HOW AND WHY WE AGE: CLINICAL IMPLICATIONS

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ABSTRACT

If ageing is perceived as a disease, then there is the potential that we can cure it! But curing ageing entails understanding it. So far, understanding ageing has remained a challenge. However, observations and research, on model organisms and humans alike, are evolving fast. In this review, we will start with a discussion of both the damage and the programmed theories of ageing. Ultimately, we will focus on calorie restriction and telomere shortening and how these relate to lifespan extension.

INTRODUCTION

Someone once said that life should be lived in reverse; die first to get it out of the way, work for forty years until you are young enough to enjoy your retirement, go to school, play, become a little baby, then spend your last nine months floating in the womb. What if, however, instead of living life backwards, we could just slow down ageing and live longer, healthier lives? What if ageing is just a disease that we could cure? So as to answer these questions, we must first attempt to understand the process of ageing, specifically, how and why we age.

THEORIES OF AGEING

In modern gerontology, theories of ageing fall into two main categories: damage (or error) and programmed theories.[1]

DAMAGE (OR ERROR) THEORIES OF AGEING

In 1882, the German biologist Dr August Weismann first introduced the ***wear and tear theory*** of ageing. In essence, his theory states that like components of a car, cells and tissues wear out from repeated use, first killing themselves and then the entire organism. 26 years later, in 1908, Max Rubner postulated the ***rate of living theory***, which states that the faster an organism's metabolism, the shorter its lifespan. Rubner created this hypothesis on observing that larger animals with slower metabolisms outlived smaller ones. In 1928, Raymond Pearl carried out a series of experiments in cantaloupe seeds and the common fruit fly *Drosophila melanogaster* further expanding Rubner's initial observation, i.e. that a slow metabolism increases lifespan. 14 years later, in 1942, Johan Bjorksten proposed the ***cross-linking theory*** of ageing, which states that an accumulation of cross-linked proteins damages cells and tissues, slowing down biological processes resulting in ageing.[2]

In 1956, the ***free radicals theory*** was developed by Dr Harman,[3] where he proposed that free radicals (e.g. superoxide) damage the macromolecular components of the cell; macromolecules (e.g. lipids, nucleic acids, proteins, and sugars) are susceptible to free radical attack. Studies show that reactive oxygen species (ROS) signalling is perhaps the most significant enzyme/gene pathway responsible for cell senescence and organismal ageing. Indeed, ROS signalling is considered as further development of the free radical theory of ageing.[4] Finally, the ***somatic DNA damage theory*** states that DNA damage accumulates with increasing age, causing cells to deteriorate and malfunction. In general, most of the damage is repaired over time, however some accumulates, primarily because the repair mechanisms (e.g. DNA polymerases) do not correct defects as rapidly as they are produced.

PROGRAMMED THEORIES OF AGEING

Three theories fall within this classification. In the ***programmed longevity theory***, ageing is the result of genes switching on and off, with senescence defined as the time when age-associated diseases such as cancer are manifested. In fact, the postulate is that genetic instability is the causing factor of both ageing and cancer. It is therefore legitimate to ask the question whether long-lived individuals actually have a more stable genetic material. Such individuals cannot avoid ageing, but ageing could be postponed due to the stable character of their genome, which is less susceptible to mutations.[5]

In the ***endocrine theory***, biological clocks act through hormones so as to control the rate of ageing. Studies have confirmed that ageing is regulated through hormones, and that the evolutionarily conserved insulin/IGF-1 signalling pathway plays an important part in the hormonal regulation of ageing.[6] Finally, in the ***immunological theory***, the immune system is programmed to weaken with time,

which leads to an increased susceptibility to infectious disease and dysregulated immune responses causing ageing and ultimately death. Indeed, a dysregulated immune response has been indirectly implicated in Alzheimer's disease[7] and cancer,[8] amongst others.

