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Chapter 7: Diagnosis of the aging process: Biomarkers, mechanisms, and multidisciplinary approaches for healthspan optimization

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Abstract

The diagnosis of the aging process involves identifying biological, physiological, and molecular indicators that reflect the progressive decline in an organism's functional capacity. Traditional clinical markers, such as decreased muscle mass, reduced bone density, and cognitive impairment, are now complemented by molecular biomarkers, including DNA methylation patterns (epigenetic clocks), telomere length, mitochondrial function, and levels of inflammatory mediators. Advances in imaging techniques, blood-based biomarker profiling, and genetic analyses have enhanced the ability to assess biological age versus chronological age. Early and accurate diagnosis of the aging process enables better risk assessment for age-related diseases and provides opportunities for personalized interventions aimed at promoting healthy aging and extending healthspan.

Keywords: Age-related Disease Risk, Biological Aging Diagnosis, Biomarkers of Aging, Epigenetic Clock, Inflammatory Markers, Mitochondrial Function, Telomere Length.

7.1. Introduction

The diagnosis of the ageing process involves identifying and assessing the biological, physiological, and functional changes that occur as individuals grow older. Unlike traditional disease diagnosis, which focuses on specific conditions, diagnosing ageing is more complex and involves evaluating gradual, systemic declines that affect

multiple body systems. Recent advances in biomedical science have introduced the concept of biological age, which may differ significantly from chronological age. Tools such as epigenetic clocks, biomarkers of cellular senescence, telomere length measurement, and metabolic assessments are increasingly being used to understand how fast or slow a person is aging at the molecular and cellular levels.

In addition to laboratory markers, physical assessments—like muscle strength, mobility, cognitive performance, and immune function—also contribute to diagnosing the ageing process. Together, these approaches offer a comprehensive view of an individual's ageing trajectory, enabling more personalized strategies for health monitoring, disease prevention, and healthy ageing interventions.

7.2 Molecular mechanism and dynamics of ageing

Ageing of unicellular and multicellular eukaryotic living beings is a tangled natural marvel, which is showed as an age-related useful decrease brought about by a dynamic dysregulation of certain cellular and organismal procedures (López-Otín et al., 2013). Numerous incessant sicknesses are related with human maturing. These maturing related maladies incorporate cardiovascular ailments, endless obstructive aspiratory sickness, endless kidney ailment, diabetes, osteoarthritis, osteoporosis, sarcopenia, stroke, neurodegenerative infections (counting Parkinson's, Alzheimer's and Huntington's illnesses), and numerous types of malignant growth (Niccoli et al., 2012; De Cabo et al., 2014).

There are numerous speculations of the biological reasons for ageing, which proposes that a wide range of systems add to the ageing process (Kirkwood, 2005; Weinert and Timiras, 2003). Kirkwood suggested that the basic reason is for the most part because of the collection of arbitrary unrepaired molecular damage after some time (Jansen-Du¨ and Osiewacz, 2002; Kowald and Kirkwood, 1996). This inevitably prompts cell defects and tissue deregulation bringing about expanded delicacy and age-related maladies (Geva-Zatorsky et al., 2006), as delineated in Figure 7.1.

Our cells have quality control frameworks with the goal that molecular harm can be perceived, fixed or expelled. Notwithstanding, because of the vitality prerequisites of these frameworks, substantial support isn't 100% proficient. Every single molecular component is defenceless to damage including DNA, proteins, lipids and organelles. Wellsprings of damage may be natural or intrinsic, for example, reactive oxygen species (ROS) and reactive nitrogen species (RNS) or extrinsic, for example, UV light, irradiation and exposer to toxins. As far as ageing, exposer to wellsprings of harm over the human life expectancy will fluctuate among people and may to a limited extent clarify the heterogeneity in how people age (Vijg and Suh,

2013). Other contributing components incorporate hereditary qualities, epigenetics, diet, physical activity.

