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Biological Basis of Aging: Theories and Explanations

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Introduction

Aging is a multifactorial process that involves diverse changes at the cellular, tissue, organ and the whole body levels, leading to decreased functioning, susceptibility to diseases and ultimately death. The maximum lifespan of an organism is a constitutional feature of speciation to polygenic controls and to environmental influences. Healthy aging and maximum longevity may depend on the genetic make-up of an organism under a strict control by the nature and nurture. Various theories have been put forward to explain the phenomenon of aging.[1] They have been broadly divided into four main categories *viz.*, evolutionary, molecular, cellular and systemic. Some of these theories may overlap at various levels of organizations. Alterations with aging of molecular events may lead to cellular changes and these, in turn, contribute to organ and systemic failure with evolutionary implications for reproduction and survival. The theories of aging are summarized in the Table 4.1 and the details of these theories with their explanations are discussed below:

Table 4.1 Theories of aging

Evolutionary	
Antagonistic pleiotropy	Genes beneficial during development and deleterious at later ages.
Disposable soma	Preferential allocation of energy resources for reproductive cells to the detriment of maintenance and survival of somatic cells.
Mutation accumulation	The force of natural selection declines leading to accumulation of deleterious mutations with effects confined to late life.
Molecular	
Codon restriction	Fidelity/accuracy of mRNA message translation is impaired with aging due to cell inability to decode the triple codons (bases) in mRNA molecules.
Somatic mutation	Exposure to radiation shortens lifespan due to an increased incidence of mutations and loss of functional genes.
Error catastrophe	Errors in information transfer due to alterations in RNA polymerase and tRNA synthetase may increase exponentially with age resulting in increased production of abnormal proteins.
Gene regulation	Changes in expression of genes regulating both development and aging.
Dysdifferentiation	Gradual accumulation of random molecular damages impair the regulation of genes expression.
Cellular	
Wear and tear	Intrinsic (e.g., oxidative processes) and extrinsic (e.g., ambient temperature) influence the lifespan.
Free radical	Free radicals formed by oxidative reaction accumulate and damage membrane, cytoplasm and nucleus
Apoptosis	Dysregulation of the process of programmed cell death leads to an imbalane in organismic homeostasis.
Systemic	
Neuroendocrine	Control of homoestasis by neural and endocrine signals becomes disorganized with aging; physiologic performance decline while pathologic responses to stress increase in number and severity.
Immunologic	Immune system reduces defenses against antigens and loses the capacity to recognize self, resulting in increasing incidence of infections and autoimmune diseases.

Adapted from: Sharma R. Theories of Aging. In. Physiological BAsic of Aging and Geriatrics, 2nd ed., Timiras PS, (ed). CRC Press, Boca Baton, FL, 1994.

Evolutionary Theories of Aging

Antagonistic Pleiotropy

The cause of senescence may be attributed to the declining force of natural selection as a function of age of adult somatic cells. Natural selection that favors genes with early beneficial effects leads to deleterious effects later on. Certain genes confer survival advantages early in life and cause harmful physiological effects in later stages of lifespan, a phenomenon termed negative or antagonistic pleiotropy.[2] Genes that specify instructions for synthesizing reproductive hormones also serve as examples of antagonistic pleiotropy. Long-term exposure of the estrogen used to enhance fertility increases the risk of breast cancer in aged women. Hypothalamus and pituitary gland control ovarian function and also contribute to aging of the ovary in rodents. At the same time, ovarian signals appear to promote aging of the hypothalamus and pituitary.

Disposable Soma Hypothesis

This hypothesis suggests that aging has evolved as a byproduct of optimization of the allocation of energy and resources for various work performed by the organism. It assumes that energy resources are better spent for maintenance of reproductive cells, responsible for species survival.[3] Maintenance and repair would include the prevention and removal of DNA damage, accuracy in macromolecular synthesis and degradation of defective proteins. This hypothesis balances the maintenance and repair of somatic cells on one side and the reproduction and fertility on the other. If more energy is used for maintenance of somatic cells, less will be available for reproduction and *vice versa,* suggesting that senescence acts as a price paid for sexual reproduction.

