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Genetic Aging: Mechanisms, Determinants and Their Role in Human Disease

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KEYWORDS

Genetic aging; DNA damage; Epigenetics; Age-related diseases, Telomere shortenings.

ABSTRACT

Aging is a universal biological phenomenon characterize by a time-dependent, decline in organismal function, manifested by a gradual increase in risk of disease and death (leading to increased vulnerability to disease and mortality). Age-related genetic and epigenetic changes… are critically implicated in major chronic and degenerative diseases, including cancer, cardiovascular diseases, neurodegenerative conditions, and metabolic syndromes. In this narrative review, we discuss key findings related to molecular mechanisms of aging and maturation processes influenced by intrinsic and extrinsic factors, and we highlight how these interconnected pathways contribute to human disease. An extensive electronic literature search was performed (Google Scholar databases) to include English language articles from 2015 to 2025. Studies have been chosen according to their relevance, scientific value and contribution to explaining genetic mechanisms of aging. The available evidence from the studies reviewed suggests that genetic aging is caused by a still-interacting series of processes, among which are genomic instability, telomere shortening, DNA damage accumulation, epigenomic dysregulation, mitochondrial dysfunction and changes in nutrient-sensing pathways. These phenomena are highly influenced by environmental, lifestyle and social modifications which lead to cellular senescence, tissue degeneration and increased susceptibility to diseases. Furthermore, knowledge from model organisms especially the nematode Caenorhabditis elegans has provided evidence for conserved function of insulin/insulin-like growth factor-1 signaling in life and health span regulation. In Overview, genetic aging may be interpreted as a multicomponent and dynamic process combining the individual genotype with epigenetic or environmental factors. A deeper understanding of these mechanisms is essential for identifying biomarkers of biological aging and developing interventions that enhance healthy aging and reduce age associated disease burden.

1. INTRODUCTION

Aging is a sophisticated and multilayered biological phenomenon that occurs in humans at molecular, cellular tissue or systemic levels [1]. It is caused by the slow, continuous build-up of molecular damage and failure of cellular repair and maintenance systems that eventually cause functional decline and greater vulnerability to disease. In turn, aging is the major risk factor for many chronic degenerative conditions such as cancer, cardiovascular diseases, metabolic syndromes and neurodegenerative diseases [2]. Molecularly, aging is described by genetic and epigenetic changes which affect both genomic integrity and cellular homeostasis [3]. Genetic aging is a process characterized by the progressive accumulation of molecular changes affecting the genome: telomere attrition, DNA damage build-up, decreased in DNA repair capacity, genomic instability and epigenetic dysregulation. Such changes perturb the normal

program of gene expression and cellular activity, leading either to a stage of cellular senescence or apoptosis [4]. Beside intrinsic genetic factors, aging is highly influenced by extrinsic determinants such as oxidative stress, chronic inflammation, environmental exposures, psychosocial stressors and lifestyle [5]. These factors also modify the speed of genetic and epigenetic aging and underpin marked interindividual variability in aging courses [6]. Infectious diseases is associated with aging, it is one feature of a broader biological aging phenomenon and a direct result of long-term risk for disease due to persistent molecular change [7]. Increasing evidence has clearly connected genetic aging and the pathogenesis of common human diseases [8]. Genomic instability and epigenetic dysregulation are predominant in cancer, mitochondrial dysfunction and defective DNA repair have become important in neurodegenerative diseases, and aging-associated genetic changes drive endothelial cell dysfunction, inflammation, and metabolic disturbance in cardiovascular/metabolic diseases [9]. These findings emphasize the importance of genetic aging as a common biological mechanism for various age-related pathologies [10].

2. AIM OF THE REVIEW

The aim of this narrative review is

1. Critically portray current knowledge on the molecular determinants driving genetic and epigenetic aging.
2. Pinpoint organ-centric innate and environmental regulators which impact genomic alterations upon aging.
3. Elucidate how these mechanisms contribute to common human diseases.
4. Synthesize the findings from molecular biology, model organism research and human epidemiology, focusing on the clinical relevance of genetic aging in health span interventions and disease prevention.

