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Chapter 5: Molecular signs of aging: How cells reveal the passage of time

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Abstract

Aging is characterized by a series of molecular symptoms that reflect the gradual deterioration of cellular structures and functions. Key molecular hallmarks include genomic instability, telomere shortening, epigenetic alterations, loss of proteostasis, mitochondrial dysfunction, deregulated nutrient sensing, and accumulation of senescent cells. These changes compromise the cell's ability to maintain homeostasis, leading to impaired tissue regeneration, increased susceptibility to disease, and functional decline across organ systems. Molecular symptoms often manifest long before clinical signs of aging appear, offering crucial insights into the biological aging process. Understanding these molecular features is essential for the development of interventions aimed at promoting longevity and preventing age-associated disorders.

Keywords: Biomarkers of Aging, DNA Damage, DNA modification, Epigenetic Changes, Genomic Instability, Homeostatic Imbalance, Inflammation activation, Nutrient Sensing Deregulation, Telomere Attrition.

5.1. Introduction

The molecular symptoms of aging are the biological changes that occur at the cellular and molecular level as organisms grow older. These symptoms reflect damage, dysfunction, or alterations in critical molecular processes that lead to aging and age-related diseases. Additional molecular signs includes increased oxidative stress, mitochondrial DNA mutations, impaired autophagy (cellular cleaning system), and changes in non-coding RNAs (e.g., microRNAs).

5.2. Symptoms of ageing at molecular level

The symptoms of ageing are usually attributed to a progressive loss of physiological functions that leads to impaired bodily functions which elevates the risk of death.

Table 5.1 Molecular symptoms of aging.

Molecular Symptom	Effect on Aging
Genomic Instability	DNA damage, mutations
Telomere Shortening	Cell aging, loss of division
Epigenetic Alterations	Abnormal gene expression
Loss of Proteostasis	Protein misfolding, cell stress
Mitochondrial Dysfunction	Energy loss, ROS accumulation
Cellular Senescence	Inflammation, tissue damage
Stem Cell Exhaustion	Impaired regeneration
Altered Communication	Chronic inflammation, immune decline

Many diseases or physiological abnormalities such as cancer, diabetes, cardiovascular disorders, and neurodegenerative diseases are therefore considered as the route via which ageing captures the body. Many molecular signs such as genomic instability, telomere shortening, epigenetic changes, reduction in proteostasis, loss of nutrient-sensing, mitochondrial dysfunction that leads to more accumulation of reactive oxygen species and elevated oxidative stress, cellular senescence, stem cell collapsing at both structural and functional level, and elevated intercellular miss-communication are accepted universally for the root cause of ageing (Figure 5.1 and Table 5.1).

5.2.1. Susceptibility to infection

Infection is a pathological process in which an animal contract a disease by the invading pathogen into the body. The infection can also be found on the skin. So, both inner and outer organs are susceptible for infection. This process is associated with the natural immunity of animals. Having strong natural immunity, an animal can surpass the pathogens even they enters into the body, but cannot sustain and impose any disorder. Ageing has found to have a negative correlation with the natural immunity in animals and human subjects. Therefore, the risk of infection by any pathogen would be high in elderly people than young population. However, young population with low immunity can also contract an infectious disease.