Mutation Accumulation

This theory has three assumptions: mutations act additively on age-specific survival or fecundity, there are mutations that affect only late age classes and all mutations have equal effects. Genetic variance for age-specific mortality rates decreases at advanced ages, an effect that may be related to the deceleration of mortality rate at later ages. Evidence suggests that mutations affect the mortality rates of particularly younger age classes than the older age classes. The accumulation of mutations leads to their combined effects, the influence of which can span several age classes. Mutation accumulation arises when the force of natural selection has declined to a point, where it has little impact on recurrent deleterious mutations with effects confined to late life.[4] However, current evidence suggests that mutation can have an important impact on aging, but the impact is not additive, is not made up of mutations with equal effects and is not confined to late age classes. Any correlated effect on fitness at early ages would tend to prevent these mutations from accruing as a function of age.

Molecular Theories

The genetic basis of aging is deduced from the duration of the three phases of the lifespan—developmental, reproductive and senescent. In most animals, the reproductive phase occupies a very significant period in the lifespan followed by a post-reproductive phase. In mammals, the time taken to reach reproductive maturity is directly correlated with maximum lifespan. Humans and other long-lived mammals take a longer time to reach reproductive maturity than other animals and continue to live longer even after reproduction has ceased. Each species has a fixed lifespan, e.g., houseflies live for 30 days, rats for 3 years, dogs for 14 years and humans for 100 years. Even the children of long-lived parents generally live longer. These observations make us believe that the lifespan is governed by our genetic make-up. There are genetic diseases such as progeria, wherein the mutation of lamin A gene leads to a 6–8 times faster aging of progeroid syndromes.

Codon Restriction

All the genetic information stored in DNA directs the structure and function of the organism, although only part of the total DNA information is utilized by the cell at a given time. The information is transferred from DNA to messenger RNA (mRNA) by the process of transcription. The functional mRNA in eukaryotic cells is derived by excision of intervening sequences (introns) and splicing. This mRNA is then translated into proteins. The codon restriction theoryof aging is based on the hypothesis that the fidelity accuracy of translation, which depends on the cell's ability to decode the triple codons (three bases) in mRNA molecules, is impaired with aging. [5] Accurate readings of codons are done by two main biomolecules: transfer RNAs (tRNAs) and aminoacyl-tRNA synthetases. Any changes in these tRNAs and aminoacyl-tRNA synthetases may alter the rate of translation.

Somatic Mutation

Alteration in the structure of DNA molecules alters the genetic message and results in differences in protein structures which lead to physiologic deficits. According to this theory, exposure to radiation damages DNA and subsequently induces mutations, which, in turn, lead to progressive loss of genes in post-mitotic cells throughout the lifespan.[6] The increased rate of mutations and loss of

functional genes decrease the rate of production of functional proteins and cause cell death. Increased exposure to X-rays shortens life expectancy and increase chromosomal aberrations in a dose-dependent manner. The frequency of chromosomal aberrations increases greatly with age. In young non-cigarette smoking adults, the frequencies of aneuploidy, breakage and structural chromosomal rearrangements are six times less than in aged individuals. However, somatic mutation theory is no longer regarded as a probable cause of aging as this theory does not explain the mutation load in different organs and tissues and also of the kinetics of mutation accumulation. Mutation accumulation has been suggested as a consequence rather than a cause of aging.

Continuous introduction of chemical lesions in the DNA by a variety of environmental, endogenous and exogenous agents leads to somatic mutations. Oxygen-free radicals and several physiological processes could act as sources of age-associated endogenous DNA damage. Exogenous agents, such as ultraviolet light, ionizing radiation and a range of chemicals in food can induce DNA damages in their target tissues, e.g., inter- and intra-chromosomal cross-links, DNA single and double-strand breaks, bulky and smaller adducts. Changes in DNA modifications and conformation involve protein-DNA complexes as well as chemical modification of the DNA molecule, e.g., DNA methylation. The mutation frequency has been observed to show organ specificity with advancing age. The hypoxanthine phosphoribosyl transferase (HPRT) locus test have shown that the mutation frequencies in humans increase with age from about 2×10^{-6} in young individuals to about 1×10^{-5} in middle-aged and old individuals.

