivy *et al.*, 2013). The activation of endogenous transposable elements greatly causes to genome instability (Burns et al., 2012), telomere dysfunction, mitochondrial dysfunction, epigenetic alterations, and proteostatic stress (Schumacher et al., 2021). Several studies have indicated that overexpression of TE is associated with an increase in immune response and inflammation (De Cubas *et al.*, 2020, Ching-Hsuan Liu *et al.*, 2020) 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 (Ochirov, 2019, Römer, 2021). 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 (Bogu *et al.*, 2019, Volkman *et al.*, 2014). Altered activity of specific transposable elements is also associated with multiple age-associated pathologies, including cancer (Di Ruocco et al., 2018) and Alzheimer's disease (AD) (Gao et al., 2018). 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 (Elsner *et al.*, 2018). 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 (Wahl *et al.*, 2021). 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 (Gorbunova *et al.*, 2021).

Conclusion

Understanding the molecular mechanisms and signaling pathways involved in aging is crucial for clarifying the complex process of aging and identifying potential targets for intervention. Molecular damages and dysfunction of cellular results such as oxidative stress, inflammation, DNA damage, telomere shortening, and cellular senescence, have been affecting the aging process via directly or indirectly. The insulin/insulin-like growth factor 1 (IGF-1) signaling pathway regulates metabolism, growth, and longevity of an organism. Reduced signaling through this pathway has been associated with increased lifespan in various organisms. Additionally, the sirtuin pathway, involved in regulating cellular metabolism, stress response, and longevity, has been implicated in the aging process. Activation of sirtuins has been shown to promote longevity and delay aging in various model organisms. Another important pathway is the mTOR (mechanistic target of rapamycin) pathway is one of the major pathways involved in aging. mTOR 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 aging-related diseases. Interventions that target mTOR signaling have shown promise in extending lifespan and improving healthspan in various model organisms. TEs are mobile genetic elements that can move within the genome and potentially disrupt gene function or regulation. They have gained attention for their role in aging as their activity can lead to genomic instability, which is a characteristic of aging. Numerous studies have suggested that TEs become more active with age, contributing to genomic instability and cellular dysfunction. Moreover, TEs can induce inflammation and alter gene expression patterns, further exacerbating the aging process. In conclusion, aging is a complex process involving multiple molecular mechanisms and signaling pathways.

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Reference

1. Abbas, M., Jesel, L., Auger, C., Amoura, L., Messas, N., Manin, G., Rumig, C., León-González, A. J., Ribeiro, T. P. & Silva, G. C. 2017. Endothelial microparticles from acute coronary syndrome patients induce premature coronary artery endothelial cell aging and thrombogenicity: Role of the ang ii/at1 receptor/nadph oxidase-mediated activation of mapks and pi3-kinase pathways. *Circulation,* 135**,** 280-296.
2. Alimirah, F., Pulido, T., Valdovinos, A., Alptekin, S., Chang, E., Jones, E., Diaz, D. A., Flores, J., Velarde, M. C. & Demaria, M. 2020. Cellular senescence promotes skin carcinogenesis through p38mapk and p44/42mapk signaling. *Cancer research,* 80**,** 3606-3619.
3. Angelier, F., Costantini, D., Blévin, P. & Chastel, O. 2018. Do glucocorticoids mediate the link between environmental conditions and telomere dynamics in wild vertebrates? A review. *General and comparative endocrinology,* 256**,** 99-111.
4. Arancio, W., Pizzolanti, G., Genovese, S. I., Pitrone, M. & Giordano, C. 2014. Epigenetic involvement in hutchinson-gilford progeria syndrome: A mini-review. *Gerontology,* 60**,** 197-203.
5. Arnoult, N., Van Beneden, A. & Decottignies, A. 2012. Telomere length regulates terra levels through increased trimethylation of telomeric h3k9 and hp1α. *Nature structural & molecular biology,* 19**,** 948-956.
6. Bagkos, G., Koufopoulos, K. & Piperi, C. 2014. A new model for mitochondrial membrane potential production and storage. *Medical hypotheses,* 83**,** 175-181.
7. Baker, D. J., Childs, B. G., Durik, M., Wijers, M. E., Sieben, C. J., Zhong, J., A. Saltness, R., Jeganathan, K. B., Verzosa, G. C. & Pezeshki, A. 2016. Naturally occurring p16ink4a-positive cells shorten healthy lifespan. *Nature,* 530**,** 184-189.
8. Bakula, D. & Scheibye-Knudsen, M. 2020. Mitophaging: Mitophagy in aging and disease. *Frontiers in cell and developmental biology,* 8**,** 239.
9. Bartke, A., Sun, L. Y. & Longo, V. 2013. Somatotropic signaling: Trade-offs between growth, reproductive development, and longevity. *Physiological reviews,* 93**,** 571-598.
10. Bartolomé, A., García-Aguilar, A., Asahara, S.-I., Kido, Y., Guillén, C., Pajvani, U. B. & Benito, M. 2017. Mtorc1 regulates both general autophagy and mitophagy induction after oxidative phosphorylation uncoupling. *Molecular and cellular biology,* 37**,** e00441-17.
11. Bernadotte, A., Mikhelson, V. M. & Spivak, I. M. 2016. Markers of cellular senescence. Telomere shortening as a marker of cellular senescence. *Aging (Albany NY),* 8**,** 3.

12. Bogu, G. K., Reverter, F., Marti-Renom, M. A., Snyder, M. P. & Guigó, R. 2019. Atlas of transcriptionally active transposable elements in human adult tissues. *BioRxiv*, 714212.
13. Burla, R., La Torre, M., Merigliano, C., Vernì, F. & Saggio, I. 2018. Genomic instability and DNA replication defects in progeroid syndromes. *Nucleus,* 9**,** 368-379.
