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Review article

MOLECULAR AND METABOLIC DETERMINANTS OF AGEING: PATHWAYS, PHENOTYPES, AND INTERVENTIONS

Kanaki Niranjan*, Movaliya Vinit

Department of Pharmacognosy, K.B. Institute of Pharmaceutical Education and Research, A constituent college of Kadi Sarva Vishwavidyalaya, Sector-23, Gandhinagar, Gujarat, India

Abstract

Background: Ageing is a universal biological process marked by a gradual, time-dependent decline in physiological functions and a higher risk of disease and death. Although multicellular organisms have mechanisms to detect and repair molecular and cellular damage, their functional capacity consistently decreases with age. This paradox has spurred extensive research.

Objective: The main theories of ageing, including genetic/programmed and random wear-and-tear processes, along with cellular mechanisms of senescence, are explored.

Key findings: Disruptions in insulin signalling are associated with multiple age-related phenotypic changes, including insulin resistance, visceral adiposity, and chronic inflammation. These alterations contribute to the development of major diseases such as type 2 diabetes, cardiovascular disorders, neurodegeneration, and cancer. Both non-pharmacological interventions (e.g., calorie restriction and exercise) and pharmacological strategies targeting AMPK activation, adipocyte function, and nutrient absorption demonstrate potential in modulating ageing and extending lifespan.

Conclusion: Ageing is a multifactorial process influenced by genetic, metabolic, and environmental factors. Targeting key metabolic pathways offers promising avenues for promoting healthy ageing.

Keywords: Ageing, Insulin signalling, FOXO transcription factors, AMPK pathway, Calorie restriction, Lifespan extension, Telomere shortening, Rasayana

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*Corresponding Author

1. Introduction

The ageing phenomenon may be defined as the progressive deterioration of physiological functions in a multi-cellular organism, leading to an increased morbidity and mortality risk (1). Ageing is the single most significant risk factor for the development of various human pathologies such as neurodegenerative conditions, cardiovascular diseases, cancer, type-2 diabetes mellitus, osteoporosis, sarcopenia, and cataracts formation (2). The understanding of the mechanism behind the biological ageing is highly important from a clinical point of view because of the potential applications in developing new therapies to slow down or prevent age-related diseases.

There appears to be a fundamental paradox in the way the ageing process functions in biological systems because of their capacity to recognise and repair molecular and cellular damages, while their functioning capacity constantly decreases with time. In response to the question about the causes of this paradox, two major classes of theories were formulated that focus on either age-related inbuilt genetic programs or accumulation of various kinds of damage. Importantly, experimental evidence has been found that indicates that ageing is an active and regulated biological process which can be modified through genetic manipulation, drug treatment, or diet (3).

This paper aims to outline the major theories of ageing, the cellular mechanisms involved in the biological ageing process, the relationship between ageing and metabolism in terms of genetics and physiology, as well as the possible therapeutic approaches to extending healthy lifespan.

2. Theories of Ageing

Competing theories of ageing can be broadly categorised into two overarching frameworks: those proposing that ageing is driven by inbuilt, genetically encoded mechanisms, and those attributing senescence to the progressive accumulation of stochastic molecular damage — the so-called wear-and-tear theories. Current evidence suggests that both frameworks are complementary rather than mutually exclusive.

2.1 Genetic and Programmed Mechanisms

Indeed, each species of animal life shows a distinct natural lifespan of anything from one day in case of mayflies (Ephemeroptera) to over one hundred years in case of some amphibians, which suggests that maximum life span is genetically programmed (4). The fact that different developmental periods like embryonic, infantile, pubertal, or mature age are genetically programmed makes one conclude that aging is also likely to be genetically controlled. Indeed, organisms of the same family demonstrate a similarity in life spans that is not related to any accidental or pathogenic causes of death, which implies that aging is genetically predetermined.