Error Catastrophe

The form and function of organisms are determined by specific structural and functional proteins. Certain proteins such as RNA polymerase and tRNA synthetases are involved in the synthesis of other proteins. Medvedev first proposed that errors in information transfer from DNA to proteins may be responsible for cellular aging.[7] This concept was extended in a search for errors in transcription and translation processes, which may lead to accumulation of proteins and cause aging. Inaccuracy may occur both in protein and DNA synthesis. The initial error in proteins may be low but errors may increase exponentially as a function of age and lead to error catastrophe and cell death. Functionally, altered enzymes are known to accumulate in various animal tissues with age and the consequent decrease in the functional activity of tissues. Although this theory enthused huge research interest for quite some time, but did not stand the tenets of the proposed hypothesis. The modified proteins during aging may arise due to post-translational oxidative modifications giving rise to an altered protein during aging.

Gene Regulation

According to this theory, senescence results from changes in the expression of genes after reproductive maturity is reached.[8] It is based on the presumption that senescence would follow a pattern similar to that of differentiation and growth, i.e., a sequential activation and repression of certain genes, which are unique to these phases. Sequential activation and repression of genes have been reported for various chains of hemoglobin during the gestational period in humans. Hemoglobin consists of $\alpha_2\varepsilon_2$ chains in the fetus at 1–2 months of gestation. In the later phase of gestation, α chain remains the same and the ε chain is replaced by the β chain, which gives rise to adult hemoglobin $\alpha_2\beta_2$. The lifespan of a species may be divided into three phases: (i) Developmental, (ii) Reproductive, (iii) Senescent. Each phase has a characteristic duration, rate, sequential time-table of events and regulatory mechanisms.

Initiation and duration of developmental and reproductive phases depend on a unique set of genes that are sequentially activated and repressed. Human genetic diseases such as progeria and progeroid syndromes are in agreement with this sequence. Progeria is caused by the mutation of an autosomal gene, lamin A on chromosome 1 in humans. In this case, the newborn child appears normal and grows normally upto about 6 years, when signs of aging (e.g., atherosclerosis, accumulation of lipofuscin, graying of hairs) appear and lifespan is shortened following expression of the mutated gene.

Dysdifferentiation

Gradual accumulation of random molecular damages impairs the normal regulation of gene activity, potentially triggering a cascade of injurious consequences. This process is called dysdifferentiation.[9] Dysregulation of gene may provide a mechanism that links the antagonistic pleiotropy and disposable soma hypotheses into a unified concept of aging. Genes are carefully regulated and proteins produced by gene activity are involved in multiple, often interacting processes. Aging may occur when the normal repair and maintenance functions of cells become dysregulated and gradually lead to impaired physiologic functions. Aberrant expression of genes may play a role in the aging process. There is increased levels of globin RNA in the liver and brain of older mice. Loss of epigenetic control may be a major causal factor for reactivation of genes in the aged. DNA methylation at C≡G bases relates to the inactivation of gene expression and decreases with age in several systems, leading to the reactivation of genes.

Cellular Theories

These theories relate to changes that occur in structural and functional elements of cells with the passage of time. They concern the biomolecules after their synthesis is over, suggesting that these changes impair the effectiveness of molecules as a function of age.

Wear and Tear

The premise of this theory originates from the fact that the lifespan of poikilotherms is shortened by increasing the environmental temperature and prolonged by decreasing it. Rates of chemical reactions increase with increasing temperatures and the reverse is true for low temperatures. An increase in the metabolic rate may shorten the lifespan by accelerating wear and tear.[10] The lifespan of different animal species are inversely proportional to the basal metabolic rate. Basal oxygen consumption rates of short-lived animals, such as rats and mice, are higher than those of long-lived animals such as elephants and humans. This theory has become outdated and theories involving the cellular and systemic systems have gained prominence as they explain specific mechanisms influencing aging.