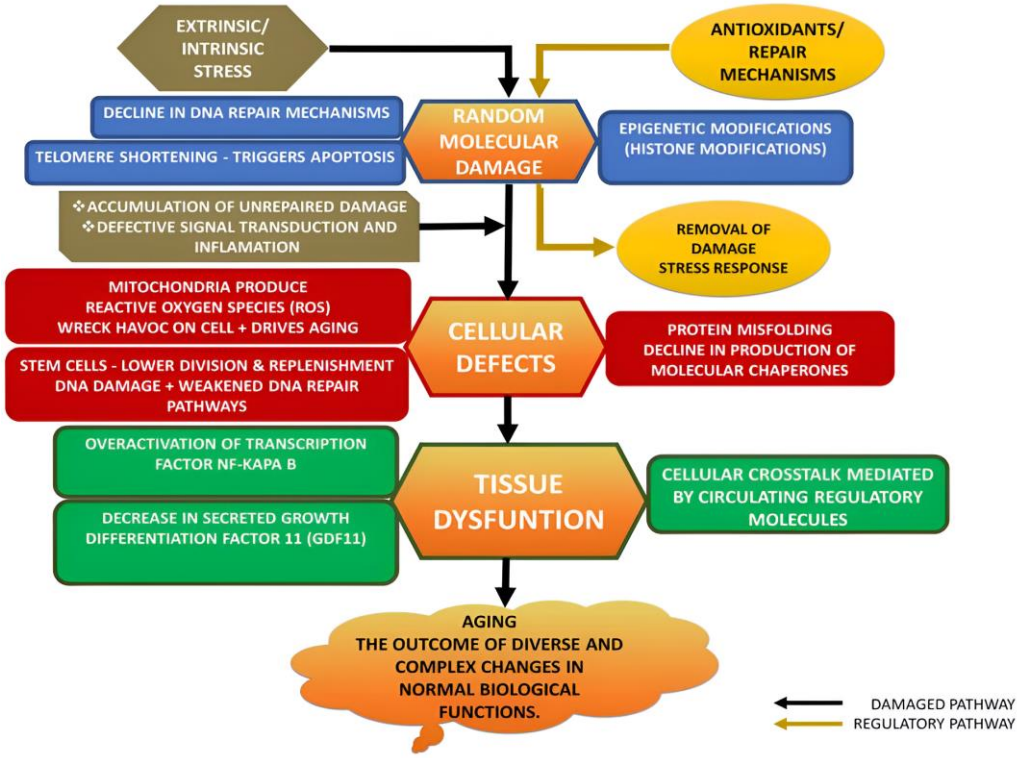

Figure 7.1 Dynamics of ageing in animals.

Numerous investigations into the molecular mechanisms of ageing have concentrated on a specific hypothesis, for example telomere shortening, accumulation of somatic mutations protein damage or mitochondrial dysfunction. In any case, in the late 1990s, it was understood that individual mechanisms can't enough clarify the ageing process (Holliday and Kirkwood, 1981) and that we expected to think about the interaction among these distinctive systems.

7.3. Molecular mechanisms of ageing

The molecular mechanism of the ageing would be the one of the essential reason is aggregation of unrepaired DNA damage has for some time been proposed as a noteworthy causal factor (Zheng, 1991). DNA is susceptible to harm because of replication errors, natural worry because of ROS and extrinsic stress, for example, UV light and irradiation. Maximum damage to DNA is identified and fixed by means of the DNA damage reaction (DDR) including ATM and p53 signaling. In any case, progressively complex sores may stay unrepaired and amassing of such sores may

prompt apoptosis, cell senescence or malignant growth. Numerous models have analyzed the job of DNA damage on cell senescence dependent on cells in culture, for example, human fibroblasts (Tan, 1994; Kirkwood and Proctor, 2003; Lahav et al., 2004; Bar-Or et al., 2004).