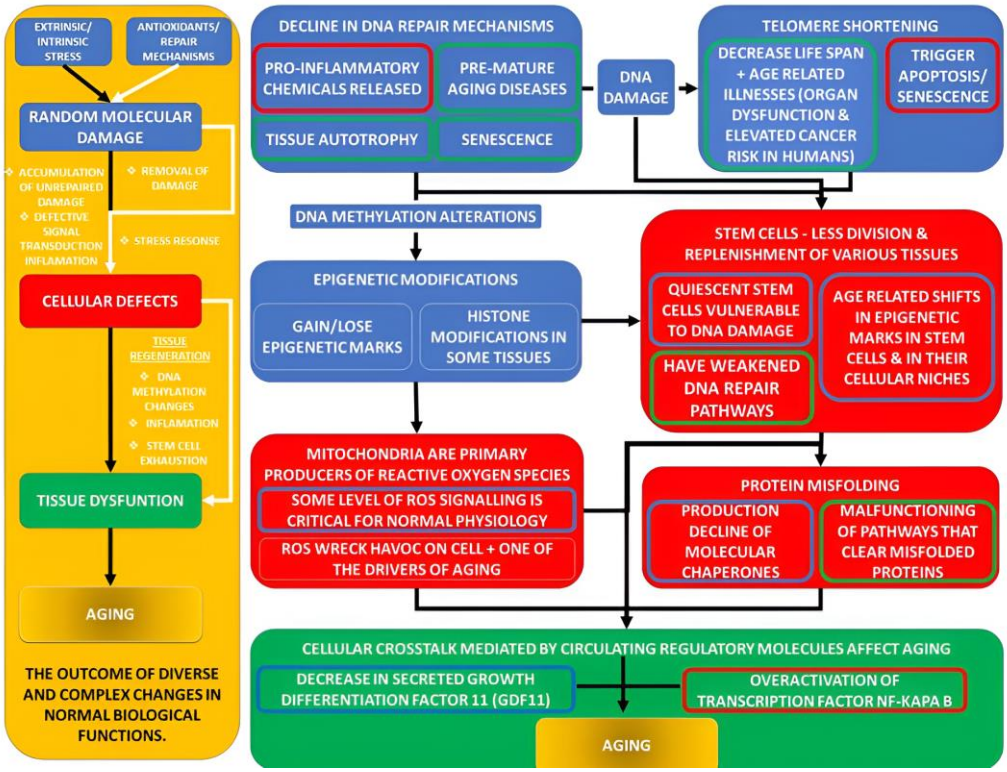

Figure 5.1. Major molecular changes in ageing

Average life expectancy in all developed countries was sharply increased in the last half of the 20th century. It is due to the advancement of healthcare systems of the nations and the health consciousness among their citizens. It leads to the accumulation of elderly portion in the population. As it is discussed, the geriatrics with low immunities are susceptible to various infectious diseases. This makes an important issues for providing healthcare's to such population. They are not only susceptible for frequent infections with severity, but also they show different and distinct features with respect to clinical presentation, laboratory results, microbial epidemiology, treatment, and infection control.

Reasons for the above higher risk of infection in elderly include epidemiological elements, immuno-senescence, and malnutrition, as well as a large number of age-associated physiological and anatomical alterations. Therefore, ageing and infections are positively correlated with each other. Many mechanisms are proposed to be clinically accepted and they include enhanced inflammation, pathogen-dependent tissue destruction, or accelerated cellular ageing through increased turnover. In normal elderly patients such infections are easy to handle but with dementia it creates more complications and ethical issues (Gavazzi and Krause, 2002).

Due to advancement in healthcare, a major fraction of the global population is found to be aged and the process of ageing is also more rapid among others due to modern life style. Currently, it is estimated that 566 million people are ≥65 years old in our planet and the number is predicted to be ~1.5 billion by 2050, particularly in developing countries. Infections associated death constitute one third of people ≥65 years old. High longevity also correlated with increased time in hospitals or long-term care facilities and exposure to drug-resistant pathogens. Indeed, the risk of nosocomial infections increases with age, independent of duration spent in healthcare facilities. Therefore, most prevalent infections affecting ageing populations including pneumonia, urinary tract infections, and wound infections and make recommendations for future research into infection in ageing populations (Kline and Bowdish, 2016).

5.2.2. Risk of heat stroke or hypothermia

Feeling cold during the winter and hot in summer depends on the difference between the temperature of the body and environment. Human body temperature is maintained at 37 °C while, environmental temperature remained less in winter, gives a feeling of colder and more in summer, gives a feel of hotness. Marinating human body temperature is called a thermoregulation and it is a unique capacity in all homeotherms. Body fat, metabolic status and energy dissipation in body keeps the homeotherms to keep their constant body temperature. However, such phenomenon is found to be deregulated in elders. Young people don't dissipate body heat faster but they do the same when becomes older. So, a big chill can turn into a dangerous problem before an older person even knows what's happening. In medical science, this serious problem is called hypothermia. Hypothermia is what happens when human body temperature gets very low. For an older person, a body temperature colder than 95 Fahrenheit can cause many health problems such as a heart attack, kidney problems, liver damage, or even any other worse health consequences.