Free Radical Theory

In the 1950s, Harman proposed the "free radical theory," postulating that damage to cellular macromolecules via free radical production in aerobic organisms is a major determinant of lifespan.[11] Free radicals are molecules containing unpaired, highly reactive electrons, which act as causal agents in the process of aging and contribute to the accumulation of oxidative damage to cellular constituents.

A more modern version of this tenet is the "oxidative stress theory" of aging, which holds that increases in the reactive oxygen species (ROS) accompany aging, leading to functional alterations, pathological conditions and even death. The free radical theory of aging is depicted in Fig. 4.1.

During aerobic metabolism, the electron transport chain in mitochondria is not only a source of ATP, but also of ROS. At moderate concentrations, ROS may have important intracellular signaling functions, particularly for the control of ventilation, nerve transmission and immune regulatory processes. ROS are also considered second messengers involved in activation of NF-κB *via* tumor necrosis factor (TNF) and interleukin-1 and in regulation of mitogen-activated protein kinase (MAPK) pathways. Through these actions, ROS affect cell function, growth and development. High levels of ROS may be incompletely neutralized by antioxidants within the cell, resulting in indiscriminate damage to cellular macromolecules (lipids, proteins and nucleic acids). ROS levels may increase in damaged or aged mitochondria and cause accumulation of ROS beyond physiological levels. Oxidative damage thus caused may be inadequately repaired or eliminated. This can lead to physiological deterioration and phenotypic changes in the elderly and increased incidences of age related diseases and may be a key determinant of maximum lifespan (MLS) of a species.

Excessive ROS can attack proteins, lipids, carbohydrates and nucleic acids leading to oxidative damage of the cells. Lipid peroxidation can lead to loss of membrane barrier function, cell lysis and cell death. Protein carbonyls, a consequence of the oxidative modifications of proteins by ROS, also accumulate with age.[12] Oxidative modification of proteins and lipids is implicated in atherosclerosis, diabetes, Parkinson's disease, hypertension and ulcerative colitis.[13]

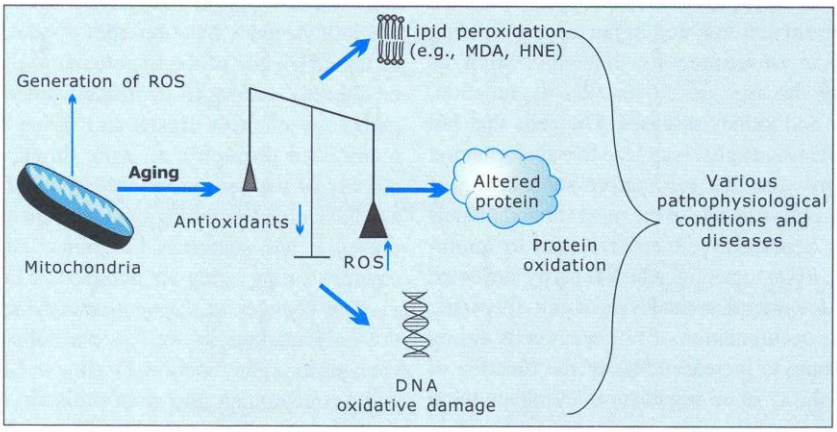

Fig. 4.1 Generation of ROS during aging leads to an imbalance between ROS and antioxidants, giving rise to high levels of lipid peroxidation, protein oxidation and DNA oxidative damage. This sequence of events leads to various pathological condition and diseases during aging.