14. Burns, K. H. & Boeke, J. D. 2012. Human transposon tectonics. *Cell,* 149**,** 740-752.
15. Burtner, C. R. & Kennedy, B. K. 2010. Progeria syndromes and ageing: What is the connection? *Nature reviews Molecular cell biology,* 11**,** 567-578.
16. Cadet, J. & Wagner, J. R. 2013. DNA base damage by reactive oxygen species, oxidizing agents, and uv radiation. *Cold Spring Harbor perspectives in biology,* 5**,** a012559.
17. Cagan, A., Baez-Ortega, A., Brzozowska, N., Abascal, F., Coorens, T. H., Sanders, M. A., Lawson, A. R., Harvey, L. M., Bhosle, S. & Jones, D. 2022. Somatic mutation rates scale with lifespan across mammals. *Nature,* 604**,** 517-524.
18. Campisi, J. 2013. Aging, cellular senescence, and cancer. *Annual review of physiology,* 75**,** 685-705.
19. Carroll, B., Nelson, G., Rabanal-Ruiz, Y., Kucheryavenko, O., Dunhill-Turner, N. A., Chesterman, C. C., Zahari, Q., Zhang, T., Conduit, S. E. & Mitchell, C. A. 2017. Persistent mtorc1 signaling in cell senescence results from defects in amino acid and growth factor sensing. *Journal of Cell Biology,* 216**,** 1949-1957.
20. Chandra, A., Lagnado, A. B., Farr, J. N., Monroe, D. G., Park, S., Hachfeld, C., Tchkonia, T., Kirkland, J. L., Khosla, S. & Passos, J. F. 2020. Targeted reduction of senescent cell burden alleviates focal radiotherapy-related bone loss. *Journal of Bone and Mineral Research,* 35**,** 1119-1131.
21. Chinta, S. J., Woods, G., Demaria, M., Rane, A., Zou, Y., Mcquade, A., Rajagopalan, S., Limbad, C., Madden, D. T. & Campisi, J. 2018. Cellular senescence is induced by the environmental neurotoxin paraquat and contributes to neuropathology linked to parkinson's disease. *Cell reports,* 22**,** 930-940.
22. Choi, J., Fauce, S. R. & Effros, R. B. 2008. Reduced telomerase activity in human t lymphocytes exposed to cortisol. *Brain, behavior, and immunity,* 22**,** 600-605.
23. Costantini, D., Marasco, V. & Møller, A. P. 2011. A meta-analysis of glucocorticoids as modulators of oxidative stress in vertebrates. *Journal of Comparative Physiology B,* 181**,** 447-456.
24. Curtin, N. J. 2012. DNA repair dysregulation from cancer driver to therapeutic target. *Nature Reviews Cancer,* 12**,** 801-817.
25. De Lange, T. 2018. Shelterin-mediated telomere protection. *Annual review of genetics,* 52**,** 223-247.
26. De Luca, C., Guadagni, F., Sinibaldi-Vallebona, P., Sentinelli, S., Gallucci, M., Hoffmann, A., Schumann, G. G., Spadafora, C. & Sciamanna, I. 2016. Enhanced expression of line-1-encoded orf2 protein in early stages of colon and prostate transformation. *Oncotarget,* 7**,** 4048.
27. De Oliveira, L. G., Angelo, Y. D. S., Iglesias, A. H. & Peron, J. P. S. 2021. Unraveling the link between mitochondrial dynamics and neuroinflammation. *Frontiers in Immunology,* 12**,** 624919.
28. De Renty, C. & Ellis, N. A. 2017. Bloom's syndrome: Why not premature aging?: A comparison of the blm and wrn helicases. *Ageing research reviews,* 33**,** 36-51.
29. Demaria, M., Ohtani, N., Youssef, S. A., Rodier, F., Toussaint, W., Mitchell, J. R., Laberge, R.-M., Vijg, J., Van Steeg, H. & Dollé, M. E. 2014. An essential role for senescent cells in optimal wound healing through secretion of pdgf-aa. *Developmental cell,* 31**,** 722-733.
30. Desdín-Micó, G., Soto-Heredero, G., Aranda, J. F., Oller, J., Carrasco, E., Gabandé-Rodríguez, E., Blanco, E. M., Alfranca, A., Cussó, L. & Desco, M. 2020. T cells with dysfunctional mitochondria induce multimorbidity and premature senescence. *Science,* 368**,** 1371-1376.
31. Di Micco, R., Krizhanovsky, V., Baker, D. & D'adda Di Fagagna, F. 2021. Cellular senescence in ageing: From mechanisms to therapeutic opportunities. *Nature reviews Molecular cell biology,* 22**,** 75-95.
32. Di Ruocco, F., Basso, V., Rivoire, M., Mehlen, P., Ambati, J., De Falco, S. & Tarallo, V. 2018. Alu rna accumulation induces epithelial-to-mesenchymal transition by modulating mir-566 and is associated with cancer progression. *Oncogene,* 37**,** 627-637.
33. Dikic, I. & Elazar, Z. 2018. Mechanism and medical implications of mammalian autophagy. *Nature reviews Molecular cell biology,* 19**,** 349-364.
34. Elsner, D., Meusemann, K. & Korb, J. 2018. Longevity and transposon defense, the case of termite reproductives. *Proceedings of the National Academy of Sciences,* 115**,** 5504-5509.
35. Fang, E. F., Scheibye-Knudsen, M., Brace, L. E., Kassahun, H., Sengupta, T., Nilsen, H., Mitchell, J. R., Croteau, D. L. & Bohr, V. A. 2014. Defective mitophagy in xpa via parp-1 hyperactivation and nad+/sirt1 reduction. *Cell,* 157**,** 882-896.
36. Fernandes, S. A. & Demetriades, C. 2021. The multifaceted role of nutrient sensing and mtorc1 signaling in physiology and aging. *Frontiers in Aging,* 2**,** 707372.
