Syed Ibrahim Rizvi *Editor*

Emerging Anti-Aging Strategies

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Foreword

Population aging is one of the main global challenges for sustainable development. The results of fundamental research of the last decade in the field of biogerontology have led to the understanding that the rate of aging can be modified by influencing the basic processes associated with aging, using pharmacological, nonpharmacological, genetic, and gene-therapy interventions, as well as regenerative technologies, with the achievement of a healthier and longer life. There are prerequisites for reducing the burden of both age-associated diseases and geriatric syndromes, primarily frailty syndrome. Managing the aging processes can prevent or at least slow down the onset and progression of these conditions.

This multifaceted book provides an overview of the entire arsenal of modern antiaging technologies.

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Preface

As humankind acquired intelligence during the evolutionary process, its first scientific pursuit involved finding ways to live longer. History is replete with human endeavor of devising ways for a longer lifespan. The ancient Indian text Rigveda (>1000 BC) mentions a drink "**amrita**" that can bestow immortality. Modern science however had little understanding of the mechanism(s) of aging until the 1950s, which is evident from the lecture of Sir Peter Medavar delivered at University College London in 1951, entitled "An Unsolved Problem in Biology."

The last few decades have witnessed tremendous advances in the understanding of molecular events which underline the process of aging. It is therefore a big achievement of science that we now have a clear understanding of the hallmarks of aging. This understanding has provided biogerontologists with putative "targets" which can be exploited for possible antiaging strategies.

The dust is now almost settling on the debate whether human lifespan can be increased. It is being acknowledged that humans have already achieved the highest limit of their lifespan. In this backdrop, antiaging strategies are thus limited to finding ways to increase the healthy lifespan. The major impediment in devising an antiaging strategy is due to the fact that the aging process is highly heterochronic.

Despite the complexities of the aging process, new scientific evidence emerging with extensive research continues to present interesting targets for devising antiaging strategies. The present book is an attempt to provide a compact source of emerging antiaging strategies which offer hope for a longer health span.

Recent evidence provides a strong support to the concept of calorie restriction as a mechanism to derive an antiaging effect. Chapters 4 and 10 provide an update on our current understanding of the effect of CR on aging. The role of nutritional supplements, for example coenzyme Q, curcumin, and spermidine, has been discussed in Chaps. 2, 8, and 11.

Circadian rhythm is being intensively investigated in relation to factors which play a role in aging. The role of melatonin in the aging process and associated disorders is discussed in Chap. 9. Metformin, the common antidiabetic drug, is being extensively investigated for its possible antiaging effects; Chap. 6 details the current status of research on metformin with respect to skin aging. Autophagy induction and sirtuin activation are again promising areas which are being actively investigated (Chaps. 3 and 14).

An interesting Chap. 16 is on the cognitive and emotional aspects of aging. Frequently, research on rodent model of aging is used to derive conclusions for humans. It thus becomes important to understand the age-adjustments with respect to rodents when the same are applied to humans (Chap. 18).

Research on antiaging may sound so exciting to humans but tinkering into nature's design may throw up unknown consequences. With many new technologies finding their way into the human lexicon, there is a need to debate on the ethical issues involved. Chapter 15 is an interesting update on the conceptual and ethical aspects.

I would like to thank all the contributors who provided me with their excellent chapters making possible the compilation of this book.

Allahabad, Uttar Pradesh, India Syed Ibrahim Rizvi

Contents

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About the Editor

Syed Ibrahim Rizvi is Professor of Biochemistry and Dean of Research and Development at the University of Allahabad, India. He is a Visiting Professor to Ohio State University, University of Rome, University of Milan, University of Athens, University of Nice, University of Szeged, University of Pisa, Karolinska Institute, Slovak Academy of Sciences, Istanbul University, and Bangladesh Institute of Health Sciences. He has also been an invited speaker to major conferences in the USA, Russia, Hungary, Italy, Saudi Arabia, Kuwait, Egypt, Bangladesh, and Thailand. Prof Rizvi has done seminal research work in the area of mechanism(s) of aging, antiaging interventions and lifespan. He has published extensively in high-impact factor journals. To date Prof Rizvi has published more than 200 research papers. He is on the editorial board of the prestigious Springer journal *Biogerontology*. Prof Rizvi has been a recipient of grants from the International Cell Research Organization, Federation of European Biochemical Societies, European Molecular Biology Organization, Organization for the Prevention of Chemical Weapons, International Foundation for Science, Department of Biotechnology (Govt. of India), and Department of Science and Technology (Govt. of India). Prof Rizvi has been conferred with the Academic Excellence Award of the University of Allahabad in 2016. He has edited a book on Anti-Aging Interventions in 2018 published by Springer Nature. Prof Rizvi has also written a large number of popular science articles which have been published in national newspapers. He is a member of Indian Gerontological Society, Society of Biological Chemists, National Academy of Sciences India, and Asian Network for Research on Antidiabetic Plants.