Cellular Senescence

A normal human cell divides a certain number of times, the number varying with cell type and culture conditions. As the cell divides, the telomeres become so short that they trigger a cell cycle checkpoint that puts the cell into a terminally non-dividing state. This state is termed as "*cellular*" or "*replicative senescence.*" Hayflick and Moorhead showed that embryo-derived fibroblasts can divide 50±10 times before reaching replicative senescence when cultured *in vitro.*[14] The potential number of divisions is known as the "Hayflick limit." In human somatic cells, the telomeres shorten due to the lack of telomerase activity, which results from the absence of expression of the reverse transcriptase subunit (TERT) of the telomerase ribonucleoprotein complex. When cells divide in the absence of telomerase activity, about 40–100 bp of the terminal telomeric repeat DNA are not replicated. This amount is a constant for various types of human cells, thus providing a kind of mitotic counter.[15] Replicative capacity of human fibroblasts in culture decreases as a function of donor's age. Cells from patients with Werner's syndrome have decreased replicative potential and accelerated telomere shortening. Telomere length in lymphocytes has been found to decline with age.

Apoptosis Theory

Apoptosis, the process of programmed cell death, is considered a vital component of various processes including normal cell turnover, proper development and functioning of the immune system, hormone-dependent atrophy, embryonic development and chemical-induced cell death. Deregulation of apoptosis has been implicated as a pathogenic mechanism for a variety of age-related human diseases. Inefficient removal of malignant cells can lead to cancer. On the other hand, excessive apoptotic cell death may result in aberrant cell loss and organ atrophy leading to the occurrence of numerous diseases, such as neurodegenerative diseases, cardiovascular dysfunction, muscular atrophy and kidney diseases. The cells that fail to die (apoptosis-resistant cells) may lead to transformation and neoplastic growth. The replicative senescence of human diploid fibroblasts is one of the most studied models for human aging. Senescent cells are resistant to serum-induced apoptosis, a phenomenon, which is partly attributed to the inability to downregulate the levels of anti-apoptotic, Bcl-2 protein. The accumulation of senescent cells during aging may contribute to increased loss of the function of organs and the inability of an organism to eliminate these cells by apoptotic mechanism may exacerbate this condition.[16] The absence of (apoptosis-susceptible cells) cells prone to apoptotic death may lead to tissue damage. The premature loss of cells in post-mitotic tissues is one mechanism by which deregulated apoptosis can exert deleterious effects during aging. Cardiovascular dysfunction is one such age-related phenomenon, which is associated with an undesired diminution in cell number.

System Level Theories

Rate of Living

This theory posits that a relationship exists between size, reduced metabolism and increased longevity. Certain amount of energy is allocated to the lifespan of every organism. The total amount of energy that could be expended by each unit mass of body tissue over life is the same, although they could use it quickly or slowly. Multispecies analysis of the positive relationship between body size and maximum captive longevity combined with the negative relationship between body size and mass-specific basal metabolic rate such that energy expended per gram per lifetime is approximately independent of body size in mammals and birds.[17] This theory has been discarded as not all alterations in metabolic rate alter longevity and treatments, such as dietary restriction profoundly affect aging rate in rodents without reducing whole animal mass specific metabolic rate.

Neuroendocrine Theory

The effectiveness of homeostatic adjustments declines with age and leads to consequent failure of adaptive mechanisms, aging and death.[18] Adaptation to external and internal stress depends on control mechanisms orchestrated by the combined interplay of the nervous and endocrine systems. The activity of several endocrine glands such as thyroid, adrenal and gonads is controlled directly by the pituitary gland. For efficient adaptation, nervous and endocrine signals must be synchronized and be responsive to the needs of the many functions they regulate. With aging some of the efficiency of the hypothalamo-pituitary axis is lost or altered, leading to decreased function and increased pathology of most organs and tissue systems. Aging is manifested through a slowing down, imbalance in the activity of the neurons and consequent neurotransmitters and hormonal alterations and their repercussions on neural, muscular and secretory functions. The neuroendocrine changes during aging are depicted in Fig. 4.2.

The changes in the neuroendocrine system represent not only markers as well as mechanisms of age-related changes in organ function. Decline in LH and FSH release and a concomitant release of prolactin in aging rat reflect age-related reduction in the release of neurotransmitters by the hypothalamus and serve as a marker of hypothalamic aging. The age-related reduction in the secretion of

melatonin by the pineal gland contributes to aging and age-related diseases as the protective actions of the antioxidant are reduced leading to changes in neuroendocrine functions, metabolism and body composition. The progressive decline in the plasma growth hormone (GH) level is among the most striking changes in the function of the neuroendocrine system during aging. It is accompanied by changes in body composition, which is attributed to a decline in GH release. The hormones, such as insulin, glucagon, glucocorticoids, GH and epinephrine, which regulate glucose metabolism decline with age. GLUT-4 is the protein responsible for glucose transport in muscle and adipose tissue. GLUT-4 mRNA levels have been observed to be reduced in older compared to younger rats.