Low or high temperature either at environmental or room can lead to hypothermia. It is found that elders are more susceptible to hypothermia and the exact cause was under-recognized up to the last decade. Hypothermia is usually fatal in elders those can dissipate their body temperature at a lower rate. However, up to some extent is preventable. On the other hand, hypothermia occurs in both cold and warm temperature. A body having less thermoregulatory activity like in elders is prone to serious health consequences. Thermoregulatory activities along with a variable combination of environmental factors, disease processes and medications, many of which are recognizable. Once diagnosed with hypothermia at low temperature, the treatment must be prompt and aggressive, and must consider several options for rewarming. Trained healthcare workers can only therefore lower the complications of hypothermia in affected especially in elderly (Dharmarajan and Widjaja, 2007).

At the current scenarios of climate change, it is noticed that a greater variability high temperature by heat waves or low temperature by snow falls are noticed. Especially, extreme heat waves can surpass the physiological threshold on all ages of population but makes elderly at a higher side of risk. Elderly above the age of 60 years are found to be more vulnerable to the environmental heat strokes. Since ageing has a strong association to the thermoregulation capacity of body in human, therefore, hypothermia or heat stroke is age dependent. The phenomenon is solely dependent on heat dissipation capacity of the body, and it is always lower in an aged body. Promotion of regular exercise as a means of improving health-related quality of life and morbidity and mortality in elderly is suggested (Balmain et al., 2018).

5.2.3. Weakening and thinning of bones

The main function of bones is to give protection, at the same time it serves as a cover for marrow and a site for calcium ion homeostasis regulation. The properties of bones differ according to age, sometimes developing in function, but in some cases, its function is to deteriorate.

All normal cells, including osteoblasts, osteoclasts, and osteocytes, have a limited lifespan, which is controlled by the number of replication cycles and external factors. According to Martin et al. (1970) the Hayflick limit of cell division showed that cells can undergo only a limited number of divisions, and with age, number of such divisions reduces. In the nucleus, the telomere lengths at the ends of genes are presumably the determinant of that number. With each cell division, the length of telomeres decreases because of the incapability of the cell to fully replicate this portion, and according to Calado (2009), once the telomere length reaches some critical point, the processes like cell senescence and apoptosis are initiated.

As per the research by Szulc and Seeman, (2009), with age passing, the amount of bone deposited with each cycle of remodeling reduces, possibly due to a decrease in the number of precursors of osteoblast cells, a reduction in the number of stem cells from which these precursors are derived, or a reduction in the lifespan of osteoblasts.

Another condition is osteoporosis which is associated with age but not a disease of ageing. There are numerous reasons for this condition and first and foremost is that not all the elderly over age 85 yrs, might show signs of skeletal fragility or possibly have fractures (Mellibovsky et al., 2007). Secondly, there are some unique genes associated with the loss of bone in rodents and humans (Richards et al., 2009), their occurrence or nonoccurrence does not offer specific protection to any age group. For example: even in very young people this condition occurs like in case of idiopathic

juvenile osteoporosis, a disease of skeletal fragility in teenagers (Rauch et al., 2002; Pludowski et al., 2006).

There are also numerous metabolic diseases associated with weakening of bones. Some of them are osteomalacia, acromegaly, renal osteodystrophy, hyperparathyroidism, osteogenesis imperfecta, and osteopetrosis. In the recent years various techniques are developed to image and diagnose these types of bone disease as explained by Patel el al. (2015).

5.2.4. Waste molecule accumulation

When development ends, age-related changes start to appear as per estimated, it is logical to suppose that the accumulation of damage may be due to its inadequate removal. In fact, the effort to explain ageing as a result of translational errors (Orgell, 1973) has failed generally. Evidently, damage removal in a developing organism is not perfect either, but the accumulation of damaged structures is prevented by their dilution associated with growth. The damage starts to accumulate substantially when growth/proliferation becomes slow or completely stops.