37. Ferrucci, L., Gonzalez-Freire, M., Fabbri, E., Simonsick, E., Tanaka, T., Moore, Z., Salimi, S., Sierra, F. & De Cabo, R. 2020. Measuring biological aging in humans: A quest. *Aging cell,* 19**,** e13080.
38. Fitsiou, E., Pulido, T., Campisi, J., Alimirah, F. & Demaria, M. 2021. Cellular senescence and the senescence-associated secretory phenotype as drivers of skin photoaging. *Journal of Investigative Dermatology,* 141**,** 1119-1126.

39. Fumagalli, M., Rossiello, F., Clerici, M., Barozzi, S., Cittaro, D., Kaplunov, J. M., Bucci, G., Dobreva, M., Matti, V. & Beausejour, C. M. 2012. Telomeric DNA damage is irreparable and causes persistent DNA-damage-response activation. *Nature cell biology,* 14**,** 355-365.
40. Fumagalli, M., Rossiello, F., Mondello, C. & D'adda Di Fagagna, F. 2014. Stable cellular senescence is associated with persistent ddr activation. *PloS one,* 9**,** e110969.
41. Gao, Y., Zhang, J. & Zhao, F. 2018. Circular rna identification based on multiple seed matching. *Briefings in bioinformatics,* 19**,** 803-810.
42. García-Prat, L., Martínez-Vicente, M., Perdiguero, E., Ortet, L., Rodríguez-Ubreva, J., Rebollo, E., Ruiz-Bonilla, V., Gutarra, S., Ballestar, E. & Serrano, A. L. 2016. Autophagy maintains stemness by preventing senescence. *Nature,* 529**,** 37-42.
43. Garcia, D. & Shaw, R. J. 2017. Ampk: Mechanisms of cellular energy sensing and restoration of metabolic balance. *Molecular cell,* 66**,** 789-800.
44. Gewirtz, D. A. 2013. Autophagy and senescence: A partnership in search of definition. *Autophagy,* 9**,** 808-812.
45. Gibson, B. A. & Kraus, W. L. 2012. New insights into the molecular and cellular functions of poly (adp-ribose) and parps. *Nature reviews Molecular cell biology,* 13**,** 411-424.
46. Gillespie, D. A. & Ryan, K. M. 2016. Autophagy is critically required for DNA repair by homologous recombination. *Molecular & Cellular Oncology,* 3**,** e1030538.
47. González, A. & Hall, M. N. 2017. Nutrient sensing and tor signaling in yeast and mammals. *The EMBO journal,* 36**,** 397-408.
48. Gorbunova, V., Seluanov, A., Mita, P., Mckerrow, W., Fenyö, D., Boeke, J. D., Linker, S. B., Gage, F. H., Kreiling, J. A. & Petrashen, A. P. 2021. The role of retrotransposable elements in ageing and age-associated diseases. *Nature,* 596**,** 43-53.
49. Günes, C. & Rudolph, K. L. 2013. The role of telomeres in stem cells and cancer. *Cell,* 152**,** 390-393.
50. Hansen, M., Rubinsztein, D. C. & Walker, D. W. 2018. Autophagy as a promoter of longevity: Insights from model organisms. *Nature reviews Molecular cell biology,* 19**,** 579-593.
51. Haussmann, M. F. & Heidinger, B. J. 2015. Telomere dynamics may link stress exposure and ageing across generations. *Biology letters,* 11**,** 20150396.
52. He, Q., Au, B., Kulkarni, M., Shen, Y., Lim, K. J., Maimaiti, J., Wong, C. K., Luijten, M. N., Chong, H. C. & Lim, E. H. 2018. Chromosomal instability-induced senescence potentiates cell non-autonomous tumourigenic effects. *Oncogenesis,* 7**,** 62.
53. He, Y., Xu, W., Xiao, Y.-T., Huang, H., Gu, D. & Ren, S. 2022. Targeting signaling pathways in prostate cancer: Mechanisms and clinical trials. *Signal Transduction and Targeted Therapy,* 7**,** 198.
54. Helman, A., Klochendler, A., Azazmeh, N., Gabai, Y., Horwitz, E., Anzi, S., Swisa, A., Condiotti, R., Granit, R. Z. & Nevo, Y. 2016. P16ink4a-induced senescence of pancreatic beta cells enhances insulin secretion. *Nature medicine,* 22**,** 412-420.
55. Henriques, C. M. & Ferreira, M. G. 2012. Consequences of telomere shortening during lifespan. *Current opinion in cell biology,* 24**,** 804-808.
56. Hernandez-Segura, A., Nehme, J. & Demaria, M. 2018. Hallmarks of cellular senescence. *Trends in cell biology,* 28**,** 436-453.
57. Herrmann, M., Pusceddu, I., März, W. & Herrmann, W. 2018. Telomere biology and age-related diseases. *Clinical Chemistry and Laboratory Medicine (CCLM),* 56**,** 1210-1222.
58. Hewitt, G., Carroll, B., Sarallah, R., Correia-Melo, C., Ogrodnik, M., Nelson, G., Otten, E. G., Manni, D., Antrobus, R. & Morgan, B. A. 2016. Sqstm1/p62 mediates crosstalk between autophagy and the ups in DNA repair. *Autophagy,* 12**,** 1917-1930.
59. Hewitt, G. & Korolchuk, V. I. 2017. Repair, reuse, recycle: The expanding role of autophagy in genome maintenance. *Trends in cell biology,* 27**,** 340-351.
60. Hood, D. A., Memme, J. M., Oliveira, A. N. & Triolo, M. 2019. Maintenance of skeletal muscle mitochondria in health, exercise, and aging. *Annual Review of Physiology,* 81**,** 19-41.
