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Mechanism behind Ageing: A Literature Review

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Immortality has become a prevalent topic among scientists and millionaires in recent years; almost everyone is trying to maintain their youth for longer. Consequently, this leaves us with a hugely important question, what is the reason for ageing? What are the possible causes of ageing? Many biologists have been looking into it and finding possible explanations, and many theories are being suggested about this question.

Firstly, an interesting theory called programmed senescence theory was suggested by Dr Davidovic; he proposed that ageing is an essential and innate part of human physiology and that ageing is programmed into our bodies. Every organism is designed to have a specific life span. This is because if our body does not eventually "wear out", human beings will have an ever-lasting life span. Programmed ageing is the theory that senescence in humans and other organisms is caused by evolved biological mechanisms to provide an evolutionary advantage.[1] Modern programmed (adaptive) theories of biological ageing assert that, in general, organisms, including mammals, have evolved mechanisms that purposely limit their lifespans in order to acquire an evolutionary advantage. Modern non-programmed theories assert that mammalian ageing is primarily caused by natural deteriorative processes and that differences in lifespan between species are due to differences in their resistance to these processes.[2] There is evidence which supports this statement. Prininger found out in 1996 that the average life span of many species doesn't change too much, elephant dies around 70 years old, and spider monkey dies around 25 years old.[3] This proves that the rate of ageing of each species of organism is more likely to be programmed in their genes as there's not much variation.

The neuroendocrine theory of ageing, developed by Vladimir Dilman, states: "The effectiveness of the body's homeostatic adjustments decreases with age, resulting to the failure of adaptive mechanisms, ageing, and death." This concept is also known as the ageing clock theory and the pacemaker theory.[4] It was discovered that as people get older, their average fasting glucose level rises from 6 to 14 milligrams per deciliter every ten years after the age of 50. Because their body cells are becoming less sensitive to insulin, which will eventually lead to diabetes; furthermore, the thyroid gland located in the neck may become lumpier after the age of 20, which leads to the metabolism slowing down over time as the thyroid hormone produced is less than the thyroid hormone being metabolised. These changes in the endocrine system causing diseases like diabetes or death were thought to be programmed by our genes, which also supports the argument of programmed senescence theory.

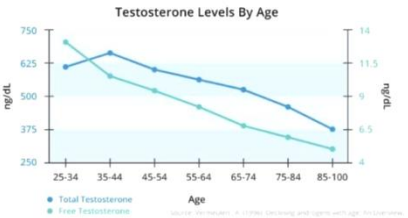

Figure 1. Level of testosterone through different ages

One of the other pieces of evidence that support the programmed theory was the immunological theory which was suggested by Louis Pasteur in the late nineteenth century. The idea that this theory was trying to proclaim is that our body's immune system weakens as we get older, no matter how well the living conditions are. This leaves us more susceptible to catching disease or even developing cancer. Scientists have found that the number of B lymphocytes in our body decreases as age increases. While the number of T lymphocytes stays constant throughout life, the number that is dividing and functioning declines as we age.[5]

The last idea which complements the programmed theory is programmed longevity which posits that ageing results from the sequential switching on and off of special genes in our bodies. So basically, ageing is controlled by our own genes. An example which supports this statement is our telomere. It is located at the end of our chromosomes and is responsible for preventing the loss of useful genes in each DNA replication, as there are always some gene losses through cell division. As the cell divide, the telomeres shorten, leading to eventual gene losses. Cancer cells contain the mutated genes, which can produce an enzyme called telomerase which maintains the length of telomeres, so cancer can continue dividing. This gives evidence to suggest that our telomerase genes are not switched on, and cells are genetically programmed to cell deat.[6] [7]

Other than the evidence which supports the programmed theory, there are also some contradictory concepts. One argument against programmed ageing was the long-held belief (Medawar, 1952; Lack, 1954; Berry & Bronson, 1992) that in the untamed, only a negligible proportion of a population dies from ageing-related causes. The absence of significant senescence in the wild would speak against the evolution of a programme for ageing by removing any potential advantage of actively destroying aged individuals (which would not normally be observed) and making it difficult to imagine how a programme to drive a process that was not actually realised could have evolved. Recent field studies have shown, however, that ageing is also observable in natural populations of a wide variety of species (Brunet-Rossinni & Austad, 2006; Bouwhuis et al., 2012; Nussey et al., 2013).[8]