Some ageing-related genes were discovered through cell culture studies and located at chromosome 1, but the exact mechanism of their influence on aging is unclear yet (5). Natural examples include aging disorders, such as the Werner syndrome characterized by mutations in WRN helicase gene that lead to premature aging followed by development of age-related pathologies, such as atherosclerosis, cataract formation, and cancers, with premature mortality in late teens or early twenties (6). One more case of an aging disorder is the Down's syndrome (trisomy 21), where premature Alzheimer's symptoms were observed among other signs of accelerated aging (7).

2.2 Wear-and-Tear Mechanisms

According to the wear-and-tear theory, the aging process occurs due to the regular loss of cells during the physiological functioning of the body as well as the gradual accumulation of sub-lethal damage within the surviving cells, ultimately leading to failure of the physiological systems to an extent that the entire body collapses (8). The wear-and-tear theory explains why each species exhibits a specific lifespan, as all individuals are subject to similar amounts of wear and tear on their cells physiologically.

The cell damage associated with the wear-and-tear theory includes: (i) Cross-links between proteins causing a reduction in the protein's functionality; (ii) Cross-links within the DNA molecules causing mutations and thus making some genes dysfunctional; and (iii) Modifications to the mitochondria DNA molecules, which are prone to oxidative changes due to their location near the respiratory chain, in addition to being devoid of any repair mechanisms.

3. Cellular Mechanisms of Ageing

At the cellular level, ageing can be attributed to several interrelated processes that disrupt cellular homeostasis and affect tissue function. Such ageing processes include the following:

Generation of free radicals: As part of the process of mitochondrial respiration and electron transport, ROS are produced because of chemical reactions within the mitochondrion. As time passes, oxidative stress resulting from ROS damages proteins, lipids, and nucleic acid molecules in the cells (10).

Shortening of telomeres: The Hayflick limit represents each round of somatic cell division as shortening the telomeric DNA sequences at the ends of chromosomes. Once telomeres become critically shortened, cell senescence sets in and may eventually lead to apoptosis (11).

Degradation of DNA repair mechanisms: With time, the efficiency of the processes involved in DNA repair declines, allowing mutations in DNA to accumulate and adversely affect gene expression (12).

Damage to mitochondrial DNA: The accumulation of somatic mutations in mitochondrial DNA leads to a decrease in oxidative phosphorylation efficacy and a further increase in free-radical formation (9).

Disruption of the control of calcium influx into cells: Disruptions in calcium levels in the intracellular environment negatively affect multiple cellular processes and contribute to the decline in cellular activity (8).

Accumulation of toxic by-products of metabolism: Accumulation of such molecules as lipofuscin or AGEs interferes with cellular metabolism and adversely impacts cell functions (9).

Activation of genes of ageing and cell death: With age, genetic regulatory programmes for ageing and apoptotic processes activate more actively and restrict cell life span (3).

As shown above, cellular ageing-related processes are closely related and represent an interdependent network of cellular damage. One particularly revealing case of cellular ageing is the so-called Hayflick phenomenon, which proved that diploid human cells have limited proliferative potential during cultivation in vitro. After 50 or so cycles of cell division, cells permanently cease dividing, entering a state of cell senescence called replicative senescence (11). The ability

to divide progressively decreases with donor age, and elderly donor-derived cells make significantly fewer divisions than foetal or adult cells.

4. Ageing and Metabolism: Genotypic Links

Ageing was thought to be an uncontrolled biological decline for much of the twentieth century. Yet genetic experiments on simpler organisms have challenged this notion by showing that ageing can indeed be controlled to some degree by genes (3). Indeed, one dramatic example of such studies came from experiments involving the nematode worm C. elegans, where it was shown that a decrease in the activity of a single gene called daf-2, which encodes an insulin/IGF-1 receptor homologue, doubled lifespan (13).

More importantly, the genes involved in controlling lifespan show evolutionary conservation. This implies that lifespan is controlled by the same set of genes in organisms ranging from worms to mammals, forming conserved pathways of longevity.

