Editorial

Dr Samarendra Kumar Basu
MBBS, DGO, FIMAMS (GO) FELLOW (IAOG),
Consultant, Senior Gynaecologist and Obstetrician,
Trained in Infertility Management, Laparoscopist
Hony Editor, JIMA

Prof Jyotirmoy Pal
MD, FRCP, FRCP, FICP, FACP, WHO Fellow,
Professor, Department of Internal Medicine,
RG Kar Medical College, Kolkata
Guest Editor, JIMA

Biology of Aging

It is difficult to identify the specific biological mechanisms causing aging as aging is a diffused process involving multiple organs due to multiple factors and aging is very slow and long term process. But it is important to understand the same in order to comprehend and manage age related diseases which are main causes of mortality in developed countries. It is also important to note that aging and lifespan differ among individual species and even among individuals of same species. Various theories have therefore been put forward to explain the complex process of aging.

THEORIES OF AGING

Evolutionary Theories : *Programmed death* - proposed by Weissman in 1882, Mutation accumulation - proposed by Medawar in 1952, Antagonistic Pleiotropy[1] - proposed by George C. Williams, Life History Theories, Disposable Soma Theory – suggested by Kirkwood and Holliday in 1979, Grandmother Hypothesis – proposed by Hamilton in 1966, Mother's Curse- Natural selection and Adaptive senectitude - Also known as "reverse antagonistic pleiotropy" and so on.

Molecular Theories : *(a) Codon Restriction* - during translation of mRNA to proteins, the ability of the cell to decode the three bases in mRNA molecules is impaired with aging. This procedure is dependent on tRNA and aminoacyl-tRNA synthetase. *(b) Somatic Mutation* - DNA damage due to exogenous and endogenous causes leads to depletion of functional genes leading to decrease production of functional proteins and eventual cell death. *(c) Error Catastrophe* – Zhores Medvedev proposed that mistakes in transfer of information from DNA to proteins may lead to cellular aging[2]. d) Gene Regulation - aging results from changes in expression of genes by sequential activation and repression of specific genes, following attainment of reproductive maturity. *(e) Dysdifferentiation* - It is the process of initiating a cascade of injurious consequences in the cell due to dysregulation of gene activity caused by accumulation of random molecular damages[3]. Impairment of the normal regulation of gene activity may link the antagonistic pleiotropy and disposable soma hypothesis to form a unified concept of aging.

Cellular Theories : (a) Free radical theory (proposed by Harman in 1956) - free radicals generated during metabolism or irradiation are a major cause for age-related damage[4]. Although, cells have many anti-oxidant mechanism for defence of the oxidative stress but with aging these defences decline leading to cellular aging or death. (b) Mitochondrial dysfunction - Aging leads to altered production of mitochondrial ATP and reactive oxygen species. COX or Complex IV is mostly affected by this resulting injury to the mitochondrial DNA. (c) Telomere Shortening - Telomere is the repetitive nucleic sequence at the end of each chromosome responsible for its protection. Cells from any organism can replicate only a certain number of times before reaching senescent phase. This number of replications is known as the Hayflick limit which is more in younger cells. Telomeres become shorter with each division and once they are too short, cell division stops. This mechanism is called the cellular clock. (d) Altered gene expression, Epigenetics and micro-RNA - With aging, there is reduced expression of genes and mitochondrial protein with increased protein that involved with inflammation and free radicals. This epigenetic state of chromosomes and micro-RNAs control the regulation of genes and protein expression in aging. (e) Impaired autophagy - Cells remove dysfunctional organelles and unwanted macromolecules from the cell by intracellular degradation, lysosomal system and ubiquitin proteasomal system - both of which are impaired with aging. This leads to accumulation of waste products like lipofuscin, a histological feature of cellular aging. Lysosomal enzymes degrades the cell components through a process called autophagy - regulated mostly through ATGs(autophagy related genes).

System Level Theory : The effectiveness of homeostatic mechanisms declines with aging, leading to consequent failure. Adaptations to stress depend on combined interaction between the nervous and endocrine systems which must be well synchronized for efficient adaptation. With aging this synchronization may be lost or altered leading to pathology of various organs.

Immunologic Theory : Aging is associated with raised inflammatory markers like CRP, ESR, cytokines like IL-6 and TNF-a which is known as Inflammaging. T cell decreases with aging while B cells over produce autoantibodies in excess leading to autoimmune diseases, cardiovascular, Alzheimer's disease and cancer.

Genetic Influences in Aging : Huge variability is seen in aging and lifespan in genetically identical population suggesting that aging not solely depend on DNA code. There are some rare genetic disease cause premature aging like Werner's syndrome (mutation of WRN gene), Hutchinson-Gilford progeria Syndrome (mutation of lamin A gene), Cockayne Syndrome (mutation in genes for DNA excision repair proteins ERCC-6 and ERCC-8). Although genes like ApoE and FOXO3A showing increased longevity, ApoE4 isoform is associated with Alzheimer's disease.

Caloric or Dietary Restriction : The reduction of calorie intake by 30% without malnutrition has been shown to increase life span and delay aging (hence periodic fasting is medically approved) by regulation of genes and pathways that control protein synthesis, mitochondrial function, cellular metabolism and autophagy; some of which are – (1) SIRT1-Sirtuins inhibit gene regulation and are regulated by NAD+ and acts on mitochondrial biogenesis. Resveratrol (agonist to SIRT1) proven to decrease cardio metabolic risks in lower species. (2) Target of rapamycin (mTOR) - mTOR is regulated by branched-chain amino acids and influence protein synthesis. Rapamycin is shown to increase lifespan in lower animals. (3) AMPK-regulated by AMP. (4) IGF-1/growth hormone - Both responds to carbohydrate intake and regulates transcription. (5) Spermidine -It regulates autophagy and thus increases lifespan. It has beneficial effects on neurodegeneration.

Exercise: Both mortality and morbidity has been reduced by regular exercise. It has been observed that regular physical activity protects against cardiovascular diseases, diabetes mellitus and osteoporosis. It has been observed that exercise and caloric restriction have synergistic activities on insulin sensitivity and inflammation.

Hormeosis : It describes the protective effects of body developed on exposure to low levels of toxins or stressors such that when exposed to high lethal level, the body is able to resist and overcome it. Caloric restriction thus can be considered as a type of hormeotic stress.

It is important to note that doctors need to understand aging better in order to manage the elderly and more importantly find strategies to delay and reduce the age associated diseases thereby increasing the life and the health span.

References

1 Rose MR — Life history evolution with antagonistic pleiotropy and overlapping generations. *Theor Popul Bio* 1985; **28:** 342-58.
2 Medvedev ZA — The molecular processes of aging. *Sowjetwiss Naturwiss Beitr* 1961; **12:** 1273
3 Cutler RG — The dysdifferentiative hypothesis of mammalian aging and longevity. In: The aging Brain, Giacobini E. et al. (Eds), Raven Press, New York: 1982
4 Harman D — Free radical theory of aging. *Mutaat Res* 1992; **275:** 257-66.