These models did exclude subtleties of the molecular components associated with the DNA damage reaction, in which cell signaling pathways including ATM/ATR, p53 and p21 are enacted, bringing about cell cycle capture to take into consideration conceivable repair. DNA damage instigated by irradiation causes dimensions of p53 and its inhibitor Mdm2 to sway, and it was anticipated that this conduct was because of negative feedback loops in the framework (Vijg and Suh, 2013; Ma et al., 2005; Proctor and Gray, 2008).

7.4. Loss of protein homoeostasis

Protein homoeostasis is vital for cell for normal function and is kept up by quality control frameworks associated with protein synthesis, folding and refolding (Labbadia and Morimoto, 2015). Proof for the role of damaged proteins in ageing is the observed increment in oxidized proteins with age in brain (Smith et al., 1991). If Proteins are vulnerable to oxidative damage those outcomes in either conformational or covalent changes. Most types of covalent damages are irreversible thus proteins with such damage should be degraded so as to forestall their gathering and cross-linking. Conformational impairment might be fixed by molecular chaperones that quandary to the uncovered hydrophobic surfaces and help with refolding. Nevertheless, it has been recommended that the chaperone framework progresses toward becoming overpowered with age prompting a further increment in damaged or misfolded proteins (So¨ti and Csermely, 2003).

7.5. Role of Heat shock protein and Molecular chaperons

Molecular chaperones Hsp90 and the transcription factor heat shock factor-1 (HSF-1) are engaged with up-regulation of feedback mechanism during stress (Zou et al., 1998). Regularly, HSF-1 is kept in an sedentary monomeric state by binding to Hsp90. conversely, under stress conditions, there is an expansion in misfolded proteins that additionally bind to Hsp90 discharging HSF-1, which can then trimerize, translocate to the core and become transcriptionally dynamic. These outcomes of increase in molecular chaperones would be able to help with refolding the denatured proteins.

Proctor et al. (2005) incorporated a mechanism for an expansion in misfolded protein with age because of expanded oxidative stress and furthermore look at the impact of harm to the molecular chaperones themselves. Meanwhile damage is an

arbitrary process, they utilized stochastic recreation and chaperone framework had the capacity to keep up homoeostasis under states of mellow or transient stress. However, incessant stress in the end prompted a moment that the harmony between molecular chaperones and misfolded proteins couldn't be kept up, so the misfolded proteins bound together to form aggregates. Chaperone Hsp70 and its role in apoptosis, which took into consideration the likelihood that cells with high state of misfolded proteins may undergo apoptosis (Proctor and Lorimer, 2011).

7.6. Autophagy

Most proteins are always turned over in the cell in spite of the fact that there is extensive fluctuation in the half-life of various proteins. There are two principle pathways for protein degradation i.e. autophagic framework and the proteasomal framework. These two systems are involved in the removal of damaged protein from the system. Oxidative damaged proteins might be removed by 20S proteasome (Davies, 2001) or the ubiquitin/proteasome framework (UPS) (Shang and Taylor, 2011), yet their productivity decreases with age prompting a development of harmed protein particularly in post-mitotic cells (Shang and Taylor, 2011). It has been speculated that harmed proteins overpower the limit of proteasomes and that combined with age-related damage to the proteasome results in a self-enhancing cycle of impairment (Gray et al., 2003).

The autophagic system consists of two important framework such as macroautophagy and chaperone-intervened autophagy (CMA), which both functionally deterioration with age (Carroll et al., 2013). CMA is up-regulated by oxidative stress so as to degrade damaged proteins (Kiffin et al., 2004). It is hindered by mutant proteins, for example, changed α-synuclein (Cuervo et al., 2004). There is cross-talk among autophagy and apoptotic pathways, and a numerical model was utilized to look at how dimensions of stress decide the switch between these two results (Tavassoly et al., 20115).