Age-related accretion of damage occurs in the organism all throughout, involving both cells with their organelles and extracellular matrix. Organisms have their own mechanisms to remove and replace damaged organelles, biomolecules and whole cells (in proliferative populations), but the removing machinery is not perfect at intrinsic level. During ageing process, accumulation of mis-repair also occurs. The mis-repairs occurring frequently will slowly deform the structure of a molecule, a cell or a tissue, making it perform ageing. In a similar manner mis-repair proteins also accumulate during any injury. Accumulation of the repairing collagen fibers then leads to the hyaline degeneration in different ageing changes, such as arteriosclerosis, liver cirrhosis, atrophy of muscular tissues etc. (Jicun & Thomas, 2007; Mishra et al., 2023).

A theoretical possibility to delay ageing by enhancing degradation of waste products is unexplored till date. This approach is supported by the fact that caloric restriction which is the most effective intervention efficient of extending the lifespan of mammals was shown to stimulate protein degradation in mouse and rat hepatocytes.

5.2.5. Telomeres shortening

Telomeres are the ends of chromosomal arms that get shortened at each cell division. Such reduction is the size of telomeres limits proliferation of cells to a finite number because its length is fixed in every organism. This mechanism resulted in limiting the replicative power of cells and hence it is associated to senescence, differentiation, or apoptosis. Recent studied indicate that telomere shortening can also

limits stem cell function, regeneration, and organ maintenance during ageing. Therefore, it can be linked with cellular physiology because each successive cell generation lost or gain certain genes that regulate metabolic pathways. So, telomere shortening is strongly linked to the ageing process. It is also believed that this mechanism also make organs susceptible to diseases, another contributing factor for ageing. Therefore, telomere shortening has an intricate relation to disease susceptibility, ageing and sometimes with cancer (Jiang et al., 2007).

Although the precise causes behind the process of ageing is not clearly understood, therefore, it is mysterious that why some species live less than a day while others live more than 400 years and some are really immortal. However, a clear relationship among telomere shortening, ageing and lifespan of a species is established. Therefore, telomere shortening is considered as one of the hallmarks of ageing. On the other hand, initial telomere length has no relation with the longevity or ageing process of animals. It means animals having a larger telomere don't survive longer and vice versa is also found to be true. However, a strong correlation between the telomere shortening rate and the lifespan of a species are well established. Telomere shortening is tolerated up to a certain length by cells. After that the cells have to follow a natural or induced death pathway. In mice this fact is well established. And in human, a mechanism such mechanisms involves induction of a persistent DNA damage response at chromosome ends and loss of cellular viability.

It must be noted that telomere shortening as a marker of ageing is not established in wide varieties of organisms. However, it is studied in birds and mammals with very different lifespans and body sizes, including mouse (*Mus musculus*), goat (*Capra hircus*), Audouin's gull (*Larus audouinii*), reindeer (*Rangifer tarandus*), griffon vulture (*Gyps fulvus*), bottlenose dolphin (*Tursiops truncatus*), American flamingo (*Phoenicopterus ruber*), and Sumatran elephant (*Elephas maximus sumatranus*). In above organisms it was tested and found correct that telomere shortening rate, but not the initial telomere length alone, is the predictor of species lifespan. Such experimental results concludes that critical telomere shortening and the consequent onset of telomeric DNA damage associated to it induces cellular senescence and are a general determinant of species lifespan (Whittemore et al., 2019).

In human, it is evidenced that telomere length acts as a promised biomarker of ageing. Although, telomere length is strongly associated with the cellular senescence and ageing in human, the phenomenon for whole human body is equivocal. Therefore, more studies on determining the relationships between loss of telomere length and mortality and how it is related to be declined and accepting with "normal" ageing in community samples are suggested. Such studies would clarify the longitudinal

measures of both telomere length and ageing-related parameters in human and non-human animals. Such studies can also be done in plant species to make the theory universal.

5.2.6. Amelioration of stiffer connective tissues

With ageing, the vasculature undergoes structural and functional changes distinguished by endothelial dysfunction, thickening of wall, low distensibility, and arterial stiffening. As ageing progresses some of the changes occurring are arterial stiffening which precedes hypertension and both of these are common in older people. Arterial stiffening is basically caused by excessive fibrosis and reduced elasticity, with increased collagen deposition, increased elastin fiber fragmentation/degeneration, calcification, laminar medial necrosis and cross-linking of collagen molecules by advanced glycation end-products (Harvey et al. 2016).

