Theories of Aging

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Dr. Neal Fedarko presented an overview of two theoretical categories that encompass explanations of human aging. They include evolutionary theories, which examine why humans age, and physiological theories, which examine how aging occurs.

The evolutionary theories predominantly focus on why aging exists and how aging has evolved as a process. Physiological theories, Dr. Fedarko explained by contrast, attempt to account for how aging occurs in humans and explicate structural and functional changes associated with aging, often focusing on specific aspects or structures that relate to advancing age (e.g., genetic programs, or genes involved in senescence; molecules and their chemical reactions such as free radicals; the activities of cell organelles; the signaling among cells and whole body systems maintaining homeostasis). Physiological theories are often subdivided into program theories, which posit aging as occurring due to intrinsic mechanisms, or may encompass random or stochastic explanations, namely, seeing aging as occurring by chance. Other accounts mix programmatic and stochastic theses.

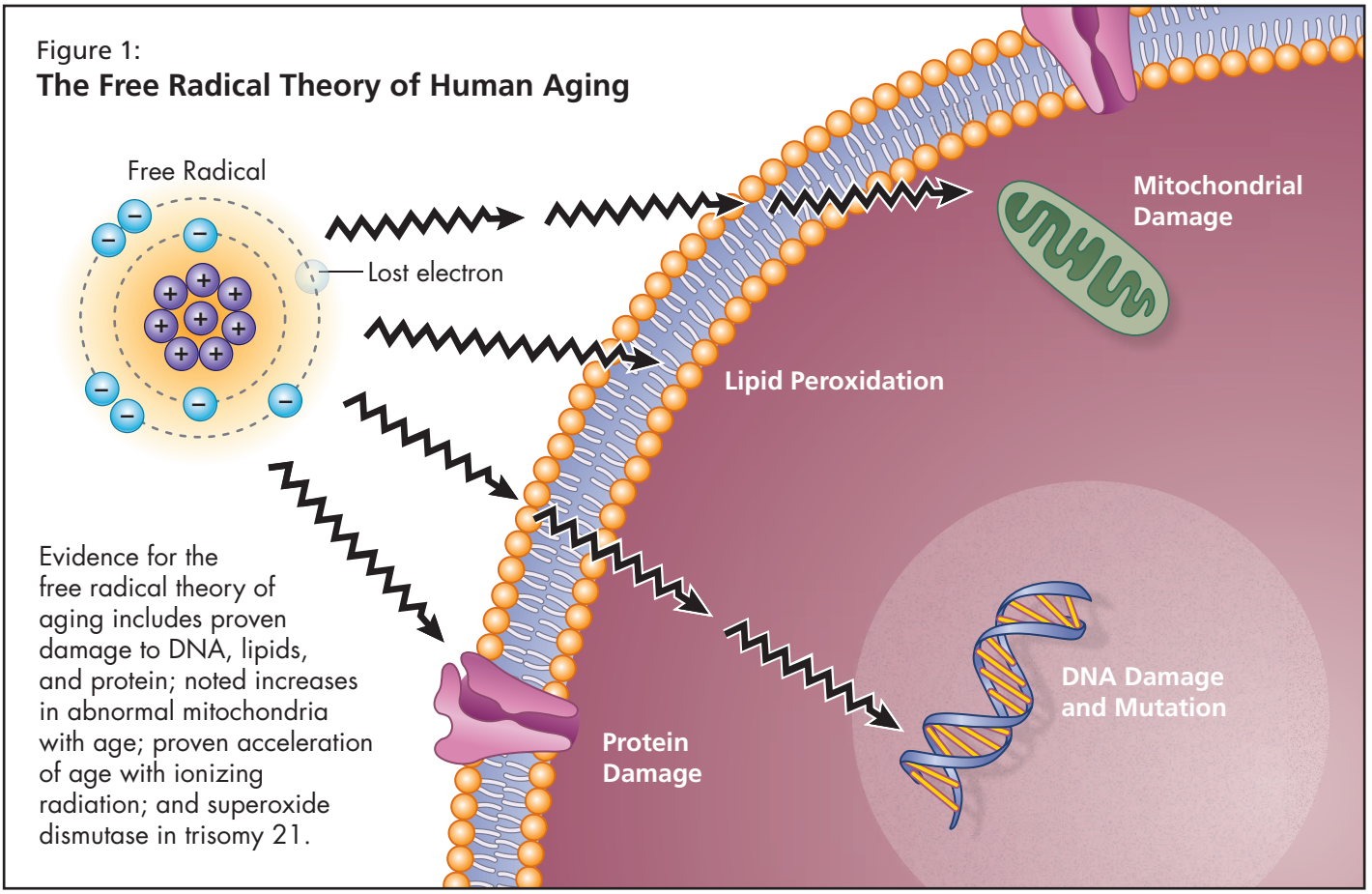
Dr. Fedarko noted that aging theories generally touch upon one another, such that evolutionary theories often incorporate aspects of genetics and behaviour.

