Geriatrics Hub

Theories of aging

Definitions, biological and psychosocial theories

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Cellular and Molecular Theories of Aging

KEY CONCEPTS: Definitions

Chronological Age: Number of years/months/days a person has been alive

Biologic Age: determined by intracellular and molecular processes – how old a person seems.

Heterogeneity of Aging: individuals within a species age at different rates; different organs may age at different rates within a single individual.

Cellular or Replicative Senescence: when diploid cells cease to divide. In younger organisms, cellular senescence is thought to function as a way to prevent damaged cells from proliferating or accumulating. Older organisms consistently have higher levels of DNA damage, shorter telomeres, and other factors that contribute to a greater quantity of senescent cells. Older stem cells replicate less frequently compared to younger stem cells. This is likely due to the accumulation of damaged DNA and increased deficiencies in DNA damage repair which become more prevalent with aging (23). There is a positive correlation of lifespan with the efficiency of DNA repair. Contributing factors include altered intercellular communication, loss of proteostasis (protein homeostasis) and genomic instability

Hayflick Limit: Human cells have a finite number of replications before they become quiescent. In 1961, using tissue cultures of fibroblast stem cells, Hayflick demonstrated a maximum of approximately 50 doublings of cells

Telomere Length: Considered a major determinant of biologic age. In 1998 Bodner demonstrated that shortened telomeres decrease time to cellular senescence. Telomeres have experimentally been shown to shorten with each successive cell division until no further replication is possible. Shortened telomeres have been found to promote stem cell exhaustion as an organism ages. While certain cells, such as egg and sperm cells, can use telomerase to restore telomeres, this is not present in most adult cells, nor is it effective, when present, after extensive stem cell division.

Proteostasis: impaired protein homeostasis by various mechanisms leading to the accumulation of ineffective and /or toxic proteins.

Necrosis: a form of cell death generally caused by external mechanisms resulting in injury and cell death associated with inflammation.

Apoptosis: Programmed Cell Death (PCD) (1972); non-degenerative, non-inflammatory active, genetically controlled process which occurs in normal adult tissues and by which multicellular organisms regulate cell numbers and remove unwanted or damaged cells.

Immunosenescence: Decreased humoral and cell-mediated immunity by virtue of decreased numbers and function of lymphocytes (B cells, T cells, NK cells) and phagocytes due to decreasing number of hematopoietic stem cells (HSC) with age. This results in reduced efficacy of the immune response to vaccinations, infections, inflammation and cells that are becoming

malignant, as well as an increased failure to recognize self (increased risk of autoimmune disease).

Epigenetic Alterations: Changes in the regulation of the expression of gene activity without alteration of genetic structure (NCI Thesaurus).

Genomic Instability: An increased tendency of the genome to acquire mutations when various processes involved in maintaining and replicating the genome are dysfunctional (MeSH). Telomere attrition and accumulation of mutations due to a progressive deficiency in the repair of DNA damage with age remain leading causes of genomic instability. Epigenetic alterations have recently emerged as key contributors genome structure and function that accompany aging, as well.

Rectangularization of the Survival Curve: Due to improved living conditions over time there has been a steep rise in life expectancy, followed by a relative plateau, with an upper limit of approximately 12 decades to the human life span. Graphically, this creates a more rectangular form, as the percentage of individuals who survive to an older age increases.

All of the above contribute to varying degrees to the theories of aging described below many of which overlap and are not mutually exclusive.

THEORIES OF AGING:

There are more than 300 theories of aging, none of them fully explain the aging process

1. Wear and Tear Theory: Dr. August Weismann, 1882. Cells and tissues gradually and inevitably deteriorate over time. This theory appears overly simplistic today, and does not take into consideration the cellular mechanisms that contribute to repair, nor does it account for the variability in aging within and between species.

2. DNA Damage Theory: (Alexander 1967). Aging as a consequence of the accumulation of nuclear DNA damage. Various mechanisms include increased apoptosis, cellular senescence, oxidative damage, cross linkages and cell dysfunction. There are 2 major types of errors that occur in DNA – damage and mutation. Damage refers to physical abnormalities in DNA which produce an abnormal structure and can be recognized and repaired. A mutation is a change in the base sequence of DNA and cannot be repaired. It is therefore replicated when the cell replicates. Although distinctly different from each other, DNA damages and mutations are related because DNA damages often cause errors of DNA synthesis during replication or repair and these errors are a major source of mutation. Mutations can cause alterations in protein function and regulation. Whereas DNA damages in frequently dividing cells, give rise to mutations, and are thus a prominent cause of cancer, the accumulation of DNA damages in infrequently dividing cells are likely a prominent cause of aging.

