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The Curious Concept of Ageing

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ABSTRACT

Ageing populations are causing a significant impact into the healthcare and political landscapes of government decision making across the world. But why do we age? This commentary piece sheds some light onto the interesting reasons behind why ageing occurs universally to us all from an evolutionary genetics perspective.

Key Words: Ageing; Evolutionary genetic

The Curious Concept of Ageing

The biological state of an organism reflects it's capacity to regulate and repair many internal biochemical and biological processes as well as effectively deal with the effects of the external environment.[1] This will depend, at least in part, upon the age of the organism. However, although it is apparent that ageing affects all living organisms, why do we age?

What is Ageing?

Ageing may be differentiated into either primary or secondary ageing (Figure 1). Primary ageing refers to the decline of the ability of an organism to maintain tissue homeostasis over time without the influence of external factors and this involves changes in biochemistry, genetics and signalling at a cellular level. Secondary ageing refers to age-related disease, such as atherosclerosis, that arises in healthy people over time without the involvement of external factors such as smoking.

Figure 1 – Primary and Secondary Ageing

Primary Ageing - damage associated with cellular metabolism which adversely affects the maintenance of cellular homeostasis	**Secondary Ageing** - age-related disease processes that arises in healthy people over time.
Oxidative Stress resulting from free radicals generated by cellular metabolism. May result in damage to proteins, lipids and DNA.	Cardiovascular Disease e.g. elevated cholesterol and hypertension that leads to subsequent atherosclerosis
Mitochondrial DNA and Chromosomal DNA damage with adverse effects upon cell metabolism and gene expression/function	Cancer – secondary to neoplastic changes in cells
Reduction in telomere length leading to limited cell replication, defective cellular repair and cellular senescence	Tissue Atrophy – results in cell loss and reduced functional and regenerative capacity of various organs e.g. heart, liver, kidney.
Dysfunctional protein handling and accumulation of damaged proteins within the cell	

Thus, primary ageing provides the biological landscape that is further sculpted by the effects of secondary ageing. Currently there are no treatments or therapies that have been demonstrated to slow or reverse the primary ageing process in humans, although caloric restriction (a reduction in caloric intake whilst maintaining all the required nutritional substances required for normal biological functioning) has shown some promise.[2-4] Various biomedical treatments known to affect longevity do so by their influence on disease development and thus modulate the secondary ageing process.

Evolutionary Genetics

Consideration of ageing from the perspective of evolutionary genetics suggests that longevity genes are not common, as we universally suffer from the effects of secondary ageing. Although it has been argued that there would be a selection pressure to pass on any longevity genes to the next generation, Peter Medawar in 1952 hypothesised that the evolutionary benefit of a longer lifespan was negligible; a hypothesis that provides the basis of the mutation accumulation theory.[5] Medawar proposed that the numbers of adults of any specific age would decrease exponentially because of inherent ecological mortality even in the absence of any ageing process. Thus, even if an animal possessed a longevity gene that mitigated the effects of ageing, the benefit would only be realised if the animal successfully escaped all causes of death (predators, disease etc).[5-6] Therefore, longevity genes have not been subjected to strong selective pressures in the natural world. Despite this, it has become apparent that there is a clear relationship between the genetic make-up of an individual and the ageing process. The existence of such longevity genes in humans is supported by the observation that the children of centenarians have a significantly reduced incidence of diabetes mellitus and heart disease compared to age matches controls.[7-8]

In 1957 George Williams proposed that genes that were of benefit to an organism at a young age could be detrimental at an older age - a concept termed antagonistic pleiotropy. These deleterious 'late-acting alleles' would be passed on to each generation as the benefits of the gene would be expressed at a reproductive age.[9] Although an intriguing concept, there are very few clear-cut examples of antagonistic pleiotropy.[10] Williams suggested a theoretical example of calcium metabolism whereby the efficient absorption of calcium and subsequent calcification of bones would benefit animals during development and growth but could facilitate vascular calcification in later life leading to cardiovascular disease.[6] It is pertinent, however, that recent work suggests that the p53 gene exhibits antagonistic pleiotropy.

The expression of p53 is up-regulated in cells exhibiting DNA damage (e.g. following UV irradiation) and p53 induces cell cycle arrest and the induction of cell death. As a result, the p53 gene is often referred to as the 'Guardian of the Genome' as it provides a defence against the development of cancer. However, the p53 gene is also important in cellular ageing. For example, there is impaired tissue homeostasis and accelerated primary ageing if the anti-proliferative properties of p53 expression are increased in normal stem cells.[11-12] Tyner and colleagues studied transgenic mice that over-expressed p53 and demonstrated that, although they were significantly resistant to spontaneous tumour formation compared to control mice, the p53 over expressing mice showed signs of accelerated ageing.[12] The features of accelerated ageing included age-related organ atrophy, reduced wound healing capacity and a reduced stress response compared to control mice.[12] Furthermore, p53 signalling may play a role in other premature ageing phenotypes via altered protease activity.[13]

The process of ageing involves many physiological changes in an organism. Over time an organism exhibits a reduced ability to maintain cellular homeostasis and this will lead to

reduced growth, defective repair and accumulated damage at a cellular and tissue level. Thomas Kirkwood suggests that the 'disposable soma theory' is an appropriate way of interpreting these cellular changes that occur over time.[6,14] The disposable soma theory considers how organisms allocate key resources such as energy between diverse processes such as growth, reproduction, cellular repair etc. Each organism will achieve a balance of resource allocation according to its particular ecological environment. For example, humans allocate more energy to monitoring DNA integrity and undertaking DNA repair than mice due to different environmental pressures and this is reflected in the higher incidence of tumours in mice.[6] This resource allocation can vary depending upon environmental changes such as increased food availability or a colder temperature. Somatic maintenance aims to provide the organism with a sound physiological condition that would be associated with survival to reproductive age and the opportunity to reproduce. Therefore, the slow accumulation of DNA damage will have no significant impact upon the survival of the species as long as energy is allocated to thermogenesis, growth and reproduction.

In conclusion, ageing itself is an interesting and intriguing concept. There are several theories attempting to explain the most natural of biological phenomenon. However, it appears that organisms undergo ageing as there has been little evolutionary pressure to select organisms possessing longevity genes and animals have typically allocated resources to ensure reproductive efficiency. The only things certain in life will remain death and taxes for some time to come.

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