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Genetics and Epigenetics of Aging and Age-Associated Diseases

1

Anam Naseer and Aamir Nazir

Abstract

Organismal aging is normally associated with a decline in bodily functions and an increase in various disease-related outcomes. Whether aging itself is a disease or is a process encountered as a consequence of biological fatigue by cellular and organismal systems has long been debated. The fact that is affirmed by decades of research is that aging leads to various adverse outcomes including diminished health and vigor, disturbed metabolism, and altered cellular homeostasis thus triggering myriad diseases. Two major factors that drive the process of aging and its associated diseases are (a) "the genetic make-up or the genome" of a person and (b) the "epigenetic events" that are largely impacted by such intrinsic and extrinsic factors of the body and are modulated by the environment/life-style factors, the genome interacts with. The epigenetic events include DNA methylations, histone modifications, and chromatin remodeling among other events that define how organismal function pursues. Effective research within the area towards the identification of specific genetic and epigenetic targets can deliver senolytic compounds and other anti-aging strategies thus promoting healthy aging and slowing the process of decline in health and related frailty.

Keywords

Aging · Genetics · Epigenetics · Histone modifications · DNA methylation

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1.1 Introduction

The term "Aging" is often described as the process of "getting old"; it emanates from the Latin word "*aevum*," signifying "age" or "everlasting time" (Vocabulary 2022). Considering the long-known direct association between declining health and increasing disease burden as a result of age progression, the phenomenon of aging has long been the topic of interest for researchers in various fields who ultimately aim at gaining insights into the science of human aging (geroscience). Aging is an irreversible and time-dependent process that results in the decline in health and vigor of an organism as it gets older. With the progressing age, circadian rhythm breaks and metabolism of the body slows down. Similarly, body stature, behavior, homeostasis, cellular proteostasis, and routine activities are also affected (Stein et al. 2022). Aging also creates a socioeconomic burden on patients and their families (De Magalhães et al. 2017). Since, the advent of the first life form on earth, quest for understanding aging and its associated phenotypes have begun and till date a complete understanding of the process evades us. However, with the advancement in medical facilities and modern technology, the average life expectancy of the world population has been increased to 73.2 years (Worldometer 2022). It is a universal and evolutionarily conserved phenomenon that has not been fully understood and leaves a larger area of research unexplored.

Advancing age expedites decline in functioning of various molecular as well as cellular components and they collectively form the "hallmarks" of aging (Fig. 1.1). These are broadly classified into nine heads namely, genomic instability, telomere attrition, altered intercellular communication, proteostasis disruption, stem cell exhaustion, cellular senescence, mitochondrial dysfunction, nutrient-sensing deregulation, and epigenetic alterations (López-Otín et al. 2013).

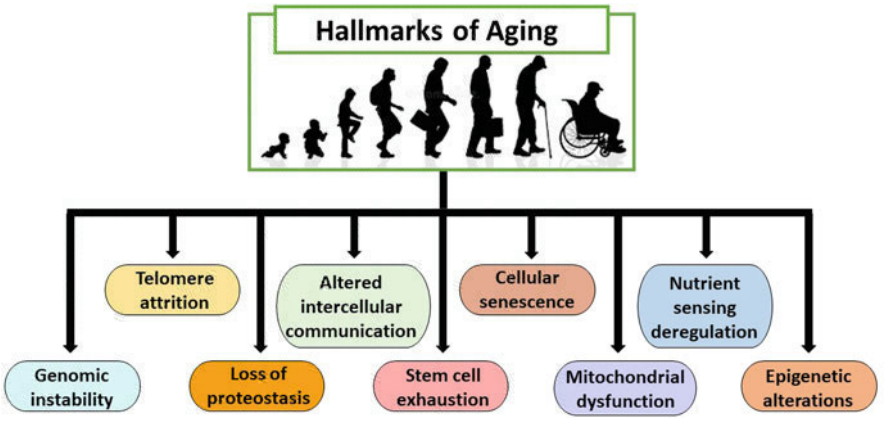

Fig. 1.1 'Hallmarks of aging'

Due to improper functioning and regulation, aging body becomes susceptible to various age-associated diseases such as neurodegenerative diseases, cardiovascular diseases, diabetes, obesity, and cancer, to name a few. These diseases occur either as a result of external environmental factors (epigenetic factors) or they are encoded in the genome of an organism (genetic factors). Genome comprises of the genetic material which codes for the information regarding the organismal development and sustenance. It contains all the information required for the basic functioning of the body at cellular, molecular and organismal levels. It is categorized into two major components: euchromatin and heterochromatin (Tamaru 2010). The active part of the genome is called euchromatin while the inactive part comprises of heterochromatin.

