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Commentary

Modern Biological Theories of Aging

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ABSTRACT: Despite recent advances in molecular biology and genetics, the mysteries that control human lifespan are yet to be unraveled. Many theories, which fall into two main categories: programmed and error theories, have been proposed to explain the process of aging, but neither of them appears to be fully satisfactory. These theories may interact with each other in a complex way. By understanding and testing the existing and new aging theories, it may be possible to promote successful aging.

Key words: Aging; Biological; Theory; Programmed; lifespan

Why do we age? When do we start aging? What is the aging marker? Is there a limit to how old we can grow? These questions are often pondered by the mankind in the past couple of hundred years. However, in spite of recent advances in molecular biology and genetics, the mysteries that control human lifespan are yet to be unraveled.

Many theories have been proposed to explain the process of aging, but neither of them appears to be fully satisfactory (1). The traditional aging theories hold that aging is not an adaptation or genetically programmed. Modern biological theories of aging in humans fall into two main categories: programmed and damage or error theories. The programmed theories imply that aging follows a biological timetable, perhaps a continuation of the one that regulates childhood growth and development. This regulation would depend on changes in gene expression that affect the systems responsible for maintenance, repair and defense responses. The damage or error theories emphasize environmental assaults to living organisms that induce cumulative damage at various levels as the cause of aging.

The programmed theory has three sub-categories: 1) Programmed Longevity. Aging is the result of a sequential switching on and off of certain genes, with senescence being defined as the time when age-associated deficits are manifested. Dr. Davidovic et al discuss the role of genetic instability in aging and dynamics of the aging process (1). 2) Endocrine Theory. Biological clocks act through hormones to control the pace of aging. Recent studies confirm that aging is hormonally regulated and that the evolutionarily conserved insulin/IGF-1 signaling (IIS) pathway plays a key role in the hormonal regulation of aging. Dr. van Heemst discusses the potential mechanism underlying IIS and aging process(2). 3) Immunological Theory. The immune system is programmed to decline over time, which leads to an increased vulnerability to infectious disease and thus aging and death. It is well documented that the effectiveness of the immune system peaks at puberty and gradually declines thereafter with advance in age. For example, as one grows older, antibodies lose their effectiveness, and fewer new diseases can be combated effectively by the body, which causes cellular stress and eventual death (3). Indeed, dysregulated immune response has been linked to cardiovascular disease, inflammation, Alzheimer's disease (AD), and cancer. Although direct causal relationships have not been established for all these detrimental outcomes, the immune system has been at least indirectly implicated (4).

The damage or error theory include 1) Wear and tear theory. Cells and tissues have vital parts that wear out resulting in aging. Like components of an aging car, parts of the body eventually wear out from repeated use, killing them and then the body. So the wear and tear theory of aging was first introduced by Dr. August Weismann, a German biologist, in 1882, it sounds perfectly reasonable to many people even today, because this is what happens to most familiar things around them. 2) Rate of living theory. The greater an organism's rate of oxygen basal