3. DETERMINANTS OF GENETIC AGING

Genetic aging is determined by a complex interplay of intrinsic and extrinsic factors that, together, determine the rate and course of molecular senescence. At the baseline, genetic determinants (i.e., inherited polymorphism/mutations in genes for DNA repair, telomere maintenance, antioxidant defense and metabolism regulation) set a baseline rate at which genome stability can be maintained [7]. Mutations in genes including FOXO3, SIRT1, and insulin/IGF-1 pathway genes contribute to increased longevity and increased resistance to stress; aging is accelerated and early-onset age-related diseases are more common if genome maintenance mechanisms fail [8].

Epigenetic control serve as dynamic link between the genome and environmental exposures (chemical and toxicant exposures, dietary and nutritional factors, lifestyle and behavior exposures and biological and physical factors) [6]. Epigenetic drift, which refers to age-induced change in DNA methylation patterns, histone modifications, and chromatin configuration, accumulates throughout aging and disturbs transcriptional stability and cell identity. In contrast to static genetic mutations, epigenetic changes are at least partially reversible and therefore they have potential as intervention targets. Epigenetic clocks are robust predictors of biological age, which capture unique aging courses of individuals [10]. Environmental and lifestyle factors effect on genome integrity and epigenetic regulation not on DNA sequence through their effects on oxidative stress, inflammation and DNA damage. Prolonged ultraviolet exposure, air pollutants, carcinogens or ionizing radiation increase the rate of loss of genomic stability and shortening of telomeres. Poor diet, lack of physical activity, smoking and psychological stress all worsen exacerbate molecular damage, while balanced nutrition, regular exercise and caloric restriction promote genome maintenance and help delay biological ageing [10]. Caloric restriction-associated metabolic and nutrient-sensing pathways such as insulin/IGF-1, mTOR, AMPK, and sirtuins coordinate energy availability with cellular repair. Dysregulation of these pathways accelerates aging by compromising components including autophagy, oxidative stress and stress resistance, while interventions such as caloric restriction or mTOR inhibition have been shown to extend both lifespan and healthspan across organisms [11]. Inflammation and the immune system act as both causes and effects of aging. Chronic subclinical inflammation, known as “inflammaging,” is the result of age-dependent alteration in immune function and contributes to DNA damage, epigenetic changes, cellular senescence leading to aging tissue dysfunction and disease [12]. Psychosocial stress and endocrinological regulation are further regulators of genetic aging. Chronic stress raises glucocorticoids, promotes oxidative stress and telomere loss, and leads to undesirable changes in epigenetic marks. The decreased sex hormones, growth hormone and melatonin associated with age add further insult to genome maintenance, mitochondrial function, and repair capacity(s) [13]. In general, rather than independently fulfilling their actions, these factors dynamically interact and collectively establish the balance between molecular lesion and cellular repair. This unified framework emphasizes the multi-scale control of aging, and sets the stage for personalizing interventions to postpone age-related decline and disease [14].

4. ROLE OF GENETIC AGING IN HUMAN DISEASE

Genetic aging constitutes a fundamental biological driver of many human diseases. Rather, age-associated genetic and epigenetic events are actively promoting cellular dysfunction, tissue degeneration and systemic susceptibility to chronic diseases [14]. Central to these processes are the mechanisms of genomic instability, telomere attrition, epigenetic regulation, and mitochondrial mitrochondrial function that interact over the lifespan first underlying disease susceptibility and severity but also potentially sensitivity to therapeutic response (Figure 1) [15].