The genome of an organism remains fixed; however, during the course of life, it becomes vulnerable and succumbs to mutations leading to age-associated diseases. Also, with advancing age certain genes, exit initially assigned dormant state (associated with heterochromatin), become active, displaying their effect on health and longevity (Lee et al. 2021). However, the epigenome (comprises of the modifications that occur posttranslationally) is flexible in nature and is influenced by external as well as factors that lead to modifications of the genetic components, such as acetylation, methylation, phosphorylation, sumoylation, and ubiquitinylation. These factors play an important role in regulating the body functions and mechanisms and it is thus vital to study the role of genetics and epigenetics in regulating aging and age-associated diseases.

1.2 Genetics of Aging

Genes form the basis for supporting any lifeform and are arranged as beads on a string, forming the core of hereditary material—DNA or RNA. Genetic material along with histone and nonhistone proteins gives rise to what we call as "genome." The genome codes for two types of sequences: the ones which carry useful information, known as exons, and the others which form the (so-called) "junk" part, known as introns. Interestingly, the introns form the major part of the genome, suggesting that although these are not expressed they play a vital role in the maintenance of genome throughout the life.

According to the genetic theory of aging, lifespan of an organism is decided by the pattern of genes coded onto its DNA. Genes which cap the DNA, known as telomeres, shed and become shorter each time the cell divides and once all the telomeres are shed then there is no room for losing valuable genes or for another cell division and the cell dies. This theory also supports the concept of cellular aging, which states that once the cell reaches its maximum division capacity (known as Hayflick limit) it becomes destined to die by a process known as apoptosis, also called programmed cell death (Shay and Wright 2000).

A large body of work has been done around deciphering the genes involved in aging and age-associated diseases. Certain aging genes and their orthologs have been identified that describe the lifespan in various organisms; for example, a very

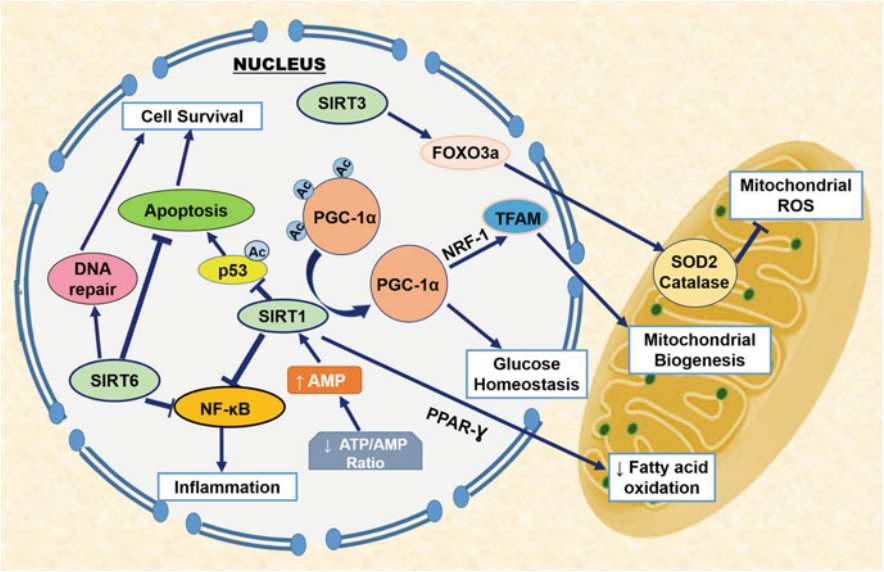

Fig. 1.2 Role of sirtuins in regulating glucose and fat metabolism, mitochondrial function, inflammation and cell survival

well-known class of enzyme, namely "sirtuins," has been long associated with longevity (Hekimi and Guarente 2003) and is evolutionarily conserved thus having its orthologs found in all organisms such as "*SIRT 1–7*" in mammals, *sir-2.1*, *sir-2.2*, *sir-2.3*, and *sir-2.4* in *Caenorhabditis elegans*, *dSir2* in *Drosophila*, *Sir2* in *Saccharomyces cerevisiae* (yeast). Sirtuins are involved in the expression of transcription factors such as AMPK, PGC-1α (Rodgers et al. 2005), p53, and NF-κB (Pillai et al. 2005) and are thus involved in regulating the processes such as glucose and fat metabolism, mitochondrial biogenesis, cell survival, and inflammatory immune response, to name a few (Fig. 1.2).

