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Ageing and Senescence

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Senescence is the state orprocess of ageing. Cellular senescenceis a phenomenon where isolated cellsdemonstrate a limited ability to divide, while organismal senescence isthe ageing of organisms. After a periodof near perfect renewal (in humans,between 20 and 35 years of age),organismal senescence is characterized by the declining ability to respond tostress, increasing homeostatic imbalance and increased risk of disease. This currently irreversible series of changesinevitably ends in death [1].

Indeed, ageing is not an unavoidable property of life. Instead, it is the result of a genetic program. Numerous speciesshow very low signs of ageing ("negligible senescence"), the best known being trees like the bristlecone pine. In humans and other animals, cellular senescence has been attributed to the shortening of telomeres with each cellcycle; when telomeres become too short, the cells die. The length of telomeres is therefore the "molecular clock", Telomere length is maintained in immortal cells (e.g. germ cells and keratinocyte stem cells, but not other skin celltypes) by the telomerase enzyme. In the laboratory, mortal cell lines can be immortalized by the activation of theirtelomerase gene, present in all cells but active in few cell types. Cancerous cells must become immortal to multiplywithout limit. This important step towards carcinogenesis implies, in 85% of cancers, the reactivation of theirtelomerase gene by mutation. Since this mutation is rare, the telomere "clock" is seen by some as aprotective mechanism against cancer. Research has shown that the clock must be located in the nucleus of each cell andthere have been reports that the longevity clock might be located in genes on either the first or fourth chromosome ofthe twenty-three pairs of human chromosomes [2,3].

In this issue of the Iraqi Journal of Medical Sciences, there are 3 researches dealing with ageing, the first one presented by Dr.May and Dr. Salih, they studied the age-related changes in human skin as a histological and morphometric study. As skin ages, it becomes thinner and more easily damaged. Intensifying this effect is the decreasing ability of skin to heal itself as a person ages.

Among other things, skin aging is noted by a decrease in volume and elasticity. There are many internal and external causes to skin aging. For example: Aging skin receives less blood flow and lower glandular activity.

Another research regarding ageing is the study presented by Dr.Saadet al, as they studied the effect of ageing on testis. It is known that as men age, testicular function declines gradually and moderately. The similarities between the consequences of hypogonadism due to known disease and those of hypogonadism due to aging alone suggest that the decline of testicular function with aging does have consequences.

Several studies demonstrate that the serum testosterone concentration declines with increasing age. Some studies show a preservation of spermatogenesis with increasing age, and others show a decline.

The third study was done by Dr.Idris etal, as they studied the ageing changes of hypothalamo-pituitary gland but in rabbit not in human. The pituitary gland is essential for a normal life span. Certain pituitary hormones and posterior pituitary hormones maintain or prolong life of hypohphysectomised or old rats. These hormones are called life-maintaining hormones.

At present, the biological basis of ageing is unknown. Most scientists agree that substantial variability exists in the rates of ageing across different species, and that this to a large extent is genetically based. In model organisms and laboratory settings, researchers have been able to demonstrate that selected alterations in specific genes can extend lifespan (quite substantially in nematodes, less so in fruit flies, and less again in mice). Even in the relatively simple and short-lived organisms, the mechanism of ageing remain to be elucidated. Less is known about mammalian ageing, in part due to the much longer lives in even small mammals such as the mouse (around 3 years).

The US National Institute on Aging currently funds an intervention testing program, whereby investigators nominate compounds (based on specific molecular ageing theories) to have evaluated with respect to their effects on lifespan and age-related biomarkers in outbred mice[4]. Previous age-related testing in mammals has proved largely irreproducible, because of small numbers of animals, and lax mouse husbandry conditions. The intervention testing program aims to address this by conducting parallel experiments at three internationally recognized mouse ageing-centres, the Barshop Institute at UTHSCSA, the University of Michigan at Ann Arbor and the Jackson Laboratory.

Many have argued that life-span, like other phenotypes, is selected.

• Evolutionary Theories: Enquiry into the evolution of ageing aims to explain why almost all living things weaken and die with age. Exceptions such as rockfish, turtles, and naked molerat are highly informative.

• Telomere Theory: Telomeres (structures at the ends of chromosomes) have experimentally been shown to shorten with each successive cell division [5]. Shortened telomeres activate a mechanism that prevents further cell multiplication. This may be particularly limit in tissues such as bone marrow and the arterial lining where cell division occurs repeatedly throughout life . Importantly though, mice lacking telomerase enzyme do not show a dramatically reduced lifespan, invalidating at least simple versions of the telomere theory of ageing. Mice may be an exception for the theory, as they have long hypervariable telomeres [6], prolonging the period after which telomere shortening would affect life-span. But wild mouse strains do not, and telomere length in these breeds is unrelated to lifespan [7].

• Reproductive-Cell Cycle Theory: The idea that ageing is regulated by reproductive hormones that act in an antagonistic pleiotropic manner via cell cycle signaling, promoting growth and development early in life in order to achieve reproduction, but later in life, in a futile attempt to maintain reproduction, become dysregulated and drive senescence (dyosis)[8].

Some theories suggest that ageing is a disease. Two examples are

• DNA Damage Theory of Ageing: Known causes of cancer (radiation, chemical and viral) account for about 30% of the total cancer burden and for about 30% of the total DNA damage. DNA damage causes the cells to stop dividing or induce apoptosis, often affecting stem cell pools and hence hindering regeneration. DNA damage is thought to be the common pathway causing both cancer and ageing. It seems unlikely that

the estimates of the DNA damage due to radiation and chemical causes has been significantly underestimated. Viral infection would appear to be the most likely cause of the other 70% of DNA damage especially in cells that are not exposed to smoking and sun light. It has been argued, too, that intrinsic causes of DNA damage are more important drivers of ageing [9,10].

• Autoimmune Theory: The idea that ageing results from an increase in autoantibodies that attack the body's tissues. A number of diseases associated with ageing, such as atrophic gastritis and Hashimoto's thyroiditis, are probably autoimmune in this way [10].

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