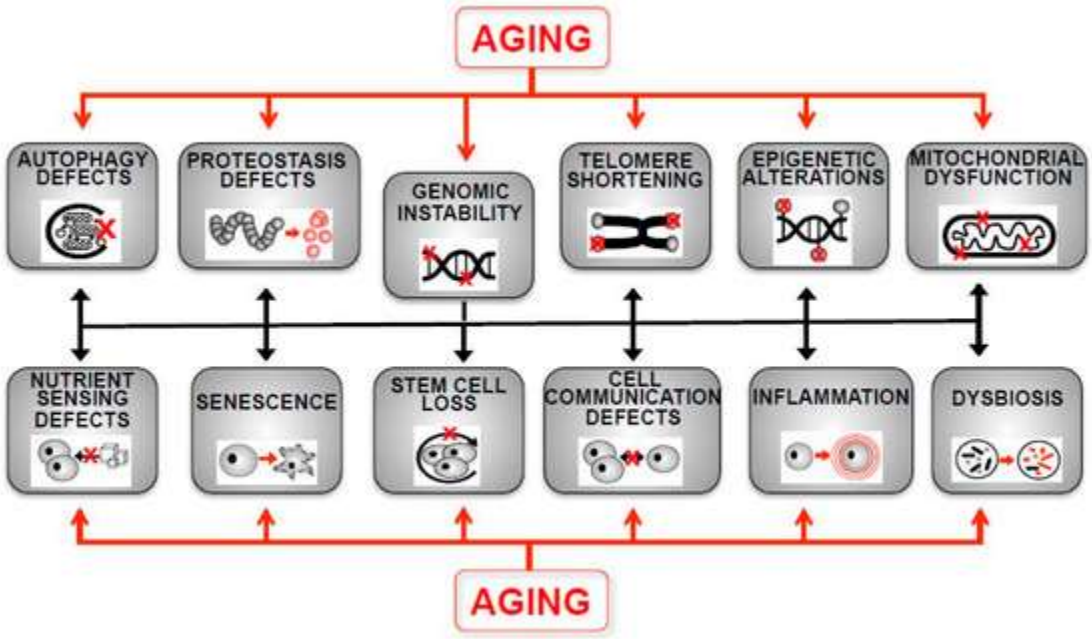

Fig1. Interconnected mechanisms of genetic aging highlight the central role of genomic instability in driving other hallmarks of aging [15].

Genetic aging is a central biological mechanism which serves as biological underpins basis for many age-related diseases, where progressive accumulation of molecular damage erode integrity and performance of cells over tissues [16]. Finally, perhaps the clearest example for a clinical manifestation of genetic aging is cancer. Progressively, genomic instability, DNA repair machinery inefficiency and telomere dysfunction result in the accrual of mutations and chromosomal alterations contributing to malignant transformation. Whereas telomere shortening early in tumorigenesis may exert an initial break on tumor development by restricting cellular replication, severe telomeric dysfunction can, paradoxically, be a source of generalized genomic instability that fuels cancer growth. Concomitantly, age-related epigenetic alterations including aberrant DNA methylations, modifications of histones or remodeling of chromatin can add to activation of oncogenes as well as silencing of tumor suppressor genes and these observations go in line with the dramatically increased incidence of cancer during aging [17].

Genetic aging is also prominent in the pathogenesis of cardiovascular disease from accumulated insults to both vascular and cardiac cells [18]. Telomere attrition in endothelial and smooth muscle cells is thought to be associated with endothelial dysfunction, increased arterial stiffness, and atherosclerosis. Concomitantly, mitochondrial impairment and increased oxidative stress perturb mitochondrial dysfunction disrupts cardiac energetics and amplifies inflammatory signaling. Epigenetic reprogramming in the vascular system changes gene expression of lipid metabolism, immune activation, and tissue regeneration, which drive cardiovascular aging promoting susceptibility to ischemia [12]. Because neuronal cells are capable of only limited regeneration, genetic aging has a strong impact on neurodegenerative disorders. Neurons are highly sensitive to synaptic failure and neuronal loss due to a gradual accumulation of DNA damage, dysfunctional protein homeostasis and mitochondrial function [19]. Epigenetic disturbances also upset gene expression necessary for synaptic plasticity and cognitive functioning. Impairments in DNA repair and mitochondrial quality control lead to toxic protein aggregation, which is implicated in neurodegenerative diseases like Alzheimer's and Parkinson's [16]. Metabolic endocrinopathies are also exacerbated by aging-related genetic alterations that impair insulin signaling, mitochondrial function and adaptive cellular stress-responsive systems [20]. They induce the deregulation of insulin/IGF-1 and mTOR that are responsible for glucose