Also, different mutations resulting in an array of genetic variants, including the mutations in nuclear as well as mitochondrial DNA, help in understanding aging in a better sense. For example, mutation in *clk-1* and *isp-1*, mitochondrial electron transport chain genes, results in decreased oxidative phosphorylation and increased lifespan in *C. elegans*. Thomas Johnson identified the gene *age-1* (class-3 PI3-K) to be the first gene mutation to be involved in increasing the lifespan in *C. elegans*. In the same model as well as in flies and mice, mutation a very well-studied pathway, that is, insulin/IGF-I signaling (IIS) pathway involving genes, such as *daf-2*, results in longer lifespan of the organism (Kenyon et al. 1993). In 1993, Cynthia Jane Kenyon showed that mutation in gene *daf-2*, responsible for dauer larva formation, doubles the lifespan in *C. elegans. daf-2* negatively regulates the gene *daf-16* which encodes for forkhead box O (FOXO) transcription factor that is involved in activities

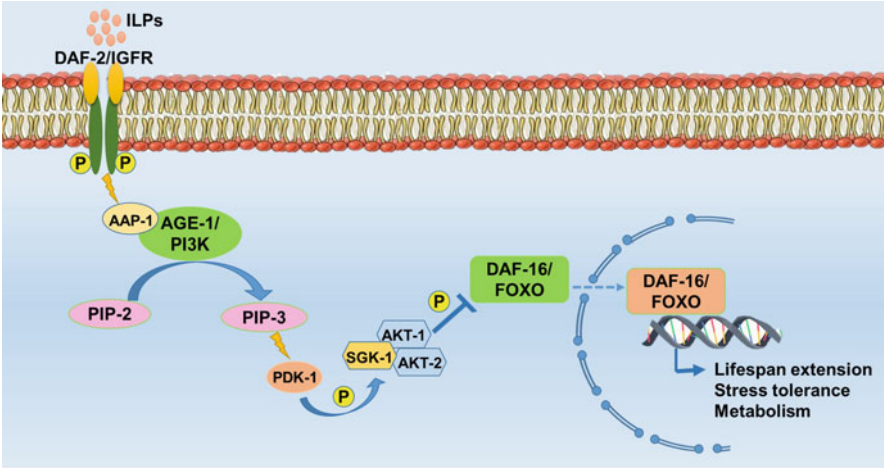

Fig. 1.3 Lifespan extension in *C. elegans* mediated by IIS pathway involving DAF-2 and AGE-1

like stress response, defense mechanisms, and detoxification (Fig. 1.3). Thus, genetic manipulation of genes has long been utilized for promoting longevity.

1.3 Epigenetics of Aging

During the course of evolution, every specie experiences a variety of environmental stressors, geographical barriers, and competition for food and habitat that leads to survival of the fittest. To adjust to the given conditions, an individual undergoes many changes that make them fit for their survival in the existing conditions. These changes become part of epigenetic alterations. These conditions include starvation, exercise, stress (physical or mental), environment (including water and oxygen supply), alcohol consumption, smoking, physical activity, and to some extent deprivation from society. Besides, it has been studied that even monozygotic twins, although they are genotypically similar show variation in their epigenomic profile (Rowbotham et al. 2015; Bell et al. 2012) suggesting a vital role of epigenetics in linking environment with genetics.

Besides, the coded information on the DNA, the genetic code undergoes changes during different biological phenomena such as transcription, translation, and post-translational modifications which lead to the transmission of information in a processed form. These modifications which are not coded by genetic material but expressed in the individuals are categorized into "epigenetic modifications". These include DNA modifications, histone posttranslational modifications, chromatin condensation, and remodeling. Most prominent DNA modification that has been linked with aging is "methylation" (Fig. 1.4).