61. Indo, H. P., Yen, H.-C., Nakanishi, I., Matsumoto, K.-I., Tamura, M., Nagano, Y., Matsui, H., Gusev, O., Cornette, R. & Okuda, T. 2015. A mitochondrial superoxide theory for oxidative stress diseases and aging. *Journal of clinical biochemistry and nutrition,* 56**,** 1-7.
62. Ishikawa, F. 2013. Portrait of replication stress viewed from telomeres. *Cancer science,* 104**,** 790-794.
63. Jeltsch, A., Ehrenhofer-Murray, A., Jurkowski, T. P., Lyko, F., Reuter, G., Ankri, S., Nellen, W., Schaefer, M. & Helm, M. 2017. Mechanism and biological role of dnmt2 in nucleic acid methylation. *RNA biology,* 14**,** 1108-1123.
64. Jeon, H.-J., Kim, Y.-S., Kim, J.-G., Heo, K., Pyo, J.-H., Yamaguchi, M., Park, J.-S. & Yoo, M.-A. 2018. Effect of heterochromatin stability on intestinal stem cell aging in drosophila. *Mechanisms of Ageing and Development,* 173**,** 50-60.
65. Johnson, S. C., Rabinovitch, P. S. & Kaeberlein, M. 2013. Mtor is a key modulator of ageing and age-related disease. *Nature,* 493**,** 338-345.

66. Jönsson, M. E., Garza, R., Johansson, P. A. & Jakobsson, J. 2020. Transposable elements: A common feature of neurodevelopmental and neurodegenerative disorders. *Trends in Genetics,* 36**,** 610-623.
67. Kaiser, A. M. & Attardi, L. D. 2018. Deconstructing networks of p53-mediated tumor suppression in vivo. *Cell Death & Differentiation,* 25**,** 93-103.
68. Kanfi, Y., Naiman, S., Amir, G., Peshti, V., Zinman, G., Nahum, L., Bar-Joseph, Z. & Cohen, H. Y. 2012. The sirtuin sirt6 regulates lifespan in male mice. *Nature,* 483**,** 218-221.
69. Kapahi, P., Kaeberlein, M. & Hansen, M. 2017. Dietary restriction and lifespan: Lessons from invertebrate models. *Ageing research reviews,* 39**,** 3-14.
70. Kauppila, T. E., Kauppila, J. H. & Larsson, N.-G. 2017. Mammalian mitochondria and aging: An update. *Cell metabolism,* 25**,** 57-71.
71. Kennedy, B. K., Berger, S. L., Brunet, A., Campisi, J., Cuervo, A. M., Epel, E. S., Franceschi, C., Lithgow, G. J., Morimoto, R. I. & Pessin, J. E. 2014. Geroscience: Linking aging to chronic disease. *Cell,* 159**,** 709-713.
72. Kirfel, P., Vilcinskas, A. & Skaljac, M. 2020. Lysine acetyltransferase p300/cbp plays an important role in reproduction, embryogenesis and longevity of the pea aphid acyrthosiphon pisum. *Insects,* 11**,** 265.
73. Kirkland, J. & Tchkonia, T. 2020. Senolytic drugs: From discovery to translation. *Journal of internal medicine,* 288**,** 518-536.
74. Kirtonia, A., Pandey, A. K., Ramachandran, B., Mishra, D. P., Dawson, D. W., Sethi, G., Ganesan, T. S., Koeffler, H. P. & Garg, M. 2022. Overexpression of laminin-5 gamma-2 promotes tumorigenesis of pancreatic ductal adenocarcinoma through egfr/erk1/2/akt/mtor cascade. *Cellular and Molecular Life Sciences,* 79**,** 362.
75. Kolesar, J. E., Safdar, A., Abadi, A., Macneil, L. G., Crane, J. D., Tarnopolsky, M. A. & Kaufman, B. A. 2014. Defects in mitochondrial DNA replication and oxidative damage in muscle of mtdna mutator mice. *Free Radical Biology and Medicine,* 75**,** 241-251.
76. Kubben, N. & Misteli, T. 2017. Shared molecular and cellular mechanisms of premature ageing and ageing-associated diseases. *Nature Reviews Molecular Cell Biology,* 18**,** 595-609.
77. Kudlow, B. A., Kennedy, B. K. & Monnat Jr, R. J. 2007. Werner and hutchinson–gilford progeria syndromes: Mechanistic basis of human progeroid diseases. *Nature reviews Molecular cell biology,* 8**,** 394-404.
78. Lanigan, F., Geraghty, J. & Bracken, A. 2011. Transcriptional regulation of cellular senescence. *Oncogene,* 30**,** 2901-2911.
79. Lee, J., Giordano, S. & Zhang, J. 2012. Autophagy, mitochondria and oxidative stress: Cross-talk and redox signalling. *Biochemical Journal,* 441**,** 523-540.
80. Lee, S.-J., Hwang, A. B. & Kenyon, C. 2010. Inhibition of respiration extends c. Elegans life span via reactive oxygen species that increase hif-1 activity. *Current Biology,* 20**,** 2131-2136.
81. Lei, J., Jiang, X., Li, W., Ren, J., Wang, D., Ji, Z., Wu, Z., Cheng, F., Cai, Y. & Yu, Z.-R. 2022. Exosomes from antler stem cells alleviate mesenchymal stem cell senescence and osteoarthritis. *Protein & cell,* 13**,** 220-226.
82. Leidal, A. M., Levine, B. & Debnath, J. 2018. Autophagy and the cell biology of age-related disease. *Nature cell biology,* 20**,** 1338-1348.
83. Li, C.-L., Pu, M., Wang, W., Chaturbedi, A., Emerson, F. J. & Lee, S. S. 2021. Region-specific h3k9me3 gain in aged somatic tissues in caenorhabditis elegans. *PLoS Genetics,* 17**,** e1009432.
84. Li, L., Chen, Y. & Gibson, S. B. 2013. Starvation-induced autophagy is regulated by mitochondrial reactive oxygen species leading to ampk activation. *Cellular signalling,* 25**,** 50-65.