At the molecular and cellular levels, ageing of arteries and hypertension-associated vascular changes are characterized by decreased level of nitric oxide production, reduced collagen turnover, increased generation of reactive oxygen species, calcification, vascular smooth muscle cell proliferation, activation of transcription factors, stimulation of "ageing" genes, induction of pro- inflammatory and pro- fibrotic signaling pathways and ECM remodeling. A few researchers such as Bonnett et al. (2007), Wang et al. (2007), Ruiz-Ortega et al. (2007) and Harvey et al. (2016) studied the molecular patterns underlying these mechanisms which include elevated expression and activation of matrix metalloproteinases, activation of transforming growth factor-b1/SMAD signaling as well as proinflammatory and profibrotic signaling pathways and galectin-3 upregulation as given in figure 5.2.

Furthermore, Harvey et al. (2016) concluded from their studies that a number of noninvasive methods currently exist to assess the large-artery stiffness in the clinical setting, including carotid-femoral PWV. Increased PWV in ageing and hypertension reflects increased stiffness of arteries and is considered as a biomarker for cardiovascular risk stratification. Mostly, over the next decade, PWV assessment may become a routine investigation in the clinical tool kit to predict hypertension and cardiovascular disease in a better manner. Another important issue focused by Snedeker and Gautieri (2014) were on relation of ageing with glycation of connective tissue especially collagen crosslinking.

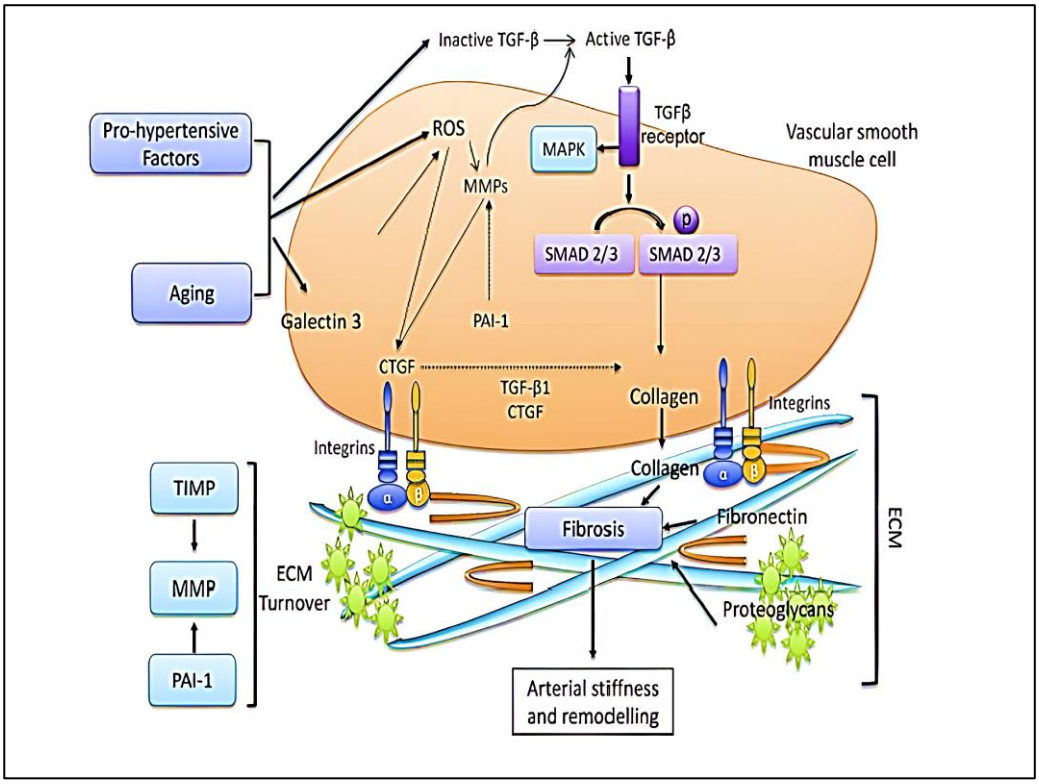

Figure 5.2. Molecular remodelling in aging

There are very huge and enormous number of therapeutics and drugs in the market and some discovered and still under clinical trials for extracellular matrix stiffness which occurs during ageing process as shown in Table 5.2 (Lampi and Reinhart-King, 2018).