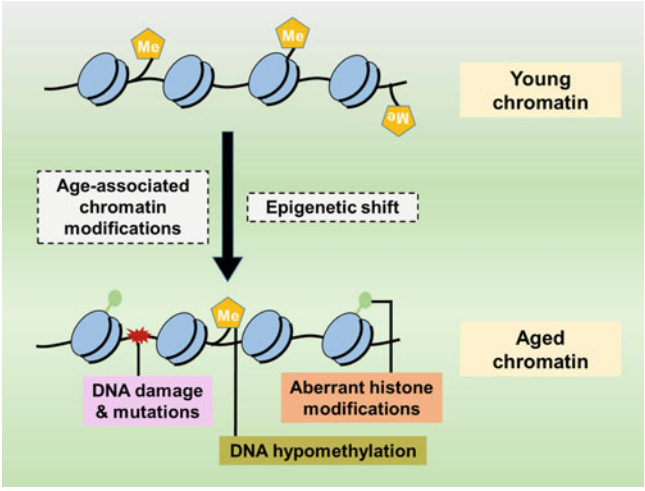

Fig. 1.4 Changes occurring in the structure of chromatin during aging

During the course of aging, the overall DNA becomes hypo-methylated (that is, DNA methylation decreases during aging). However, if we talk about site-specific methylations, there is a variation. Age-specific differentially methylated regions or CpGs show an increase in methylation at specific sites, which involve the promotors of bivalent chromatin domain in precursor or stem cells and in polycomb target genes (Rakyan et al. 2010; Teschendorff et al. 2010; Horvath 2013; Raddatz et al. 2013).

Besides this, sexual disparity also plays an important role in deciding the exposure to age-associated disease. It has been reported and widely accepted that women live longer than men. The global life expectancy on average (in 2016) was 69.8 years for males and 74.2 years for females (World Population Review 2022). Having said that, there is also an increase in DNA methylations with aging and vulnerability towards age-associated diseases for male population. A study identified that with advancing age, there was hyper-methylation of around 36 CpGs. Thus, methylation at Y-chromosome proves to be an important target to study male aging (Li et al. 2022).

DNA methylation has mostly been studied in CpG islands, associated with 5-cytosine residues in CpG islands (5mC). It is found in most eukaryotes including vertebrates. However, for long, DNA methylations were thought to be completely absent in organism like *Caenorhabditis elegans*. Lately, studies have found that instead of the conventional 5mC, methylation at 6-adenine residues (6 mA, which is mostly found in prokaryotes) is prevalent in *Tetrahymena*, *Oxytrichafallox*, *Paramecium aurelia*, *Chlamydomonas reinhardtii* (Fu et al. 2015), *Caenorhabditis elegans* (Greer et al. 2015), *Drosophila melanogaster* (Zhang et al. 2015), and

Table 1.1 Types of histones (Nelson et al. 2008)

S. no.	Histone		Molecular weight (kDa)	Number of amino acids
1.	H1 (Linker histone)		21.1	223
2.	H2A	Core	13.9	129
3.	H2B		13.7	125
4.	H3		15.2	135
5.	H4		11.2	102

plant species like *Arabidopsis thaliana* and *Oryza sativa* (Karanthamalai et al. 2020), to name a few.

In addition to DNA, another most important component that is responsible for getting epigenetically modified is a class of proteins known as "histones." These are a group of positively charged basic proteins that are associated with negatively charged nuclear DNA. These are conserved and play a key role in nucleosome formation and DNA compaction in eukaryotes; however, they are absent in prokaryotes (except Archaea domain). Histones are of five types as described in Table 1.1.

During any biological process, histones undergo various modifications such as methylation, acetylation, and phosphorylation that give rise to either activation or repression of genes associated with them. Their arrangement in the DNA sequence forms a code, known as "histone code" which governs the expressions of associated genes (Strahl and Allis 2000). Over the past few years, specific histone modifications associated with aging have been identified and a large area of research has been done in this field. Most of these include methylation at histone 3 lysine residues which are closely associated with longevity and lifespan regulation. These methylations include:

- H3K4me3
- H3K9me3
- H3K27me3
- H3K36me3

H23K4me3 is the activating modification which regulates the lifespans. In mammals, the complexes that are involved in generating H23K4me3 include (1) Trithorax-related complex, (2) Trithorax complex, and (3) COMPASS complex. In worms, this modification is controlled by a complex consisting of ASH-2, SET-2, and WDR-5. It has been found that decrease in the methyltransferase components promotes longevity whereas decrease in demethylase components, such as knock-down of *rbr-2*, reduces the lifespan and vice versa (Han and Brunet 2012; Yu et al. 2019; Sen et al. 2016; Greer et al. 2010).

Contrastingly, **H3K27me3** is the repressive modification, regulated by UTX-1 (histone demethylase) and PRC2 complex (Polycomb repressive complex 2, which catalyzes H3K27me3). During the course of aging, the level of H3K27me3 elevates in worms and flies (Yu et al. 2019; Sen et al. 2016).

H3K9me3, another histone methylation responsible for transcriptional silencing, is regulated by MET-2, which prevents DNA damage and instability in genome during aging (Yu et al. 2019).

H3K36me3 is associated with activating transcription and is also one of the most important histone modifications. In yeast, it has been found that loss of a histone demethylase coded by gene *Rph1* results in lifespan extension by increasing the levels of H3K36me3 (Sen et al. 2015). Also, in *C. elegans* it has been studied that knockdown of *met-1*, a H3K36me3 methyltransferase, results in global decrease in H3K36me3 levels thus reducing the lifespan (Pu et al. 2015). These results suggest that this modification is important for maintaining longevity.