homeostasis, insulin sensitivity, and lipid metabolism. In addition, shortening of telomeres not only in pancreatic β-cells but also in peripheral tissue deteriorates metabolic flexibility, and epigenetic changes provide further support for maladaptive gene expression patterns by which the risk for T2DM and its complications is enhanced [21]. Immune function in humans is profoundly altered with age, resulting in immunosenescence and chronic low-grade inflammation, this including: 1. Immune cells are limited by genomic instability and telomere shortening in their proliferative capacity leading to diminished adaptive immune response. 2. Exhibit persistent pro-inflammatory transcription owing to lifelong epigenetic remodeling 3. Circulating BAFF levels increase with age and contribute to greater risk of infection, impaired vaccine response, and heightened incidence of chronic inflammatory and autoimmune diseases in elderly individuals [19]. The comorbidity with senescence-related diseases in aged communities indicates that genetic aging is systemic. Common molecular pathways—genomic instability, mitochondrial dysfunction and cellular senescence—acting in parallel can be targeted to protect multiple organ systems. This intersectional pathology is thought to be the reason why single disease treatment strategies for the elderly have limited efficacy, and supports a rationale to target basic aging processes [22].

5. INSULIN CONTROL OF *C. ELEGANS* METABOLISM, DEVELOPMENT, AND LONGEVITY

While all somatic cells have the same genome, aging largely arises from dynamic epigenetic remodeling that alters gene expression programs that play a critical role in integrating genetic predisposition with environmental exposures. Family history in general affects susceptibility to age-related diseases through a combination of inherited factors, shared environmental factors and gene-environment interactions. Environmental factors including nutrition, psychosocial stress, early-life adversity and social conditions all result in lasting modifications of the epigenetic code to influence gene expression and disease risk over a lifetime [23]. Important epigenetic mechanisms such as DNA methylation, histone modification and regulation of gene expression by non-coding RNAs can modulate the chromatin structure and transcription activity. Age-related dysregulation of these processes underlies the activation and silencing of genes relating to cardiovascular health, metabolism and stress response, rendering them inflamed, metabolically compromised and vulnerable to chronic diseases. DNA methylation patterns additionally serve as the foundation for epigenetic clocks, tools that provide estimates of biological age and predict health-related endpoints [24]. Critical developmental windows, such as gametogenesis, embryonic development and early postnatal development are highly susceptible due to the profound epigenetic reprogramming that establishes long-term gene regulation. Early environmental and social experiences may have long-term effects on brain development, stress regulation, and cognitive function [25]. Genetic aging is the life-long interplay between inherited genomic integrity and environmentally induced epigenetic changes. Delineation of these mechanisms offers key insights into the etiology of age-related diseases and suggests therapeutic strategies, such as targeting senescent cells [26], altering epigenetic regulation or optimizing metabolism to drive healthy ageing and decrease multimorbidity (Figure 2) [27].