3. Oxidative Damage / Free Radical Theory: increased levels of reactive oxygen species (ROS) from dysfunctional mitochondria promote aging (Gerschman 1954, Denham Harman 1956). It is now thought that the presence of ROS are integral to normal cell homeostasis, and actually protect cells from damage, however, beyond a certain threshold, the concentration of free radicals can negatively impact the cellular environment and exacerbate DNA damage.

4. Error Catastrophe Theory: Leslie Orgel (1963); refers to the extinction of an organism as a result of an exponential increase in the accumulation of errors with age, resulting in an excessive number of mutations which leads to a critical level of ineffective or toxic proteins.

5. Programmed Aging (Biological Clock): Incorporates the concepts of apoptosis, the Hayflick Limit, and the progressive shortening of telomeres with each division. It is based on the premise that mammals purposely deteriorate with age because a limited life span provides evolutionary benefits. This can also help to explain the concept of the rectangularization of the survival curve.

6. Altered Intercellular Communication: incorporates neuro-endocrine (hypothalamo-pituitary-adrenal (HPA) axis) and immunologic theories, whereby failure or dysfunction of cells with systemic and integrative function gradually cause

homeostatic failure. The metabolic, neuroendocrine and immune responses observed with caloric restriction may be explained in part by this theory. In certain species caloric restriction increases longevity in association with increased tissue sensitivity to insulin, decreased oxidative damage, enhanced defenses against stress, infections and cancer, and reduction of cross-linking in collagen. This has not been proven in humans, however.

7. Cross-Linking Theory: Johan Björkstein in 1942; aging results from the accumulation of intra- and inter-molecular covalent bonds, termed "cross-links." Over time, these cross-links result in the alteration of the chemical and biological properties of the cell which in turn can translate into significant dysfunction of body systems. There are several age-related manifestations of the accumulation of cellular cross-links and the resulting cellular dysfunction. For example, cross-links are associated with the loss of elasticity in skin and muscle tissue, stiffening of blood vessel walls, changes in the lens of the eye, delayed wound healing, and reduced joint mobility in aging individuals.

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Psychosocial Theories of Aging

Psychosocial theories of aging refer to theories that focus on the social and psychological aspects of successful aging. Three major psychosocial theories have been proposed to attempt to explain successful aging. These include the activity theory, disengagement theory and the continuity theory.

Activity Theory:

- The Activity Theory, proposed by Havighurst & Albrecht (1961), posits that there is a positive relationship between a person's level of activity and life satisfaction, which in turn increases how positively a person views him/herself and adjusts to old age.
- Successful aging is supported by maintenance of high activity levels according to this theory, those who remain active and engaged tend to report greater life satisfaction and have healthier lives.
- Implicit in this theory is that with the exception of biological changes older individuals have virtually the same psychological and social needs as middle-aged adults.
- They defined activity as "any regularized or patterned action or pursuit that is regard as beyond routine physical or personal maintenance"
- One limitation of this theory is that it fails to acknowledge that the activity being performed should be engaging, challenging and fulfilling rather than simply busy work.

Disengagement Theory:

- Disengagement Theory, developed by Cumming and Henry (1961), describes aging as an "*inevitable, mutual withdrawal or disengagement, resulting in decreased interaction between the aging person and others in the social system that he/she belongs to*"
- Disengagement is described as an irreversible, circular and self-perpetuating process characterized by the loss of central task (work/family), social withdrawal, and decreased investment in the "ego".
- Overall according to disengagement theory, social disengagement is thought to be an adaptive response to aging in which older person relinquish roles while maintaining a sense of self-worth (high morale). This voluntary surrender of activity is thought to permit orderly transfer of power from older to younger generations to the benefit for the individual and society.
- While this theory has been largely discounted today, it has an important place in the history of gerontology as one the earliest psychosocial theories.

Continuity Theory

- The central premise is that in the process of making adaptive choices, older adults attempt to preserve/maintain existing Internal and external structures (e.g. habits, preferences, lifestyles and relationships) by using continuity (i.e. applying familiar strategies in familiar areas of life).
- Notably, continuity is described as a subjective perception that changes are consistent with one's personal history. It can be either internal or external.
    - Internal continuity is individually defined and based on one's beliefs, temperament, affect, experiences, preferences, dispositions and skills.
    - In contrast external continuity is defined in terms of remembered physical and social environments, relationships and activities. It arises from being in familiar environments, practicing familiar skills and interacting with familiar people.
- With that said, optimum continuity refers to when an individual feels that the pace and degree of change occurring is in line with their personal preferences, social demands and coping capacity.
- Overall continuity is thought to represent an adaptive strategy wherein adults draw upon their past experiences to deal with changes associated with normal aging.
- This theory however fails to consider those who have unhealthy habits and lifestyles in their middle age. Such individuals age poorly and will continue to further deteriorate (likely at an accelerated pace) in older age if their lifestyle choices do not improve.
- The theory also is not very helpful in understanding the reality of pathological aging.

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