Second most commonly occurring modification at lysine residues of histone tail after methylations is acetylation which is thought to epigenetically regulate longevity. It involves the addition of acetyl group with the help of enzyme histone acetylases (HATs) or the removal of the added acetyl group via histone deacetylases (HDACs). The common acetylation marks associated with aging includes H3K23ac, H4K12ac, and H3K9ac. However, the response associated with these modifications vary and are dependent on the position of the lysine residue that is acetylated. For example, in *Drosophila,* reduction in H3K23ac levels results in impaired neuronal behavior, learning, and courtship activities (Li et al. 2018). However, decrease in H4K12ac prolongs the lifespan (Peleg et al. 2016).

In addition to HATs, the role of HDACs is also proven to be very critical in maintaining lifespan. For example, a very well-known class of NAD+ dependent class III HDACs called "sirtuins" have been extensively studied to be involved in promoting longevity. The pro-longevity effects of these conserved proteins (Kaeberlein et al. 1999; Imai et al. 2000; Tissenbaum and Guarente 2001) were described by Leonard Guarente for the first time in 1991.

Apart from genetic manipulation, another important phenomenon, known as "calorie restriction" increases longevity. It is the process by which the intake of calories is restricted to an extent that does not cause lethality. According to studies conducted in various model organisms, restriction of diet or calories (to around 30%) has proved to be beneficial. It epigenetically modifies the genome and increases the longevity in mice as well as flies and worms and to some extent (about 50%) in lemurid primate (*Microcebus murinus*) (Pifferi et al. 2018).

However, calorie restriction when applied in combination with genetic manipulation results in additive response towards lifespan extension.

Apart from DNA and histones, chromatin structure also undergoes transient changes with aging. During aging, the chromatin loosens and loses its original form and as a result the once silent genes associated with heterochromatin become active and begin to express themselves resulting in aging anomalies. One of the important and most studied chromatin remodeling complex includes SWI/SNF (switch/sucrose non-fermenting complex) (Zhou et al. 2019). It is responsible for activating transcription while another chromatin remodeling complex, that is, polycomb repressive complex (PRC) silences transcription (Bracken et al. 2019; Stanton et al. 2017). This contrasting role of these complexes along with other

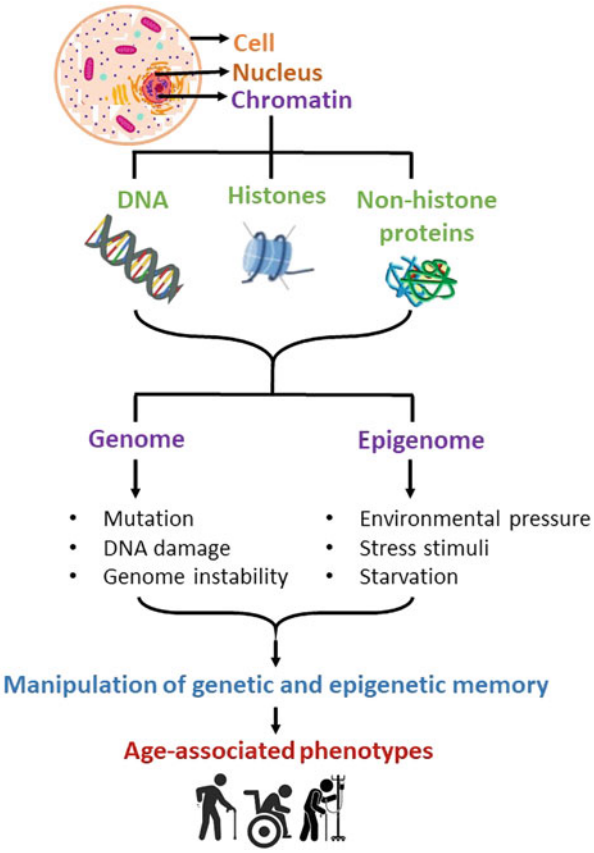

Fig. 1.5 Role of genome and epigenome in aging

mentioned modifications is important for chromatin regulation, which gets disturbed during aging.

Thus, synergism between genome and epigenome either via mutations or through environment-induced epigenomic interventions leads to manipulation of genetic and epigenetic memory hence leading to aging-associated phenotypes (Fig. 1.5).