Evolutionary theories of aging reach back toward Charles Darwin, who stated nothing explicitly about aging. His successors suggested aging was a mechanism of natural selection that would weed out competitors for finite resources. A contemporary (1950s) evolutionary theory offered by P.B. Medawar known as the mutation accumulation theory (1952) described aging not as adaptive but as a byproduct of physiological events. Mutations, he held, are not screened out but accumulate over time, and they cause aging.

Another contemporary evolutionary theory is the antagonistic pleiotropic theory (1957) offered by G.C. Williams. He hypothesized that genes can have several traits, known as pleiotropy. These can have positive as well as negative effects, which would affect fitness in antagonistic ways. Pleiotropic mutations offer beneficial effects on the young (improved reproductive fitness) but harmful effects on the aged (reduced maintenance of the body). Aging is a product of the pressure of natural selection on these pleiotropic genes.

The trend in the evolutionary theory of aging is to combine the three and state that with increasing age, mortality rises, health and function decline, and that

Figure 1:
The Free Radical Theory of Human Aging



reproductive fitness declines over time. Natural selection is seen as exerting weak effects on mortality.

Dr. Fedarko then reviewed the physiological theories of aging that explore how we age. This question has interested physicians and philosophers as early as Galen (AD 129–c. 199), who saw aging as due to changes in bodily humours.

Posing the question of how we age invites the converse formulation, How do we live as long as we do? This is the approach of gerontology, Dr. Fedarko explained. Every physiological theory of aging identifies a maintaining or homeostatic structure as well as a corresponding theory of that system's malfunction.

Dr. Fedarko offered numerous examples of maintenance or homeostatic systems (e.g., DNA repair, synthesis fidelity, clearance of defective RNA / proteins) that suggest factors in longevity and their corresponding theories of damage or malfunction (e.g., DNA damage, protein errors, and protein modifications) that account for mechanisms of aging.

For example, DNA repair is a target theory of genetic damage. Genes and chromosomes are susceptible to inactivating insults from radiation or other damaging agents. The evidence for the DNA damage theory gives rise to an aging phenotype. There is a demonstrated correlation between the amount of whole body irradiation and a shortened lifespan. There will be a consequent degree of somatic mutations in human T-lymphocytes with increasing age. Premature aging syndromes (e.g., Werner's, Hutchinson-Gilford, ataxia telangiectasia, Cockayne's) also offer compelling evidence. These accelerated aging syndromes share genes that are involved in DNA repair or metabolism, suggesting that if DNA cannot be maintained or repaired there is aging.

All physiological theories of aging have evidence against their explanatory power. Evidence against the DNA theory of aging addresses the theory's implication that longevity should correlate with ploidy—namely, a benefit to more chromosome copies. The more copies, the longer you would live. But the theory is incorrect. The other inherent aspect is that mutations must occur over time, but mutations in DNA are not thought to occur at a high enough rate to give rise to aging phenotypes. It is proven that DNA damage, mutations, and chromosome abnormalities increase during aging, but it is not clear whether they are they contributory or merely associated with aging.

Among the other physiological theories described was the free radical theory of aging, which Dr. Fedarko named the most prominent theory of aging at present (Figure 1). Defense against oxygen free radicals is the homeostatic mechanism, and oxidative damage is theorized as a major contributor to aging. Free radicals can attack DNA and cause DNA base adducts, and modify DNA structure. Free radicals can also attack lipids, causing lipid peroxidation that builds over time. Oxidative damage can have an effect on long-lived cells such as neurons. Dr. Fedarko described the theory as important because of the causative role oxidation is perceived to have on other mechanisms of aging, namely, that is causes a cascade of further damage. It is seen as a causative agent in theories such as error catastrophe and protein modification theory.

Evidence for the theory includes proven damage to DNA, lipids, and protein; noted increases in abnormal mitochondria with age; proven acceleration of age with ionizing radiation; and superoxide dismutase in trisomy 21. However, counterevidence shows that antioxidant therapy does not increase lifespan (although some argue that the right therapeutic formulations have not been found) and that human cells already have effective defenses against radicals; others doubt the causative role of oxidation and see free radical damage as a secondary consequence of other processes.

Several theories once offered as causative theories of aging are now seen as stochastic agents that potentiate other aging mechanisms. Here Dr. Fedarko included the once-prominent toxic theory of aging that held that we accumulate toxic products in our bowel. The idea of toxic insults now contributes to other theories, such as the notion that UV exposure, smoking, and other environmental insults lead to phenotypic changes.

Dr. Fedarko detailed several other theories of aging, including the immunological and endocrine theories of aging, offering positive and negative evidence for each. On balance, he noted that most theories offer themselves as a sole account for human aging, but most embody aspects that synergize with other aging mechanisms. Dr. Fedarko suggested that one not view the many theories of aging as competing or mutually exclusive. Overall the varying accounts of aging reflect current understanding of the multiple maintenance and homeostasis mechanisms that allow for human longevity.