Firstly, the programmed theory states that the functioning of organs and cells decreases as the organism reaches nearer the end of its lifespan. But the truth is that not all organisms follow a similar trend. There are organisms which die immediately after they have reached the peak of their physiological abilities. A typical example is the male *Argiope* spider; they die shortly after copulation by a programmed stop of the heartbeat and are then eaten by the female. This counting example showed that either the programmed theory does not apply to all organisms or it is not right. Secondly, there is a dramatic increase in the average life expectancy from 30 years in 1900 to around 70 years in 2000, which opposes the idea that each species has a similar lifespan. This enormous rise is caused by improved living conditions and the health care

system. As the economy grew extremely fast in the last centuries, the incidence of famine and lack of medical care decreased. In the past, people were more likely to get sick from contaminated food and water due to poor hygiene, and this number decreased a lot due to the boost in the economy. The fact that environmental factors can play an essential part in the ageing of people is opposed to the idea of the process of ageing being programmed by our genes.[9,10]

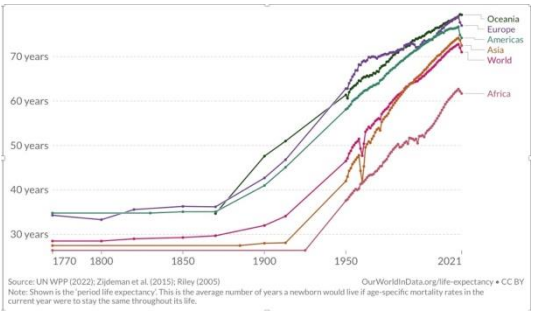

Figure 2: The average life expectancy across different continents from 1770 to 2021

On the other hand, the dramatic increase in life expectancy after Second World War illustrated that ageing could be affected by another factor, most likely to be environmental, as it is the biggest change to our life from the 20th century to the 21st century. For instance, the average life expectancy of women outlived men in the 20th century due to medical advances in the hygiene of hospitals. This greatly reduces the death caused by infection after childbirth. There are a lot of different theories which suggest various environmental factors.

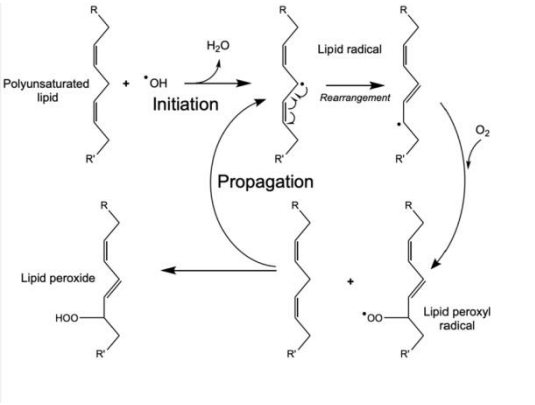

Figure 3: Process of lipid peroxidation figure 4A

One of the most widely accepted and developed theories is the "oxidative stress hypothesis" (Ghezzi et al., 2017), which advanced and modified the free radical theory of ageing (Harman, 1956). A free radical is a type of reactive oxygen species (ROS), including highly reactive chemicals which contain oxygen formed from diatomic oxygen (O_2). These ROS can be produced endogenously and exogenously. The most common production of ROS in our body is oxidative phosphorylation, which happens in the mitochondrion. During this stage, electrons leak from the electron transport chain

and react with the oxygen molecule to form a superoxide molecule (a type of free radical). These ROS can also be generated from external factors outside the body, for instance, due to overexposure to UV light and cigarette smoking. The increased production of ROS could cause a number of different deleterious effects on macromolecules in our body, such as phospholipids, which make up the cell membrane through lipid peroxidation. One hydroxyl molecule reacts with the unsaturated fatty acid tail of phospholipid and causes a series of reactions which lead to a rupture in the cell membrane (figure 4A); this leads to cell lysis and dead.[11] Another significant damage caused by ROS is DNA oxidation. It happens when a hydroxyl molecule reacts with a guanine base to form 8-hydroxylamine (figure 4B). This will break up the hydrogen bonds formed between the guanine and adenine bases which result in DNA mutation. All these effects will lead to an imbalance between cell death and cell growth in our body. Therefore, it accelerates the rate of ageing.[12]