1.4 Case Studies of Age-Associated Diseases

The field of aging biology research is expanding with every passing second and a tremendous amount of novel work is being conducted every day. However, till date, no direct measurement of aging has been developed, meaning there is a lacuna for standard measuring techniques with respect to aging. However, other parameters associated with aging, such as quantification of cancer-associated genes, DNA damage proteins, behavioral changes, etc., can be estimated easily, forming the basis for analyzing the phenomenon of aging. Different strategies have been

employed to prevent the early onset of aging and also to delay the symptoms of age-associated diseases.

One of the important methods to delay early aging is to adopt a healthy lifestyle. It plays a very essential role in framing one's epigenome expression of metabolism boosting and immune responsive genes and vice versa. Thus, the proverb is truly stated that "*we are, what we eat*." Eating healthy and staying fit is the key to delay the signs of aging. Besides this, genetic manipulation has also been observed to yield good results in terms of alleviating the harmful effects of age-associated diseases. It is well demonstrated in case of obesity, type 2 diabetes, neurodegeneration, cancer, and cardiovascular diseases (discussed ahead).

1.4.1 Obesity

Obesity has recently been addressed as public health concern globally. This condition involves higher body to mass ratio (known as body mass index, BMI). A person is said to be obese if his/her BMI is 30.0 or more. Furthermore, obesity is subcategorized into: class 1 (BMI: 30–<35), class 2 (BMI: 35–<40), and class 3 (BMI: 40 or more) obesities. Class 3 obesity is also known as "severe obesity" (Centers for Disease Control and Prevention 2022). According to WHO, around 13% of the world's population was estimated to be obese in 2016 (World Health Organization 2022a), suggesting a rapid increase in reduced life expectancy. Studies have shown that due to obesity, life expectancy in men and women after 40 years of age, has been reduced by 5.8 and 7.1 years, respectively (Tam et al. 2020). Thus, obesity causes early onset aging-associated symptoms and also increases the risk of other age-associated diseases like hypertension, CVDs, ischemic heart disease, and stroke, to name a few.

One of the major causes of this condition can be attributed to a sedentary lifestyle. The absence of physical exercise and loads of processed food intake results in extra calories that are not metabolized thus it keeps on depositing in the form of extra fat leading to obesity. Mechanistically, obesity targets multiple pathways genetically and epigenetically. Excess amount of calories causes increased ROS production, damage to nuclear machinery and endoplasmic reticulum, altered Ca^{2+} flux, stressed mitochondrial DNA, impaired autophagy, reduced homeostasis, cellular senescence, and an increase in epigenetic age (López-Otín et al. 2013). Obesity also reduces the telomere length in white blood cells (Valdes et al. 2005; Kim et al. 2009; Buxton et al. 2011) thus causing early aging.

1.4.2 Type 2 Diabetes

Type 2 diabetes is a disease resulting from increased blood glucose levels due to either inactive lifestyle, obesity, or progressing age. Aging poses a severe risk factor for the onset of this disease. Also, people with obesity (another age-associated disease) have a high risk of developing type 2 diabetes. With increasing age, there

is a decline in metabolic activity, increased oxidative stress, neuroinflammation, impaired insulin secretion, and sensitivity (Chia et al. 2018).

According to the international diabetes federation, by the year 2021, the total population of adults suffering from diabetes was around 537 million. It is estimated that by the year 2030 the world population suffering from diabetes will reach 643 million (International Diabetes Federation 2022). Out of the total diabetic population, around 95% account for type 2 diabetes (World Health Organization 2022b).

1.4.3 Neurodegeneration

Neuronal damage and degeneration increase with advancing age. Moreover, the genomic and epigenomic composition might enhance or suppress the event of neurodegeneration. In elderly individuals, the most prominent age-associated neurodegenerative diseases include Alzheimer's disease (AD) and Parkinson's disease (PD). AD involves decrement in memory and learning ability, reduced cognition, and dementia. It is associated with the deposition of protein aggregates of amyloid-β (Aβ) (plaques) and hyper-phosphorylated tau (forming neurofibrillary tangles). PD involves decreased coordination, motor function dysregulation, tremors, shaky movements, and dementia, caused due to aggregation of misfolded α-Synuclein protein (Hou et al. 2019). It is estimated that by the year 2050, the global rate of dementia will rise to around 152.8 million (Nichols et al. 2022).

Genetic mutations in apolipoprotein E (*APOE*) ε4 allele, *PRESENILIN 1/2*, APP pathway, *SNCA*, *DJ-1*, *PINK1*, or *PRKN* genes form the genetic basis of neurodegenerative diseases; while, environmental pressure such as diet or heavy metal toxicity (including aluminum, copper, zinc, etc.) (Modgil et al. 2014) form the epigenetic basis of neurodegeneration. Both genetic and epigenetic factors have a combinatorial effect like misfolding of aggregated proteins, decrease in protein clearance, impaired autophagy and apoptosis, increased production of ROS, and cellular senescence. These signs overlap with those of aging.