85. Li, Z., Zhou, D., Zhang, D., Zhao, J., Li, W., Sun, Y., Chen, Y., Liu, H., Wilson, J. X. & Qian, Z. 2022. Folic acid inhibits aging-induced telomere attrition and apoptosis in astrocytes in vivo and in vitro. *Cerebral Cortex,* 32**,** 286-297.
86. Lin, S.-C. & Hardie, D. G. 2018. Ampk: Sensing glucose as well as cellular energy status. *Cell metabolism,* 27**,** 299-313.
87. Liu, C.-H., Grandi, N., Palanivelu, L., Tramontano, E. & Lin, L.-T. 2020. Contribution of human retroviruses to disease development—a focus on the hiv–and herv–cancer relationships and treatment strategies. *Viruses,* 12**,** 852.
88. Liu, X., Li, M., Xia, X., Li, X. & Chen, Z. 2017. Mechanism of chromatin remodelling revealed by the snf2-nucleosome structure. *Nature,* 544**,** 440-445.
89. Liu, Y., Sanoff, H. K., Cho, H., Burd, C. E., Torrice, C., Ibrahim, J. G., Thomas, N. E. & Sharpless, N. E. 2009. Expression of p16ink4a in peripheral blood t-cells is a biomarker of human aging. *Aging cell,* 8**,** 439-448.
90. Loi, M., Cenni, V., Duchi, S., Squarzoni, S., Lopez-Otin, C., Foisner, R., Lattanzi, G. & Capanni, C. 2016. Barrier-to-autointegration factor (baf) involvement in prelamin a-related chromatin organization changes. *Oncotarget,* 7**,** 15662.
91. López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M. & Kroemer, G. 2013. The hallmarks of aging. *Cell,* 153**,** 1194-1217.
92. Ma, Y., Qi, M., An, Y., Zhang, L., Yang, R., Doro, D. H., Liu, W. & Jin, Y. 2018. Autophagy controls mesenchymal stem cell properties and senescence during bone aging. *Aging cell,* 17**,** e12709.

doi:10.20944/preprints202410.1563.v1

93. Maciejowski, J. & De Lange, T. 2017. Telomeres in cancer: Tumour suppression and genome instability. *Nature reviews Molecular cell biology,* 18**,** 175-186.
94. Marchi, S., Guilbaud, E., Tait, S. W., Yamazaki, T. & Galluzzi, L. 2023. Mitochondrial control of inflammation. *Nature Reviews Immunology,* 23**,** 159-173.
95. Mathew, R., Karp, C. M., Beaudoin, B., Vuong, N., Chen, G., Chen, H.-Y., Bray, K., Reddy, A., Bhanot, G. & Gelinas, C. 2009. Autophagy suppresses tumorigenesis through elimination of p62. *Cell,* 137**,** 1062-1075.
96. Mathew, R., Kongara, S., Beaudoin, B., Karp, C. M., Bray, K., Degenhardt, K., Chen, G., Jin, S. & White, E. 2007. Autophagy suppresses tumor progression by limiting chromosomal instability. *Genes & development,* 21**,** 1367-1381.
97. Maynard, S., Schurman, S. H., Harboe, C., De Souza-Pinto, N. C. & Bohr, V. A. 2009. Base excision repair of oxidative DNA damage and association with cancer and aging. *Carcinogenesis,* 30**,** 2-10.
98. Menck, C. F. & Munford, V. 2014. DNA repair diseases: What do they tell us about cancer and aging? *Genetics and Molecular Biology,* 37**,** 220-233.
99. Mittelbrunn, M. & Kroemer, G. 2021. Hallmarks of t cell aging. *Nature immunology,* 22**,** 687-698.
100. Monaghan, P. & Ozanne, S. E. 2018. Somatic growth and telomere dynamics in vertebrates: Relationships, mechanisms and consequences. *Philosophical Transactions of the Royal Society B: Biological Sciences,* 373**,** 20160446.
101. Moore, L. D., Le, T. & Fan, G. 2013. DNA methylation and its basic function. *Neuropsychopharmacology,* 38**,** 23-38.
102. Moqrich, A. 2014. Peripheral pain-sensing neurons: From molecular diversity to functional specialization. *Cell Reports,* 6**,** 245-246.
103. Morsli, S., Doherty, G. J. & Muñoz-Espín, D. 2022. Activatable senoprobes and senolytics: Novel strategies to detect and target senescent cells. *Mechanisms of Ageing and Development,* 202**,** 111618.
104. Mossad, O., Batut, B., Yilmaz, B., Dokalis, N., Mezö, C., Nent, E., Nabavi, L. S., Mayer, M., Maron, F. J. M. & Buescher, J. M. 2022. Gut microbiota drives age-related oxidative stress and mitochondrial damage in microglia via the metabolite n 6-carboxymethyllysine. *Nature neuroscience,* 25**,** 295-305.
105. Muñoz-Espín, D. & Serrano, M. 2014. Cellular senescence: From physiology to pathology. *Nature reviews Molecular cell biology,* 15**,** 482-496.
106. Nacarelli, T., Azar, A. & Sell, C. 2016. Mitochondrial stress induces cellular senescence in an mtorc1-dependent manner. *Free Radical Biology and Medicine,* 95**,** 133-154.
107. Nacarelli, T., Lau, L., Fukumoto, T., Zundell, J., Fatkhutdinov, N., Wu, S., Aird, K. M., Iwasaki, O., Kossenkov, A. V. & Schultz, D. 2019. Nad+ metabolism governs the proinflammatory senescence-associated secretome. *Nature cell biology,* 21**,** 397-407.
108. Nelson, G., Kucheryavenko, O., Wordsworth, J. & Von Zglinicki, T. 2018. The senescent bystander effect is caused by ros-activated nf-κb signalling. *Mechanisms of ageing and development,* 170**,** 30-36.