4.1 The Insulin/IGF-1 Signalling Pathway

The Insulin/Insulin-like Growth Factor (IGF-1) signalling (IIS) pathway is considered one of the most highly studied longevity pathways. The DAF-2 insulin/IGF-1 homologue triggers PI3K homologue AGE-1 to phosphorylate AKT kinases (homologues AKT-1 and AKT-2), that subsequently phosphorylates FOXO transcription factor DAF-16 and suppresses its activity. Suppression of DAF-2 activity promotes translocation into the nucleus of activated transcription factor DAF-16 to promote transcription of various longevity genes related to stress resistance, metabolic homeostasis, and cellular health (13,15).

IIS pathway shows an extraordinary level of conservation in other organisms like Drosophila melanogaster and mammals. Activation of the insulin/IGF-1 receptor in mice triggers a cascade of phosphorylation resulting in the phosphorylation of transcription factors FOXO1, FOXO3, FOXO4, and FOXO6 and suppression of their activities (16). Genetic inhibition or pharmacological interference with IIS pathway promotes longevity and enhances stress resistance in diverse biological models (15).

4.2 FOXO Transcription Factors

FOXO family transcription factors are an example of a subfamily of transcription factors, which are considered key determinants of longevity following from insulin and IGF-1 signaling pathways (16). Four paralogues of FOXO transcription factors (FOXO1, FOXO3, FOXO4, FOXO6) participate in regulation of a wide range of physiological functions in mammals that are directly involved in longevity and aging:

Autophagy regulation: FOXO upregulates the process of autophagy leading to the degradation of toxic proteins and organelles. Considering that aging leads to gradual accumulation of damaged proteins in the cytoplasm, induction of autophagy via FOXO signaling can play a crucial part in restraining proteotoxic stress (17).

Antioxidative response: FOXO enhances the ability of cells to cope with oxidative damage by inducing the transcription of antioxidative enzymes such as SOD and catalase (18).

Maintenance of stem cell homeostasis: FOXO participates in preserving the regenerative function of stem cells. Aging is usually accompanied by progressive shift towards cell accumulation at the expense of cell loss due to age-related decline of stem cell regenerative function. The action of FOXO transcription factors in stem cell niches facilitates self-renewal capacity and ensures normal cell turnover (19).

The role of FOXO3 polymorphisms in longevity has been established by several human epidemiological studies (16).

5. Ageing and Metabolism: Phenotypic Links

5.1 The Role of Insulin: From Homeostasis to Pathology

Insulin exerts dual effects in metabolic and ageing processes that can be visualized on a spectrum ranging from positive effects to adverse effects based on the physiological situation. During normal metabolic conditions, insulin helps in maintaining glucose homeostasis via its suppression of hepatic gluconeogenesis and insulin-dependent glucose uptake in peripheral cells, specifically skeletal muscles. At the same time, insulin increases energy stores by means of adipogenesis where excess energy is stored in adipose tissues in the form of triglycerides.

In contrast, prolonged excessive caloric consumption results in the formation of hypertrophic and lipotoxic adipocytes with increased lipolysis and thus high circulating free fatty acid (FFA) concentrations and pro-inflammatory cytokine secretion, especially TNF-α. This interferes with insulin function in target organs and creates a vicious circle consisting of insulin resistance and hyperinsulinaemia. Furthermore, with age comes a shift in fat depot distribution from subcutaneous fat to visceral fat, further contributing to adverse effects of hyperinsulinaemia and insulin resistance (20).

The adverse consequences of prolonged hyperinsulinaemia and insulin resistance in aging include a variety of effects with clinical implications. Increased visceral fat tissue induces increased production of adipokines and FFAs, chronic sub-clinical inflammation, and renal sodium retention and endothelial dysfunction that contribute to the development of arterial hypertension and atherosclerosis as well as cardiovascular diseases. MAP kinase (MAPK) activation due to hyperinsulinaemia enhances the proliferation of tumour cells, increasing the risk of cancer. In addition, neuroinflammation caused by insulin resistance in periphery may contribute to the development of Alzheimer's disease (21).