7.7. FOXO signaling

The transcription family protein known as Fork head box O proteins (FOXO) are conserved all through species from *Caenorhabditis elegans* to Human and it has for quite some time been realized that balance of these proteins can increment or abatement life expectancy (Greer et al., 2007; Kenyon, 2010). Dalle Pezze al. (2012) demonstrated that an increase in FOXO3A activity decreased mitochondrial size and reduced DNA damage showing that FOXO3A adjustment could assume a key job in cell senescence (Wimmer et al., 2014). Smith and Shanley (2010) have demonstrated the detail mechanism of post-translational changes on FOXO proteins explored the impact of ROS on FOXO activation and translocation (Wimmer et al., 2014; Smith and

Shanley; 2010). As a result low oxidative stress, FOXO up-regulated the anti-oxidant defense, while under chronic oxidative stress, it is down-regulated.

7.8. Cytokines

Cytokines are very crucial in the regulation of inflammatory reactions. Their communications are intricate and how they change with age is a significant in a various illnesses. One of the important and major cytokines is interleukin-1 (IL-1) and its significance in infection and its interactions changes in IL-1 signaling with age. Proctor et al. (2014) demonstrated that the collaborations between IL-1 and Oncostatin M (OSM) and their cooperative energy prompts inordinate ligament obliteration. The research group additionally demonstrated the role of IL-1 with cartilage ageing and with various different cytokines, to indicate how changes with age can prompt the progress of cartilage breakdown conditions (Hui et al., 2016).

7.9. Tissue regeneration

A decrease in tissue recuperation is another colossal strategic concern in cell ageing and it is expected a reduction or loss of ability of stem cells and change the intercellular communication (Lo´ pez-Ot´ın et al., 2013; Pekovic and Hutchison, 2008). There are various molecular mechanisms adding to this decrease including assembly of DNA damage, telomere shortening, epigenetic changes and loss of protein homoeostasis (Samani et al., 2001). Taking everything into account, the ceaseless activation of cell reactions decrease in tissue work because of stem cell weariness and intrusion of intercellular signaling process (Lo´ pez-Ot´ın et al., 2013; Samani et al., 2001).

7.10. Dynamics of Mitochondria in Ageing

One of the principle reasons in ageing process is related with the accumulation of damaged mitochondria, which might be because of a debility in mitochondrial turnover and damaged mitochondria have impaired energy metabolism. Kirkwood (Kowald and Kirkwood, 2000) was proposed that a compensatory system of mitochondria that decline rate of degradation, which results in clonal expansion of damaged mitochondria. Likewise, aged muscle filaments regularly contain a diminished number of mutant mtDNA. Some researchers recommend that mitochondrial damage amasses quicker in post-mitotic tissues than mitotically active tissues. Significantly, the researchers recommend that in vitro investigations of ageing underestimate the influence of mitochondrial-related cell degradation to cell ageing (Kowald and Kirkwood, 2000).

Mitochondria have been seen to attempt a complex fusion– fission cycle process (Chauhan et al., 2014). Kowald and Kirkwood (2011) suggested that fusion is

essential, because of the migration of mitochondrial genes to the nucleus and that mitochondrial fusion is the basic system directing the aggregation of mitochondrial mutants with age, while fission may enhance this amassing (Kowald and Kirkwood, 2011; Kowald et al., 2005). Mouli et al. (2009) discovered that amid states of raised damage, the selectivity of a combination occasion is especially significant as it permits an expansion in the recurrence of fusion without including damaged content expulsion. Tam et al. (2013) showed that low fission– fusion diminished mtDNA mixing bringing about an uneven dissemination of mutant mtDNA inside mitochondria and expanded stochasticity from a mitophagic occasion. Subsequently, clonal extension of mutant mitochondria turned out to be progressively more frequent. Additionally, they recommended that defensive retrograde signaling relied upon fusion– fission productivity (Tam et al., 2013) and decrease in the rate of fusion– fission cycling may reflect a foundational adjustment to delay life expectancy by lessening damage spread (Figge et al., 2012).