Hypothalamic-pituitary-adrenal (HPA) axis responsible for stress tolerance undergoes age-related changes.[19] Glucocorticoid receptor expression and glucocorticoid binding in the hippocampus and other brain areas decline significantly during aging, which are attributed to reduced sensitivity to negative feedback inhibition of the HPA axis by natural glucocorticoids or agonist, such as dexamethasone. Age-related decline in melatonin may contribute to changes in the function of HPA axis. Chronic treatment with melatonin to rats exposed to high doses of dexamethasone increases sensitivity to glucocorticoid feedback indicating that melatonin protects the HPA axis from glucocorticoid induced deterioration.

Immunologic Theory

The immune system is programmed to decline over time which leads to an increased susceptibility to infectious diseases. Evidence showed that the effectiveness of the immune system peaks at puberty and gradually declines thereafter with advancement in age. The immunological theory of aging is based on the following observations: (i) There is a quantitative and qualitative decline in the ability of the immune system to produce antibodies, (ii) there are age-related changes in the ability to induce particular subsets of T cells and to produce different types of cell-mediated responses and (ii) there is at least correlative evidence linking these alterations to the involution of the thymus.[20] Dysregulated immune response has been linked to cardiovascular disease, inflammation, Alzheimer's disease (AD) and cancer. The immunological changes during aging are depicted in Fig. 4.3.

Concluding Remarks

Based on the above theories and their explanations, aging seems to be a multifactorial process and there is no single theory at present that explains all the phenotypic changes,