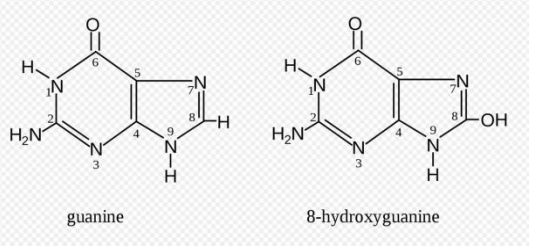

Figure 4: Skeleton formula of guanine and 8-hydroxyguanine

Although the concept of free radical theory has been very useful in the explanation of oxidative damage to our body, there are still some studies which show the limitation of this theory; our body will experience some inevitable damages that are caused by infidelity, heterogeneity, and imperfectness of biological reactions occurs, which is likely to result from genotype, dietary. It is hard to test the effect of reactive oxygen species in our body on its own. So, whether oxidative damage is, the answer to ageing is undetermined.[13]

Cross-linked theory, suggested by Johan Bjorkten in 1942, also mentioned another environmental factor that could affect the rate of ageing. The theory states the incidence of glycation increases, with glucose and protein being covalently linked in the presence of oxygen. These covalent bonds will disturb the basic functioning of protein molecules like collagen, which might lead to the stiffening of blood vessels, delayed wound healing and a change in the eye lens. One of the examples applies slices would turn from yellow to brown as they are exposed to oxygen in the air. Also, it was believed that these cross-links occur more when the blood contains a high concentration of sugar, as diabetics often have two to three more times cross-linked proteins in the body than non-diabetics. This might prove that food with a high glycemic index will speed up the rate of ageing if the cross-linked theory is right.[14]

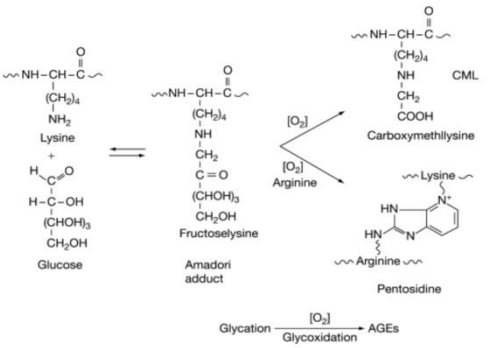

Figure 5: Process of glycation

Nowadays, it is hard to justify all the environmental factors of ageing or whether some of the current theories are correct or not due to the limitations in the experimental side when we are trying to measure the effects of each environmental factor on ageing because it is almost impossible to standardise other factors that could affect the speed of ageing as well. Like the diet, amount of exercise, genes… From my perspective, ageing is determined by more than one type of factor. The programmed theory results from primary ageing, which is the degeneration of organs as a result of their uses over time; this is likely to be coded by our genes. And all the theories suggest environmental factors result from secondary ageing. Secondary ageing changes in the organisms that are a result of a disease process, as well as damages due to life events, such as the experience of head trauma. For example, a neurotransmitter associated with memory, acetylcholine, becomes less abundant with age, and brain receptors of acetylcholine also decline in sensitivity. This proved that the decline in memory is programmed in our life, which could lead to the development of dementia or Alzheimer's disease. This is the primary ageing aspect in the degeneration of memory. However, there are also many other factors which increase the risk of dementia; only about 70 per cent of the risk of Alzheimer's disease is believed to be genetic. Life events such as head injury, smoking, inactivity and obesity which are secondary ageing aspects, may increase the risk of dementia as well.[15,16]

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