Therefore, it appears that the continuous excess of insulin is disadvantageous and a decrease in its level while providing enough insulin to maintain glucose homeostasis may increase life span. Of course, it is essential to break a cycle of insulin resistance and hyperinsulinaemia either pharmacologically or by lifestyle change to achieve such a lifespan-extending effect (3).

5.2 The AMPK Pathway

AMP-activated protein kinase (AMPK) is a conserved serine/threonine kinase which functions as a central regulator of energy balance and longevity (22). AMPK is stimulated via phosphorylation and is also a direct sensor for intracellular levels of AMP relative to ATP. These conditions occur in energy deprivation states such as during exercise or caloric restriction. On stimulation, AMPK acts to regulate food intake and expenditure.

The effect of AMPK activation on life span is mediated at least in part through inhibition of mTOR complex and its downstream effector S6K. A reduction in TOR via genetics in C. Elegans and Drosophila results in a 30% increase in life

span, and knock-out of S6K in mice affords protection from aging and high calorie diet induced obesity and insulin resistance (23). Rapamycin, an inhibitor of mTOR, has been shown to be a maximal lifespan extender in mice even when given late in life (24). Over-expression of AMPK increases the life span of C. Elegans, Drosophila and yeast indicating the conservation of this pathway throughout evolution (22).

6. Non-Pharmacological Interventions

6.1 Calorie Restriction

CR-short for calorie restriction (i.e. Reduced calories without malnutrition)- is the most rigorously verified non-genetic factor currently known to lengthen the lifespan of a variety of model organisms (25). By increasing insulin sensitivity, lowering plasma insulin levels, and thus reducing visceral adiposity, CR counters the negative effects of hyperinsulinaemia. Indeed, studies in rodents have shown for over seventy years that mean and maximum lifespan are significantly increased by caloric restriction; the restricted rodents also show reduced disease susceptibility and delayed onset of myriad age-related physiological changes such as obesity, impaired learning, memory deficits, loss of motor control and dermal changes (25). CR is probably acting via multiple mechanisms-reduced IIS signaling, enhanced activity of sirtuins and AMPK, reduction in oxidative damage, enhanced autophagy etc. Data in humans include epidemiological data regarding chronically modest populations, as well as intervention data where restriction has improved risk factors. However, concerns remain about long-term applicability in humans, and long-term efficacy and safety.

6.2 Physical Exercise

The cellular AMP:ATP ratio is increased when muscles are working, thereby stimulating AMPK and mimicking many of the molecular effects of CR, in the whole body (22). Physical activity increases insulin sensitivity, decreases abdominal fat accumulation, reduces inflammation and improves cardiovascular and musculoskeletal performance, and epidemiologically, physical activity is correlated with decreased overall mortality and reduced age-related disease incidence, thus a non-pharmacological approach to ageing healthy (26).

7. Pharmacological Interventions and Drug Discovery

With increasing knowledge about the molecular mechanisms of aging as well as the limitations of behavioural interventions, there is significant effort and enthusiasm for developing pharmacological methods that can affect aging. The three major drug discovery targets that can be inferred from the above mechanistic scheme are as discussed below.

7.1 Pharmacological Approaches to Calorie Restriction

To promote reduced caloric intake, two pharmaceutical approaches have been used, inhibition of feeding behaviour and blocking absorption of nutrients. Several appetite suppressants, like sibutramine, block the reuptake of serotonin and noradrenaline into the central nervous system thus stimulating the reuptake of the neuro-transmitters in the feeding response. Absorption can be blocked using G1 lipase inhibitors, like orlistat (blocking absorption of fat), or -Glucosidase inhibitors, like acarbose and miglitol, which slow digestion of carbohydrate and diminish the postprandial glucose and insulin response (27).