7.11. Clinical markers for normal and early ageing

Apart from the six hallmarks of ageing i.e. genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion and altered intercellular communication, there are several additional molecular markers also considered to ascertain the onset on faster ageing processes (Xia et al., 2017). The American Federation for Ageing Research (AFAR) has proposed four important criteria for a molecule preferably to be considered as biomarker for ageing. As per AFAR, the molecular markers must predict the rate of ageing, it must able to monitor a basic events that underlies whole processes of the ageing, the marker must be able to convey about process of ageing not the effects of disease, the biomarker must independently and repeatedly be tested in a non-invasive way i.e. without harming the person and finally, the molecule must traceable or identified or common in humans as well as in laboratory animals, so that works on it can be carried out (Xia et al., 2017). However, many gerontologists found that molecule(s) obeying all above criteria set by AFAR in human are unlikely to be identified. Therefore, while identifying molecular markers of ageing; any two or three combinations of the above criteria such as “a biomarker that must able to predict the rate of ageing and it must be able to monitor the fundamental events of ageing processes” are considered.

At the first hand, DNA and chromosomes are considered as the basic hubs to give signals for the ageing process. The telomere constitutes ribonucleoprotein complexes and it becomes shorter after each successive replication. The shortening of telomere as discussed earlier is positively associated with cardiovascular diseases, cancer and many neurological disorders, on the other hand which are common in the

ageing process (Balasubramanyam et al., 2007; Wang et al., 2012; Baragetti et al., 2015; Morgan et al., 2018; Badran et al., 2021; Chen et al., 2021). The association between DNA damage and repair is an intricate process and highly required for is believed to be decreases with age.

7.12. Neural Dysfunction

Morphology to molecule level changes are occurs in brain with increasing age. Frontal cortex of brain shrink upto 50% so memory decline occurs and brain activation becomes more bilateral for memory tasks. At cellular level there may be changes in dentritic arbour, spines and synapses. Dendritic sprouting may occur thus maintaining a similar number of synapses **(**Kolb and Wishaw, 1998) and compensating for any cell death (Li et al., 2004**)**. Conversely a decrease in deudritic synapses or loss of synaptic has also been described. In normal ageing white matter may decline and the myelin sheath deteriorate after around the age of 40 years.

According to **(**Parkin, 1997) memory functions can be broadly divided into four sections – episodic memory, Semantic memory, procedural memory and working memory. Episodic and semantic memory are important regarding ageing because episodic memory decline from middle age onwards (Nyberg and Ba¨ckman, 2004) and semantic memory increases gradually from middle age to the young elderly but then declines in the very elderly.

All these changes may be due to neurotransmitters like dopamine and serotonin. The level of dopamine decrease 10% per decade from early adulthood and associated with declines in cognitive and motor performances. Serotonin level also falls with increasing age and implicated in the regulation of synaptic plasticity (Gurvich et al., 2018). Sex hormones also affect the cognitive process in adulthood. And that change in sex hormone occurs in ageing particularly in women at menopause.

Conclusion

The diagnosis of the ageing process is an evolving field that combines clinical evaluation with emerging molecular and physiological markers to better understand how individuals age. By distinguishing between chronological age and biological age, modern diagnostic approaches offer more accurate insights into a person's health status, functional decline, and risk of age-related diseases. Tools such as epigenetic clocks, telomere length analysis, and biomarkers of inflammation and cellular senescence are helping scientists and clinicians assess ageing at a deeper level. When combined with functional assessments like cognitive tests, physical fitness evaluations, and organ performance metrics, they provide a comprehensive picture of the ageing process. In conclusion, diagnosing ageing is not about labeling age as a disease, but

rather about identifying early signs of decline to promote healthier, longer lives. With continued research and technological advancements, the ability to monitor and manage the ageing process will play a crucial role in preventive healthcare and personalized medicine.

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