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metabolism, the shorter its life span (5). The rate-of-living theory of aging while helpful is not completely adequate in explaining the maximum life span (6). Dr. Rollo proposes a modified version of Pearl's rate of living theory emphasizing the hard-wired antagonism of growth (TOR) and stress resistance (FOXO) (7). 3) Cross-linking theory. The cross-linking theory of aging was proposed by Johan Bjorksten in 1942 (8). According to this theory, an accumulation of cross-linked proteins damages cells and tissues, slowing down bodily processes resulting in aging. Recent studies show that cross-linking reactions are involved in the age related changes in the studied proteins (9). 4) Free radicals theory. This theory, which was first introduced by Dr. Gerschman in 1954, but was developed by Dr. Denham Harman (10, 11), proposes that superoxide and other free radicals cause damage to the macromolecular components of the cell, giving rise to accumulated damage causing cells, and eventually organs, to stop functioning. The macromolecules such as nucleic acids, lipids, sugars, and proteins are susceptible to free radical attack. Nucleic acids can get additional base or sugar group; break in a single- and double-strand fashion in the backbone and cross link to other molecules. The body does possess some natural antioxidants in the form of enzymes, which help to curb the dangerous build-up of these free radicals, without which cellular death rates would be greatly increased, and subsequent life expectancies would decrease. This theory has been bolstered by experiments in which rodents fed antioxidants achieved greater mean longevity. However, at present there are some experimental findings which are not agreed with this early proposal. The review by Igor Afanas'ev shows that reactive oxygen species (ROS) signaling is probably the most important enzyme/gene pathway responsible for the development of cell senescence and organismal aging and that ROS signaling might be considered as further development of free radical theory of aging (12). 5) Somatic DNA damage theory. DNA damages occur continuously in cells of living organisms. While most of these damages are repaired, some accumulate, as the DNA Polymerases and other repair mechanisms cannot correct defects as fast as they are apparently produced. In particular, there is evidence for DNA damage accumulation in non-dividing cells of mammals. Genetic mutations occur and accumulate with increasing age, causing cells to deteriorate and malfunction. In particular, damage to mitochondrial DNA might lead to mitochondrial dysfunction. Therefore, aging results from damage to the genetic integrity of the body's cells.

Since the 1930s, it has been found that restricting calories can extend lifespan in laboratory animals (13). Many studies were performed to try to elucidate the underlying mechanisms. However, our knowledge remains limited at the genetic and molecular levels until 1990 (14). Recently, Michael Ristow's group has provided evidence that this effect is due to increased formation of free radicals within the mitochondria causing a secondary induction of increased antioxidant defense capacity (15). In this special issue, Dr. Shimokawa and Dr. Trindade discuss recent findings on restricting calories-related genes or molecules in rodent models, particularly on the roles of fork head box O transcription factors, AMP-activated protein kinase, and sirtuins (particularly SIRT1) in the effects of restricting calories in rodents (14).

Some neurological diseases are considered to be at high risk with increasing age, for example, AD, which is diagnosed in people over 65 years of age. Discovery of molecular basis of the processes involved in their pathology or creating and studying aging model systems may help our better understanding the aging processing. In the early stages, the most commonly recognized symptom of AD is inability to acquire new memories. Recent studies show that endogenous neural stem cells in the hippocampus of adult brain may involve in memory function (16). Consistently, neural stem cell function in the hippocampus decreases with increased aging (17), but the reasons are still unclear. It is well-known that telomere maintenance appears to be essential for the prolonged persistence of stem cell function in organs with extensive cell turnover (18). In 1961, Dr. Hayflick theorized that the human cells ability to divide is limited to approximately 50-times, after which they simply stop dividing (the Hayflick limit theory of aging) (19). According to telomere theory, telomeres have experimentally been shown to shorten with each successive cell division (20). Certain cells, such as egg and sperm cells, use telomerase to restore telomeres to the end of their chromosome, insuring that cells can continue to reproduce and promote the survival of the species. But most adult cells lack this capacity. When the telomeres reach a critical length, the cell stops replicating at an appreciable rate, and so it dies off, which eventually leads to the death of the entire organism. Telomerase cannot completely prevent telomere shortening after extensive stem cell

division either, providing a putative mechanism for the timely limit of stem cell replicative history and subsequent progressive decay in the maintenance of organ homeostasis at old ages (18, 21). A recent study shows that telomeres shorten with age in neural stem cells of the hippocampus and that telomerase-deficient mice exhibit reduced neurogenesis as well as impaired neuronal differentiation and neuritogenesis (22). Taken together, these findings indicate the link among brain aging, neural stem cells and neurological diseases. Dr. Taupin discusses the association of aging with neurogenesis by emphasizing the role of adult neurogenesis in the pathogenesis of neurological diseases (23).

Overall, while multiple theories of aging have been proposed, currently there is no consensus on this issue. Many of the proposed theories interact with each other in a complex way. By understanding and testing the existing and new aging theories, it may be possible to promote successful aging as well as to enhance the lifespan of mankind.

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