Collagen crosslinking elevates at maturation due to the enzymes involved in it, with age and occurrence of diabetes, the connective tissue stiffness has been shown to further increase as proven from the studies by numerous experts (Saito and Marumo 2010; Bank et al. 1998; Lai-Fook and Hyatt, 2000; Sell et al., 1992; Haut et al., 1992; Torp et al., 1974). This tissue stiffening has been associated with non-enzymatic, oxidative reactions between glucose and collagen which lead to the formation of so-called advanced glycation end-products (AGEs) (Avery and Bailey, 2005, 2006). Several approaches has been tried to break these AGEs. N therapeutic approach the most recent and widely used crosslink breaker is alagebrium (ALT-711) which was shown able to reverse carotid artery stiffness. Another amelioration method discovered by Monner and Wu (2003), Mennela et al. (2005) and Capuano et al. (2007) were by protein deglycation using enzymes such as Amadoriases, Fructosyl Amino Acid Oxidases (FAODs) or Fructosyl Amine Oxidases (FAOX). These enzymes, found in

fungi and bacteria, are able to cleave low molecular weight Amadori product (i.e., glycated amino acids) and yield the free amine, glucosone and hydrogen peroxide (Figure 5.2).

Table 5.2. Extracellular matrix stiffness seen during ageing process.

Table 1. Therapeutics in latest clinical trials with primary end points specific to ECM stiffness.

Target	Drug name (trade name/company)	Category	Highest completed trial	Current trials relevant to ECM stiffness
miR-29	MRG-201 (miRagen Therapeutics Inc.)	MicroRNA	Phase 1	None
CTGF	FG-3019 (Fibrogen)	Monoclonal antibody	Phase 2	Phase 2
TGFβ signaling	Pirfenidone (Esbriet/Genentech)	Small molecule, mechanism unknown	Approved: Idiopathic lung fibrosis	Phase 1–3
TGFβ	GC1008 (Fresolimumab/Genzyme)	Monoclonal antibody	Phase 2	Phase 1–2
VEGF, FGF, and PDGF receptors	Nintedanib (Ofev/Boehringer Ingelheim)	Small molecule, tyrosine kinase inhibitor	Approved: Idiopathic lung fibrosis	Phase 1–3
LOXL2	GS-6624 (Simtuzumab/Gilead)	Monoclonal antibody	Phase 2 No efficacy in fibrosis or cancer	None
LOX	Tetrathiomolybdate	Copper chelator	Phase 3 (Wilson's disease)	Phase 2
$\alpha_v\beta_6$	BG00011/STX-100 (Biogen)	Monoclonal antibody	Phase 2	None
FAK	VS-6063/PF-04554878 (Defactinib/Verastem)	Small molecule	Phase 2	Phase 1–2
FAK	GSK-2256098 (GlaxoSmithKline)	Small molecule	Phase 1	Phase 1–2
NF-κB	Bortezomib (Velcade/Takeda)	Small molecule	Approved: Multiple myeloma	Phase 2

5.2.7. Declining energy homeostasis

Curran (2018) have recently described in details about the loss of homeostasis during ageing process. Cell or body homeostasis is an important requirement for the normal functioning. As human body age, it lost the control over the homeostasis. It is also opined that for a natural or healthy ageing, the maintenance of cell- and organism-level homeostasis are important. This is not only required for a particular time point as

age specific event, rather regular homeostasis maintenance is required though out the lifespan of a person. So, cell or body homeostasis has an intricate relation with all the hallmarks of ageing. So, across the lifespan it is essential for observing a healthy ageing process.

Each and every biological event that has control over homeostasis impacts the ageing process. Although, biological mechanisms that regulate the process of homeostasis are multifaceted, they finally control the health and longevity processes (Paital et al., 2016). Any external agent such as food, life style, environment or internal processes such as hormonal titre, biochemical regulation of digestion, absorption, ingestion, excretion, circulation, nerve conduction can impact organism's health and longevity.