109. Nguyen, G. H., Tang, W., Robles, A. I., Beyer, R. P., Gray, L. T., Welsh, J. A., Schetter, A. J., Kumamoto, K., Wang, X. W. & Hickson, I. D. 2014. Regulation of gene expression by the blm helicase correlates with the presence of g-quadruplex DNA motifs. *Proceedings of the National Academy of Sciences,* 111**,** 9905-9910.
110. Nikolac Perkovic, M., Videtic Paska, A., Konjevod, M., Kouter, K., Svob Strac, D., Nedic Erjavec, G. & Pivac, N. 2021. Epigenetics of alzheimer’s disease. *Biomolecules,* 11**,** 195.
111. Ning, Y.-C., Cai, G.-Y., Zhuo, L., Gao, J.-J., Dong, D., Cui, S., Feng, Z., Shi, S.-Z., Bai, X.-Y. & Sun, X.-F. 2013. Short-term calorie restriction protects against renal senescence of aged rats by increasing autophagic activity and reducing oxidative damage. *Mechanisms of ageing and development,* 134**,** 570-579.
112. Ock, S., Lee, W. S., Ahn, J., Kim, H. M., Kang, H., Kim, H.-S., Jo, D., Abel, E. D., Lee, T. J. & Kim, J. 2016. Deletion of igf-1 receptors in cardiomyocytes attenuates cardiac aging in male mice. *Endocrinology,* 157**,** 336-345.
113. Ogrodnik, M., Miwa, S., Tchkonia, T., Tiniakos, D., Wilson, C. L., Lahat, A., Day, C. P., Burt, A., Palmer, A. & Anstee, Q. M. 2017. Cellular senescence drives age-dependent hepatic steatosis. *Nature communications,* 8**,** 15691.
114. Ogrodnik, M., Salmonowicz, H. & Gladyshev, V. N. 2019. Integrating cellular senescence with the concept of damage accumulation in aging: Relevance for clearance of senescent cells. *Aging cell,* 18**,** e12841.
115. Ohtani, N. 2022. The roles and mechanisms of senescence-associated secretory phenotype (sasp): Can it be controlled by senolysis? *Inflammation and regeneration,* 42**,** 11.
116. Ovadya, Y. & Krizhanovsky, V. 2014. Senescent cells: Saspected drivers of age-related pathologies. *Biogerontology,* 15**,** 627-642.
117. Paluvai, H., Di Giorgio, E. & Brancolini, C. 2020. The histone code of senescence. *Cells,* 9**,** 466.
118. Passos, J. F., Nelson, G., Wang, C., Richter, T., Simillion, C., Proctor, C. J., Miwa, S., Olijslagers, S., Hallinan, J. & Wipat, A. 2010. Feedback between p21 and reactive oxygen production is necessary for cell senescence. *Molecular systems biology,* 6**,** 347.

119. Perluigi, M., Di Domenico, F. & Butterfield, D. A. 2015. Mtor signaling in aging and neurodegeneration: At the crossroad between metabolism dysfunction and impairment of autophagy. *Neurobiology of disease,* 84**,** 39-49.
120. Pfeiffer, V. & Lingner, J. 2012. Terra promotes telomere shortening through exonuclease 1–mediated resection of chromosome ends. *PLoS genetics,* 8**,** e1002747.
121. Qiang, L., Zhao, B., Shah, P., Sample, A., Yang, S. & He, Y.-Y. 2016. Autophagy positively regulates DNA damage recognition by nucleotide excision repair. *Autophagy,* 12**,** 357-368.
122. Rabinovitch, R. C., Samborska, B., Faubert, B., Ma, E. H., Gravel, S.-P., Andrzejewski, S., Raissi, T. C., Pause, A., Pierre, J. S.-. & Jones, R. G. 2017. Ampk maintains cellular metabolic homeostasis through regulation of mitochondrial reactive oxygen species. *Cell reports,* 21**,** 1-9.
123. Rinon, A., Molchadsky, A., Nathan, E., Yovel, G., Rotter, V., Sarig, R. & Tzahor, E. 2011. P53 coordinates cranial neural crest cell growth and epithelial-mesenchymal transition/delamination processes. *Development,* 138**,** 1827-1838.
124. Rodić, N., Sharma, R., Sharma, R., Zampella, J., Dai, L., Taylor, M. S., Hruban, R. H., Iacobuzio-Donahue, C. A., Maitra, A. & Torbenson, M. S. 2014. Long interspersed element-1 protein expression is a hallmark of many human cancers. *The American journal of pathology,* 184**,** 1280-1286.
125. Römer, C. 2021. Viruses and endogenous retroviruses as roots for neuroinflammation and neurodegenerative diseases. *Frontiers in Neuroscience,* 15**,** 648629.
126. Roos, C. M., Zhang, B., Palmer, A. K., Ogrodnik, M. B., Pirtskhalava, T., Thalji, N. M., Hagler, M., Jurk, D., Smith, L. A. & Casaclang-Verzosa, G. 2016. Chronic senolytic treatment alleviates established vasomotor dysfunction in aged or atherosclerotic mice. *Aging cell,* 15**,** 973-977.
127. Ryzhkova, A. I., Sazonova, M. A., Sinyov, V. V., Galitsyna, E. V., Chicheva, M. M., Melnichenko, A. A., Grechko, A. V., Postnov, A. Y., Orekhov, A. N. & Shkurat, T. P. 2018. Mitochondrial diseases caused by mtdna mutations: A mini-review. *Therapeutics and clinical risk management***,** 1933-1942.
128. Salminen, A. & Kaarniranta, K. 2012. Amp-activated protein kinase (ampk) controls the aging process via an integrated signaling network. *Ageing research reviews,* 11**,** 230-241.