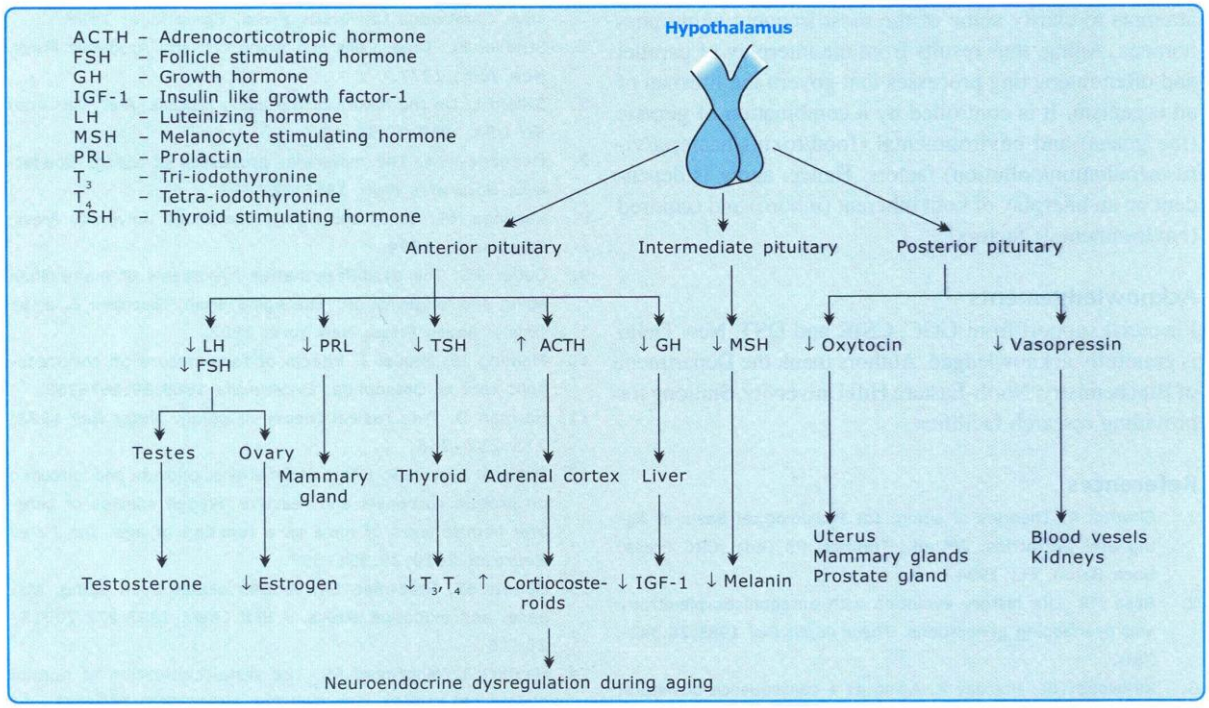

Fig. 4.2 Effect of aging on the neuroendocrine system. The age-related decrease in the level of LH, FSH, PRL, TSH, GH, MSH, oxytocin, vasopressin and increase in the ACTH level lead to alterations of the hormonal effects on the peripheral endocrine glands.

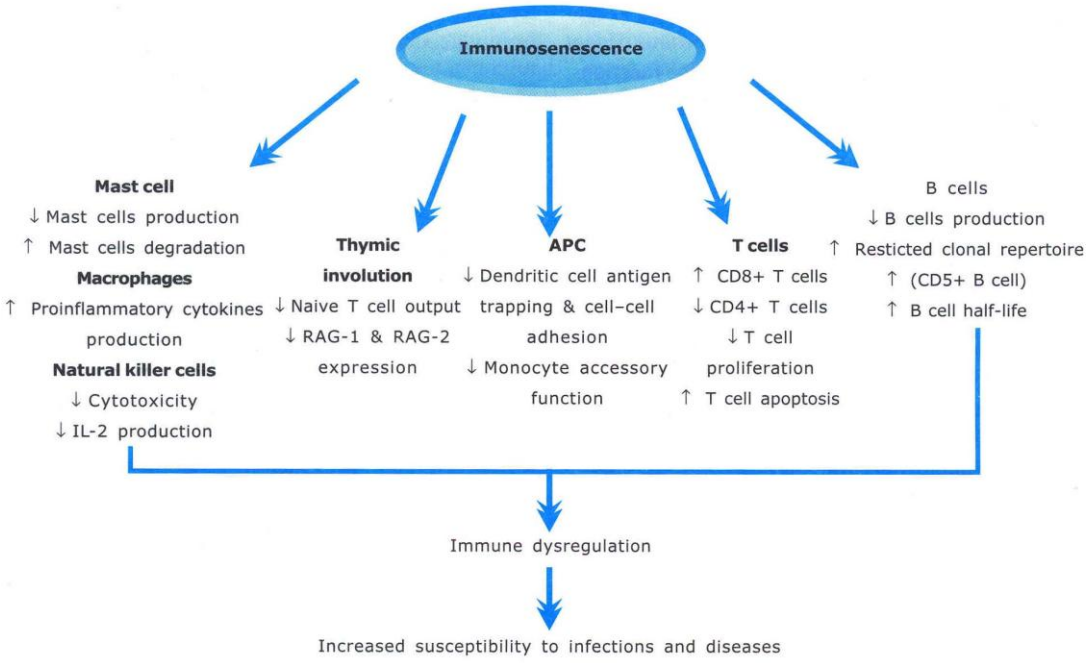

Fig. 4.3 Immunologic theory of aging. Immune dysregulation gives rise to increased susceptibility to infection and diseases during aging. (RAG-1 & RAG-2, recombination activating gene-1 & 2; IL-2, interleukin-2)

which occur during aging. However, each one of them attempts to clarify some of the most frequent aging phenomena. Aging, thus results from the interplay of parallel and often interacting processes that govern the lifespan of an organism. It is controlled by a combination of genetic (the genes) and environmental (food/toxins/bacteria/viruses/radiation/pollution) factors. Hence, aging is dependent on an interplay of both inherent (inborn) and acquired (environmental) factors.

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