Body has its own natural homeostasis capacity, however, in relation to the fluctuations of any of the above the internal or external parameters can force body to adaptive a new homeostasis rule. Such adaptive homeostasis acts as a transient modulation against the temporary fluctuations to any normal process in body or in short acts as a stress-protective measure against those internal or external stimuli which initiate deviations to normal homeostasis.

Such adaptive homeostasis enables organisms to adjust with continual deviations and it ensures body for an optimal function. Therefore, biologically, the adaptive homeostasis acts as molecular or biochemical shock (stress) absorber. For examples, the NRF2 system acts as the signal transduction analogue against oxidative stress that arrives due to any internal or external stress to body. NRF2 directs signals to many enzymatic system including antioxidant enzymes such as superoxide dismutase, catalase and glutathione reductase. Such transcription of NRF2 system shows a rapid response in young organisms and the rate of rapid response is slowly lost as the body ages. It indicates that with age the body declines the capacity of adaptive homeostasis. Hence, aged organisms cannot cope to a higher level of stress, whereas, a young body can do it easily. This is a simple demarcation of young and adult or aged in relation to homeostasis and ageing (Kuchel, 2020).

There are many cytoprotective pathways get switched on as a juvenile body gets younger. Slowly, these mechanisms are also lost with time, giving the opportunity to the body to age faster or slower that depends how quickly or slowly the (adaptive) homeostasis is lost by the body, respectively. The chronic activation of cytoprotective pathways can lead to pleiotropic outcomes. In *C. elegans*, activated SKN-1/NRF2 stemming from defective mitochondrial homeostasis, drives early reproductive senescence in males. It is a bright example of how homeostasis is also related to

mitochondrial functionality leading to energy homeostasis. The endocrine secretions that are associated with the relevant physiological systems also contribute to control homeostasis process because they direct the metabolic pathways.

At molecular level it is noticed that the educed signaling of growth hormone alters the metabolism of methionine, in turn it upregulates defense mechanisms and maintains young DNA methylation patterns, all of which lead to lifespan extension in rodents. Therefore, molecular events such as methylation or demethylation can also contribute to homeostasis maintenance as well as to the ageing process. In last few decades few drugs such as the anti-diabetic medicine metformin can modulate metabolism by regulating sugar level as well it shows involvement in anti-ageing associated events. Its function is found to be conserved along the animal kingdom ranging from helminthes to human. Metformin is found to maintain the nuclear pore and nuclear leakiness and it down regulates mTOR signaling system. mTOR signaling system is considered as an ageing enhancing event and therefore, it also de-regulate body homeostasis.

Homeostasis does not mean to only at cell or at body level. It can start with molecular level, to cell, to organ and finally to body response level. So, regulation of any molecule such as NRF2 or mTOR can regulate homeostasis and finally, the prolonged affects to ageing. As our understanding of the intricacies of this regulation of homoeostasis is developed so that's the capacity of human body to capitalize on these systems to improve health across the lifespan. Emerging work points to Nrf2-Keap1 signal transduction pathway inhibitors, including Bach1 and c-Myc, both of whose tissue concentrations increase with age, as possible major causes for age-dependent loss of adaptive homeostasis (Pomatto and Davies, 2017).

Conclusion

The main molecular symptoms of aging includes genomic Instability, telomere Shortening, epigenetic alterations, loss of proteostasis, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. The molecular symptoms of aging reflect the underlying biological processes that drive the gradual decline in cellular and tissue function over time. Key features such as genomic instability, telomere shortening, epigenetic alterations, mitochondrial dysfunction, and loss of proteostasis collectively contribute to the deterioration of the body's repair, regenerative, and immune systems. These molecular changes not only serve as hallmarks of aging but also as potential biomarkers and targets for intervention. Understanding them provides valuable insight into why aging occurs and how it leads to age-related diseases such as cancer, neurodegeneration, cardiovascular disorders, and metabolic dysfunction. Importantly, many of these molecular symptoms are not

fixed-they are influenced by lifestyle, environment, and emerging medical technologies. As a result, the study of molecular aging opens new opportunities for developing anti-aging therapies, promoting healthy longevity, and extending not just lifespan, but healthspan.

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