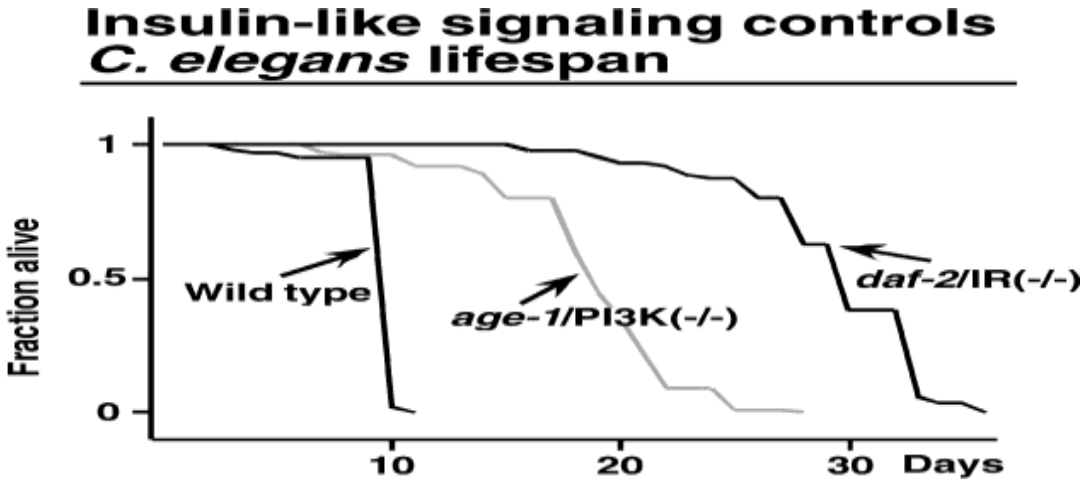

Fig 2. Regulation of life span by the daf-2 insulin signaling pathway. *C. elegans* animals bearing reduction of function mutations in the insulin-like receptor gene daf-2 or the downstream phosphatidylinositol kinase 3 gene age-1 live much longer than wild type [28].

The IIS pathway functions in a broader neuroendocrine system that receives and integrates environmental signals such as nutrient levels, temperature, and population density to control developmental choices and energy storage [29]. Under unfavorable environmental conditions, this pathway induces dauer diapause, an alternative developmental stage that is stress-resistant and long-lived. Two main classes of mutants defective in this process have been isolated from genetic screens: dauer-constitutive and dauer-defective mutants. These genetic interactions formed the basis to develop parallel signaling pathways that converge on dauer formation and life span regulation [29].

Epistasis analysis indicates that *daf-2,age-1,pdk-1,daf-18 and akt-1,akt-2*, but not daf-16 are associated with the longevity-regulating function of the IIS in C. elegans. Diminished IIS activity promotes the activation and nuclear translocation of FOXO transcription factor daf-16, which upregulates genes implicated in resistance to stress, autophagy, detoxification, and metabolic balance. Concurrently, the *daf-7,daf-1,daf-4,daf-8,daf-14,daf-3* pathway is an insulin-like transforming growth factor (TGF) β–like signaling system that intersects with IIS in control of dauer arrest and age-appropriate phenotypes [30].

Crucially, the insulin/IGF-1 signaling is highly conserved evolutionarily, from worms to mammals and man. In humans, disturbed insulin/IGF-1 signaling is strongly linked to age-associated diseases such as type 2 diabetes mellitus, obesity, cardiovascular disease, cancer and neurodegenerative disorders [31]. Therefore, genetic manipulation of the IIS not only affects lifespan but also health span, highlighting its essential function in human genetic aging and disease susceptibility [32]. Modulations in IIS activity influence various aspects of aging including oxidative damage, mitochondrial dysfunction, chronic inflammation and cellular senescence. Downregulation of the IIS promotes increased resistance to cellular stress and a delay in the onset age-related pathologies, while prolonged activation is thought to accelerate aging and elevate disease susceptibility [33]. Cumulatively, studies of C. elegans suggest that insulin-like signaling represents a central genetic pathway involved in aging. These evolutionary conserved pathways are major longevity and age-related disease risk factors, highlighting the translational importance of model organism research into the genetics of human aging and identification of potential therapies [34].

6. CONCLUSION

Aging is a mix of many factors that act in an integrated manner and include both genetic, epigenetic, cellular, and environmental determinants. At the center of this process is genomic instability which crosstalk's with other hallmarks of ageing in order to drive loss of function and disease susceptibility. The hallmarks of aging including telomere shortening, epigenetic modification, mitochondrial dysfunction, cellular senescence and inflammation. The epigenetic regulation of the genome is increasingly recognized as pivotal in mediating relationships between genetic predilection and exposure to environmental and social determinants of health, which accounts for much of the interindividual variation observed in age-related profiles. Gero science approaches including, DNA methylation–based biomarkers represent powerful tools for quantifying biological aging, examining early-life and social exposures that drive changes in the pace of aging, and evaluating interventions before disease onset. The fusion of molecular biology with social and behavioral sciences is also critical to reduce health disparities, and facilitate the development of interventions that support healthy aging and equity in health across populations.