CALORIE RESTRICTION AND ITS IMPLICATIONS

Since the 1930s, it has been found that ***caloric restriction*** (CR) without malnutrition increases lifespan and delays the onset of age-associated diseases in species ranging from yeast to worms to mice to monkeys. For example, at the University of Wisconsin, a few years ago, Colman et al.[9,10] subjected a group of rhesus monkeys of about the same age to CR. CR monkeys ate 30% fewer calories than they ate prior to the start of the study. Over time, it was clear that the monkeys on CR looked younger than those on a normal diet at the same age. Colman et al. also found that the monkeys on the normal diet had 4x greater risk of developing age-associated diseases than those subjected to CR. In addition, brain scans of the CR monkeys, when compared to their well-fed counterparts, showed significantly less atrophy (or cell loss) along the surface of the brain, giving applied insight into Alzheimer's disease. Specifically, this is because the human brain shrinks with normal ageing, but its shrinking doubles in people with Alzheimer's.

It has been discovered that down-regulation of the Ras, Sch9 and Tor pathways mediate part of the effects of CR.[11] Similarly, nutrient sensors termed sirtuins are known to mimic the effects of CR. STACs, or sirtuin-activating compounds, can in theory extend lifespan. In fact, resveratrol and other STACs were found to activate sirtuins and increase lifespan in *Caenorhabditis elegans* and *Drosophila melanogaster,*[12] however their effect on human ageing remains unclear.

Perhaps the best example of CR in humans is that of the Okinawa population. Situated at the southern tip of Japan in the Pacific Ocean, the indigenous Okinawa islanders live for about 110 years on a CR diet. The Okinawa diet is 20% lower in calories than that of an average Japanese. It is rich in anti-oxidants, seafood and vegetables, and it is low in fat and sugar.[13] Okinawans are also active on a daily basis through their traditional practice of martial arts, which also contributes to reduced stress.

TELOMERE SHORTENING AND ITS IMPLICATIONS

Like aglets on shoelaces, telomeres keep chromosome ends from fraying and sticking to each other. In doing so, the genetic material is held intact. It is well-known that each time a cell divides, telomeres shorten. If telomeres get too short and cells are no longer able to divide, senescence occurs. It is this shortening process that is associated with ageing, cancer, and a higher risk of death. Case in point, geneticist Richard Cawthon at the University of Utah established that shorter telomeres are linked to shorter lives.[14] In his study, Cawthon divided people into two groups based on telomere length. Overall, he found that people with longer telomeres live an average of five years more than those with shorter telomeres. Cawthon also showed that people with shorter telomeres are 8x more liable to die from infectious disease and 3x more likely to die from heart disease.

Of note is the disorder known as dyskeratosis congenita where telomeres get short much faster than normal. Some of the manifestations resemble premature ageing (similar to progeria), such as cirrhosis of the liver, a higher risk of infections, intestinal disorders, leukaemia and other blood cancers, and pulmonary fibrosis. In addition, patients are more prone to endure balding, grey hair, and softening of the bones. However, the main consequence of the disorder is progressive bone marrow failure, causing early mortality.[15] With all this, one is lead to presume that restoring telomere length could treat ageing and/or age-associated disorders. Professor Elizabeth Blackburn, who was awarded the Nobel Prize in Physiology or Medicine in 2009, co-discovered telomerase, an enzyme that halts telomere shortening and can even lengthen them.[16,17] For this reason, after its discovery, telomerase was reputed to be the new fountain of youth, as evidenced in Jaskelioff et al.'s experiment.[18] Jaskelioff et al. showed that mice that are engineered to lack telomerase become prematurely old, whereas when the enzyme is replenished, the mice's health is restored.

Similarly, scientists have exploited telomerase in the lab to keep human cells dividing beyond their normal, or Hayflick, limit without allowing them to become cancerous. In general, the implications for this are wide. If telomerase were to be used to "immortalise" human cells, we would then be able to mass-produce cells for transplantation, including cartilage cells for curing arthritis, insulin-generating cells for diabetes, muscle cells for muscular dystrophy, and skin cells for treating burns and wounds. In addition, having a limitless source of human cells could also help with efforts to test new drugs and gene therapies.

CONCLUSION

Overall, understanding the causal processes that deteriorate with age is critical if we are to meet the growing healthcare requirements of ageing human populations. However, this is not a straightforward task; ethical and societal implications of ageing research should also be taken into consideration. For example, how would treating human ageing affect society? What should the ultimate goals of ageing research be?

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