129. Schriner, S. E., Linford, N. J., Martin, G. M., Treuting, P., Ogburn, C. E., Emond, M., Coskun, P. E., Ladiges, W., Wolf, N. & Van Remmen, H. 2005. Extension of murine life span by overexpression of catalase targeted to mitochondria. *science,* 308**,** 1909-1911.
130. Schumacher, B., Pothof, J., Vijg, J. & Hoeijmakers, J. H. 2021. The central role of DNA damage in the ageing process. *Nature,* 592**,** 695-703.
131. Sedivy, J. M., Kreiling, J. A., Neretti, N., Cecco, M. D., Criscione, S. W., Hofmann, J. W., Zhao, X., Ito, T. & Peterson, A. L. 2013. Death by transposition–the enemy within? *Bioessays,* 35**,** 1035-1043.
132. Sen, P., Dang, W., Donahue, G., Dai, J., Dorsey, J., Cao, X., Liu, W., Cao, K., Perry, R. & Lee, J. Y. 2015. H3k36 methylation promotes longevity by enhancing transcriptional fidelity. *Genes & development,* 29**,** 1362-1376.
133. Sen, P., Shah, P. P., Nativio, R. & Berger, S. L. 2016. Epigenetic mechanisms of longevity and aging. *Cell,* 166**,** 822-839.
134. Singh, P. P., Demmitt, B. A., Nath, R. D. & Brunet, A. 2019. The genetics of aging: A vertebrate perspective. *Cell,* 177**,** 200-220.
135. Sirbu, B. M. & Cortez, D. 2013. DNA damage response: Three levels of DNA repair regulation. *Cold Spring Harbor perspectives in biology,* 5**,** a012724.
136. Storer, M., Mas, A., Robert-Moreno, A., Pecoraro, M., Ortells, M. C., Di Giacomo, V., Yosef, R., Pilpel, N., Krizhanovsky, V. & Sharpe, J. 2013. Senescence is a developmental mechanism that contributes to embryonic growth and patterning. *Cell,* 155**,** 1119-1130.
137. Stratton, M. R., Campbell, P. J. & Futreal, P. A. 2009. The cancer genome. *Nature,* 458**,** 719-724.
138. Sugimoto, M. 2014. A cascade leading to premature aging phenotypes including abnormal tumor profiles in werner syndrome. *International journal of molecular medicine,* 33**,** 247-253.
139. Sun, N., Youle, R. J. & Finkel, T. 2016. The mitochondrial basis of aging. *Molecular cell,* 61**,** 654-666.
140. Sun, W., Samimi, H., Gamez, M., Zare, H. & Frost, B. 2018. Pathogenic tau-induced pirna depletion promotes neuronal death through transposable element dysregulation in neurodegenerative tauopathies. *Nature neuroscience,* 21**,** 1038-1048.
141. Sun, Y., Coppé, J.-P. & Lam, E. W.-F. 2018. Cellular senescence: The sought or the unwanted? *Trends in Molecular Medicine,* 24**,** 871-885.
142. Swenberg, J. A., Lu, K., Moeller, B. C., Gao, L., Upton, P. B., Nakamura, J. & Starr, T. B. 2011. Endogenous versus exogenous DNA adducts: Their role in carcinogenesis, epidemiology, and risk assessment. *Toxicological sciences,* 120**,** S130-S145.
143. Tateossian, H., Morse, S., Simon, M. M., Dean, C. H. & Brown, S. D. 2015. Interactions between the otitis media gene, fbxo11, and p53 in the mouse embryonic lung. *Disease models & mechanisms,* 8**,** 1531-1542.
144. Templeman, N. M. & Murphy, C. T. 2018. Regulation of reproduction and longevity by nutrient-sensing pathways. *Journal of Cell Biology,* 217**,** 93-106.

145. Toyama, E. Q., Herzig, S., Courchet, J., Lewis Jr, T. L., Losón, O. C., Hellberg, K., Young, N. P., Chen, H., Polleux, F. & Chan, D. C. 2016. Amp-activated protein kinase mediates mitochondrial fission in response to energy stress. *Science,* 351**,** 275-281.
146. Trifunovic, A., Hansson, A., Wredenberg, A., Rovio, A. T., Dufour, E., Khvorostov, I., Spelbrink, J. N., Wibom, R., Jacobs, H. T. & Larsson, N.-G. 2005. Somatic mtdna mutations cause aging phenotypes without affecting reactive oxygen species production. *Proceedings of the National Academy of Sciences,* 102**,** 17993-17998.
147. Valentin-Vega, Y. A., Maclean, K. H., Tait-Mulder, J., Milasta, S., Steeves, M., Dorsey, F. C., Cleveland, J. L., Green, D. R. & Kastan, M. B. 2012. Mitochondrial dysfunction in ataxia-telangiectasia. *Blood, The Journal of the American Society of Hematology,* 119**,** 1490-1500.
148. Van Der Laan, L., Cardenas, A., Vermeulen, R., Fadadu, R. P., Hubbard, A. E., Phillips, R. V., Zhang, L., Breeze, C., Hu, W. & Wen, C. 2022. Epigenetic aging biomarkers and occupational exposure to benzene, trichloroethylene and formaldehyde. *Environment international,* 158**,** 106871.
149. Vermeij, W., Dollé, M., Reiling, E., Jaarsma, D., Payan-Gomez, C., Bombardieri, C. R., Wu, H., Roks, A., Botter, S. & Van Der Eerden, B. 2016. Restricted diet delays accelerated ageing and genomic stress in DNA-repair-deficient mice. *Nature,* 537**,** 427-431.
150. Vermulst, M., Wanagat, J., Kujoth, G. C., Bielas, J. H., Rabinovitch, P. S., Prolla, T. A. & Loeb, L. A. 2008. DNA deletions and clonal mutations drive premature aging in mitochondrial mutator mice. *Nature genetics,* 40**,** 392-394.