Future Research Directions and Clinical Implications

Future studies should thus pursue longitudinal and mechanistic approaches to further understand the biological pathways involved in aging processes such as cellular senescence, mitochondrial dysfunction, genomic instability and chronic low-grade inflammation. Additionally, further exploration of the potential associations through large-scale multicenter cohort studies is warranted to account for the genetic, environmental and lifestyle-related modifiers of aging trajectories. Additionally, incorporation of omics-based approaches (genomics, epigenomics, proteomics and metabolomics) may elucidate better healthy versus pathological aging predictive biomarkers. From the standpoint of clinical implications, knowledge of the biological determinants and mechanisms that lead to aging is now widely believed to be critical for doing so permit early risk stratification tailored preventive strategies and novel interventions aimed at prolonging health span rather than simply lifespan. However, translating to clinic needs solid validation, standardized assessment tools and properly designed interventional trials for safety and efficiency.

Conflict of Interest

The authors declare no conflict of interest.

Publication agreement

I have read and approved the final version of the manuscript for publication.

Data Availability
I declare that all data has been included in the manuscript.

Author's contribution
G.M.K. collected and analyzed the data and wrote the manuscript.

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الشيخوخة الجينية: آلياتها ومحدداتها ودورها في الأمراض البشرية

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الملخص

تعدّ الشيخوخة ظاهرة بيولوجية كونية تتميّز بانخفاض تدريجي معتمد على الزمن في كفاءة وظائف الكائن الحي، ويتجلى ذلك في الازدياد المتصاعد لمخاطر الإصابة بالأمراض والوفيات. وترتبط التغيرات الجينية واللاجينية المرتبطة بالتقدم في العمر ارتباطًا وثيقًا بالعديد من الأمراض المزمنة والتنكسية الكبرى، بما في ذلك السرطان، وأمراض القلب والأوعية الدموية، والاضطرابات العصبية التنكسية، والمتلازمات الأيضية. في هذه المراجعة السردية، نستعرض أبرز النتائج المتعلقة بالآليات الجزيئية للشيخوخة وعمليات النضج المتأثرة بعوامل داخلية وخارجية، مع تسليط الضوء على كيفية تداخل هذه المسارات البيولوجية وتأثيرها في تطور الأمراض لدى الإنسان. وقد أُجري بحث إلكتروني موسع عبر قواعد بيانات Google Scholar لتضمين الدراسات المنشورة باللغة الإنجليزية خلال الفترة من 2015 إلى 2025، وتم اختيار الدراسات بناءً على صلتها العلمية وقيمتها البحثية وإسهامها في تفسير الآليات الجينية للشيخوخة. تشير الأدلة المتاحة إلى أن الشيخوخة الجينية تنجم عن سلسلة متشابكة من العمليات البيولوجية، تشمل عدم الاستقرار الجينومي، وقِصَر التيلوميرات، وتراكم أضرار الحمض النووي، واضطراب التنظيم اللاجيني، واختلال وظيفة الميتوكوندريا، والتغيرات في مسارات استشعار المغذيات. وتتأثر هذه الظواهر بدرجة كبيرة بالعوامل البيئية ونمط الحياة والمتغيرات الاجتماعية، مما يؤدي إلى حدوث الشيخوخة الخلوية، وتنكس الأنسجة، وزيادة القابلية للإصابة بالأمراض. علاوةً على ذلك، وفرت الدراسات على الكائنات النموذجية، ولا سيما الدودة الخيطية *Caenorhabditis elegans* ، أدلة مهمة على المحافظة التطورية لمسار إشارات الإنسولين/عامل النمو الشبيه بالإنسولين-1 في تنظيم العمر والصحة الوظيفية. وبوجه عام، يمكن تفسير الشيخوخة الجينية على أنها عملية ديناميكية متعددة المكونات تنشأ عن التفاعل بين النمط الجيني للفرد والعوامل اللاجينية والبيئية. ويُعد الفهم الأعمق لهذه الآليات أمرًا جوهريًا لتحديد المؤشرات الحيوية للشيخوخة البيولوجية وتطوير تدخلات علاجية تعزز الشيخوخة الصحية وتحد من عبء الأمراض المرتبطة بالعمر.

الكلمات المفتاحية
الشيخوخة الجينية؛ تلف الحمض النووي؛ علم التخلق؛ الأمراض المرتبطة بالعمر؛ تلف التيلوميرات.