7.2 Regulating Adipocyte Function

Studies of genetically modified mice have illustrated how alterations to adipocyte physiology can have a significant impact on longevity. Transgenic mice, carrying a construct that substitutes the transcription factor C/EBP with the dominant negative form C/EBP, develop lean animals whose adipocytes display increased mitochondrial content leading to an imbalance from fat storage to dissipation. Notably, the life span of C/EBP/ transgenic mice is increased by 22% compared to controls (28). These studies demonstrate that the transcription factors that regulate differentiation and physiology of adipocytes are drug target candidates in longevity therapies.

PPAR agonists another strategy by which adipocyte energy metabolism can be regulated. In adipocytes, activation of PPAR induces gene expression that promotes the catabolism of fats and dissipation of energy rather than storage. GW-501506 (GlaxoSmithKline) and pioglitazone (Mitsubishi Pharmaceuticals) were previously shown to have the ability to modulate adipocyte energy expenditure in pre-clinical trials (29).

7.3 Activating AMPK

The fourth, and final, major approach to lifespan extension is to pharmacologically activate AMPK. The biguanides metformin and phenformin activate AMPK via phosphorylation, and in non-diabetic rodents treated with phenformin, maximum lifespan has been reported to be extended by as much as 20% (30). Since metformin is now the primary choice treatment for type 2 diabetes mellitus, the use of metformin as an anti-aging drug is under investigation. Epidemiological evidence suggests that type 2 diabetic individuals treated with metformin display reduced mortality rates when compared to non-diabetic controls (31). A study to determine if metformin has an effect on age-associated disease in humans, known as TAME (Targeting Aging with Metformin), is now underway. AICAR is an example of a purine analogue that also activates AMPK, and new, small molecule activators are also under investigation.

8. Challenges and Future Directions

Although progress in aging biology over the last 30 years has been enormous, there remain formidable hurdles to translate this knowledge into therapeutic interventions. These include:

The identification of new chemical entities directed against the identified targets of the signaling pathways that control the aging process still poses a considerable medicinal chemistry challenge. It will require sophisticated drug discovery strategies and thorough preclinical target validation, considering the complexity and redundancy of these pathways and achieving selectivity and acceptability toxicity profile.

Well-validated biomarkers of the aging process are needed to run clinical trials of anti-aging drugs. Today, most studies of aging use chronological age as a surrogate outcome; the development of markers of biological age, such as telomere length, DNA methylation age, or markers of inflammation profiles, could be of particular interest for the validation of intervention efficiency. Extensive preclinical and clinical studies will be required for regulatory authorities to accept the use of these markers, which represents a challenging task.

Traditional Ayurvedic medicine uses many herbs as 'Rasayanas' (rejuvenative) drugs, and their mechanisms may

provide a fertile ground for identifying new anti-aging leads. These include herbs such as Withania somnifera (ashwagandha), Emblica officinalis (amla), Bacopa monnieri and Tinospora cordifolia that have been used for centuries to improve the well-being and longevity. Identification of the compounds that are active in these herbs and their mechanisms of action may reveal new potential therapeutic targets and leads in a systematic investigation based on current pharmaceutical and phytological knowledge (32).

Future of medicine will involve a shift from predominantly curative approaches to the diseases associated with aging toward rejuvenative strategies focusing on the maintenance of the physiological functioning and health span throughout life. The integration of modern genomics and metabolomics with drug discovery and traditional medicine may herald the arrival of the next generation of anti-aging drugs.

9. Conclusion

The complex multifactorial biological process of ageing, influenced by genetic programs, stochastic molecular damage and metabolic dysregulation, has recently been understood as an adjustable phenomenon instead of a phenomenon, that can be altered through genetic modification and drugs, by influencing evolutionarily conserved pathways including the insulin/IGF-1 signaling pathway, FOXO mediated transcription and AMPK activation. The results obtained from calorie restriction and exercise programs imply that healthy life span extension is possible by modulation of these signaling pathways and various drugs targeting caloric intake, adipocyte function and AMPK activation are under pre-clinical or clinical investigation, but many barriers exist in target validation, biomarker development and translation from model organisms to human clinical studies. Nevertheless, the progress made in aging biology promises longer, and healthy life span in human being.

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