1.4.4 Cardiovascular Diseases (CVDs)

For the older population, that is, above 65 years of age, cardiovascular diseases have been one of the most common causes of death worldwide (Chiao et al. 2016). It is estimated that by the year 2030, CVDs will account for 40% of total diseases in the elderly and will become the leading cause of death in them (Groff and La Vigne 2002).

CVDs include diseases like hypertension, stroke, myocardial infarction, and atherosclerosis. With aging, the cardio-vasculature becomes inefficient thus making the body vulnerable to these diseases. Conditions such as hypertrophy, stiffness of arteries, and deregulated heart rate result in the weakening of vasculature and blood circuitry. These result in increased oxidative stress, increased inflammatory

cytokines, DNA damage, and cardiomyocyte senescence (North and Sinclair 2012). Thus, apart from excess fatty acids and cholesterol, aging is another risk factor for developing CVDs.

1.5 Therapeutic Strategies to Modulate Aging

Epidemiologic and predictive modeling studies reveal that the aged population (60 years and above) would be at a whopping 2.1 billion by the year 2050 (World Health Organization 2022c) thus making a larger chunk of population prone to age-associated diseases. Proactive measures by researchers as well as healthcare providers will include having efficient strategies in place towards countering such burden and promoting "healthy aging." Various therapeutic strategies that are being researched and employed, delay the signs of aging and improve health span; this includes the development of potential anti-aging drugs and altered dietary regimes, that will aid in modulating aging, genetically or epigenetically. Drugs such as metformin, rapamycin, and resveratrol are involved in targeting multiple pathways that are hampered during aging. For example, metformin is tested to increase longevity in *C. elegans* and also it has positive effects on learning, memory, and tau protein clearance in SAMP8 mice. It functions by decreasing insulin signaling (Liu et al. 2011) and mTOR pathways (Nair et al. 2014) and activating AMPK signaling (Cho et al. 2015) thereby maintaining glucose homeostasis, decreasing ROS (Batandier et al. 2006), repairing DNA damage (Algire et al. 2012; Cabreiro et al. 2013), and enhancing tumor suppression. Similarly, a widely known inhibitor of mTOR pathway has been shown to increase the average lifespan in case of yeast, worms, and flies (Johnson et al. 2013). Also, a phytoalexin known as resveratrol is found to improve health span and longevity in case of yeast and worms. This compound functions by activating sirtuin proteins (Cao et al. 2018; Alcaín and Villalba 2009; Price et al. 2012; Wood et al. 2004). Apart from these FDA-approved drugs, certain senolytic compounds, such as quercetin and dasatinib, have also been implicated to have a potential in regulating health span and longevity by selectively clearing the senescent cells thus inducing apoptosis (Tse et al. 2008). Besides, several dietary regimes such as calorie restriction or intermittent fasting also improve lifespan and health (Vera et al. 2013) by regulating energy-sensing pathways, involving AMPK, NAD+/NADH, and sirtuins. In a recent human study, it has been found that 14% calorie restriction improves immunometabolism (Spadaro et al. 2022).

In summary, it appears prudent to identify such pharmacological modulators that specifically target genetic and epigenetic changes associated with aging. Research in this direction can aid in identifying such specific targets and further design of new chemical entities or repurposing of existing drugs can be tested against such targets. The future direction should be having newer molecules in this space, which promote healthy aging and better the quality of life in old age.

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Coenzyme Q as an Antiaging Strategy

2

Guillermo López-Lluch

Abstract

Aging is a very complex process in which many factors are involved. As a common factor the accumulation of damaged cell and tissue structures, impair cell activity at different levels ending in the malfunction of organs and cell death. In this process, dysfunctional mitochondria play a very important role. Coenzyme Q is a key factor in the activity of mitochondria and in the protection of cells against lipid peroxidation. Its levels decrease during aging and supplementation improve cell functionality and delay the progression of age-related diseases. In this chapter, the importance of CoQ in aging and the strategies to restore levels in the cell and organs are shown. These strategies can help to improve health during aging and demonstrate that the maintenance of CoQ levels can be considered a good antiaging strategy.

Keywords

Coenzyme Q · Aging · Mitochondria · Metabolism · Antioxidant

2.1 Introduction

Aging is a complex process that must not be considered a disease. As Suresh Rattan indicated in 2014, aging is the consequence of the loss of the capacity to maintain the capacity to respond to stress and buffer the damage produced by internal and external injuries (Rattan 2014). The decay in the capacity to respond to stress is associated

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