151. Vijg, J. 2014. Somatic mutations, genome mosaicism, cancer and aging. *Current opinion in genetics & development,* 26**,** 141-149.
152. Vijg, J. 2021. From DNA damage to mutations: All roads lead to aging. *Ageing Research Reviews,* 68**,** 101316.
153. Vijg, J. & Dong, X. 2020. Pathogenic mechanisms of somatic mutation and genome mosaicism in aging. *Cell,* 182**,** 12-23.
154. Volkman, H. E. & Stetson, D. B. 2014. The enemy within: Endogenous retroelements and autoimmune disease. *Nature immunology,* 15**,** 415-422.
155. Von Zglinicki, T. 2002. Oxidative stress shortens telomeres. *Trends in biochemical sciences,* 27**,** 339-344.
156. Wang, J. Y., Peng, S. H., Ning, X. H., Li, T., Liu, S. J., Liu, J. Y., Hong, B. A., Qi, N. N., Peng, X. & Zhou, B. W. 2017. Shorter telomere length increases age-related tumor risks in von hippel-lindau disease patients. *Cancer Medicine,* 6**,** 2131-2141.
157. Wang, Y., Yuan, Q. & Xie, L. 2018. Histone modifications in aging: The underlying mechanisms and implications. *Current stem cell research & therapy,* 13**,** 125-135.
158. Wang, Y., Zhang, N., Zhang, L., Li, R., Fu, W., Ma, K., Li, X., Wang, L., Wang, J. & Zhang, H. 2016. Autophagy regulates chromatin ubiquitination in DNA damage response through elimination of sqstm1/p62. *Molecular cell,* 63**,** 34-48.
159. Wątroba, M. & Szukiewicz, D. 2016. The role of sirtuins in aging and age-related diseases. *Advances in medical sciences,* 61**,** 52-62.
160. Wiley, C. D., Velarde, M. C., Lecot, P., Liu, S., Sarnoski, E. A., Freund, A., Shirakawa, K., Lim, H. W., Davis, S. S. & Ramanathan, A. 2016. Mitochondrial dysfunction induces senescence with a distinct secretory phenotype. *Cell metabolism,* 23**,** 303-314.
161. Wood, J. G., Hillenmeyer, S., Lawrence, C., Chang, C., Hosier, S., Lightfoot, W., Mukherjee, E., Jiang, N., Schorl, C. & Brodsky, A. S. 2010. Chromatin remodeling in the aging genome of drosophila. *Aging cell,* 9**,** 971-978.
162. Wood, R. D. 2018. Fifty years since DNA repair was linked to cancer. Nature Publishing Group UK London.
163. Wu, Z., Zhang, W., Song, M., Wang, W., Wei, G., Li, W., Lei, J., Huang, Y., Sang, Y. & Chan, P. 2018. Differential stem cell aging kinetics in hutchinson-gilford progeria syndrome and werner syndrome. *Protein & cell,* 9**,** 333-350.
164. Yang, W. & Hekimi, S. 2010. A mitochondrial superoxide signal triggers increased longevity in caenorhabditis elegans. *PLoS biology,* 8**,** e1000556.
165. Yi, S.-J. & Kim, K. 2020. New insights into the role of histone changes in aging. *International journal of molecular sciences,* 21**,** 8241.
166. Yousefzadeh, M., Henpita, C., Vyas, R., Soto-Palma, C., Robbins, P. & Niedernhofer, L. 2021. DNA damage—how and why we age? *Elife,* 10**,** e62852.
167. Yue, L. & Yao, H. 2016. Mitochondrial dysfunction in inflammatory responses and cellular senescence: Pathogenesis and pharmacological targets for chronic lung diseases. *British journal of pharmacology,* 173**,** 2305-2318.
168. Zhang, P., Kishimoto, Y., Grammatikakis, I., Gottimukkala, K., Cutler, R. G., Zhang, S., Abdelmohsen, K., Bohr, V. A., Misra Sen, J. & Gorospe, M. 2019. Senolytic therapy alleviates aβ-associated oligodendrocyte progenitor cell senescence and cognitive deficits in an alzheimer's disease model. *Nature neuroscience,* 22**,** 719-728.

169. Zhang, W., Li, J., Suzuki, K., Qu, J., Wang, P., Zhou, J., Liu, X., Ren, R., Xu, X. & Ocampo, A. 2015. A werner syndrome stem cell model unveils heterochromatin alterations as a driver of human aging. *Science,* 348**,** 1160-1163.
170. Zhao, L., Cao, J., Hu, K., He, X., Yun, D., Tong, T. & Han, L. 2020. Sirtuins and their biological relevance in aging and age-related diseases. *Aging and disease,* 11**,** 927.
171. Zhou, D., Borsa, M. & Simon, A. K. 2021. Hallmarks and detection techniques of cellular senescence and cellular ageing in immune cells. *Aging Cell,* 20**,** e13316.
172. Zhu, D., Wu, X., Zhou, J., Li, X., Huang, X., Li, J., Wu, J., Bian, Q., Wang, Y. & Tian, Y. 2020. Nurd mediates mitochondrial stress–induced longevity via chromatin remodeling in response to acetyl-coa level. *Science advances,* 6**,** eabb2529.
173. Zhu, Y., Liu, X., Ding, X., Wang, F. & Geng, X. 2019. Telomere and its role in the aging pathways: Telomere shortening, cell senescence and mitochondria dysfunction. *Biogerontology,* 20**,** 1-16.
174. Zhunina, O. A., Yabbarov, N. G., Grechko, A. V., Starodubova, A. V., Ivanova, E., Nikiforov, N. G. & Orekhov, A. N. 2021. The role of mitochondrial dysfunction in vascular disease, tumorigenesis, and diabetes. *Frontiers in Molecular Biosciences,* 8**,** 671908.