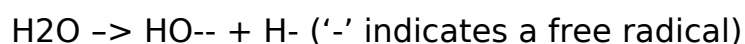


The free radical theory of aging



The process of aging is a result of increasing damage of our body's tissues which occurs over a length of time. The accumulated damage to our biological DNA is the cause by which inhibition of the cells to function and express its appropriate genes. This leads to or is responsible for the raised susceptibility of disease and death linked to the time-related changing process of aging. This process is a universal biological phenomenon which indicates that both genetic and environmental factors donating to aging. All together the nature of the aging process has been subject to substantial opinion in the way we age.

Over the years, many theories have soared to illustrate the way aging occurs. The free radical theory of aging (FRTA) is the most accepted theory to describe aging which was put forward by Dr Denham Harman in 1956 carried out at the University of Nebraska. The 'free radical' term describes any molecule that varies from a typical molecule that retains a single free unpaired electron, a property which oxidises other molecules in an exceedingly volatile and damaging way. Otherwise radicals may possibly be generated by the breakage of a covalent bond in such that one-half of the divided electrons in an oxidation-reduction reaction. These radicals are responsible for aging, some diseases and tissue damage. A simple example to illustrate this is the reaction of water with the sun:



Here water is split into a hydroxyl radical and a hydrogen atom.

The FRTA expresses that aging is the build up of oxidative damage to bodily cells and tissues that encounters this due to aerobic metabolism. Harman

based his theory on the three opinions: "(1) irradiation causes premature aging; (2) irradiation creates oxygen radicals, which may mediate its effects; and (3) cells produce oxygen radicals under normal conditions".

Commencing this he hypothesised that the manner by which a high reactive free radical such as a presence of an OH group will put forth its effect an ambiguous effect. They are also likely to react with other cellular components including nucleoproteins and nucleic acids, proteins and lipids. Also given that genes will be affected by these radicals, rarely it would be probable that mutations and cancer would occur occasionally. This led Harman to conclude that ageing and age-related diseases may be due to oxidative damage which adaptable by genetic and environmental factors. Subsequently with regards to free radicals in ageing has advanced to an extent to become one of the more reasonable theories of the ageing process.

A different idea is chemical damage, which indicates damage to long-lived organic polymers in the body caused by chemical mediators within the body these include oxygen and sugars, which are responsible for aging. Chemical damage to structural cells and DNA can lead to mutations which result in loss of its functions.

Later Joe McCord and Irwin Fridovich of Duke University discovered an enzyme in 1969, superoxide dismutase (SOD), exclusively operating to impair the superoxide radical, SOR ($O_2^{\cdot-}$). This is a type of free radical produced when an additional electron is uplifted by an oxygen molecule. This produces a number of short-lived intermediates including the formation of superoxide ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2) and the hydroxyl radical (OH). Both the superoxide and hydroxyl radicals have a free electron in their

outer orbit and are highly reactive oxidants. Hydrogen peroxide is also toxic to cells and a cause of further free radical generation, particularly when reacting with reduced transition metals to form hydroxyl radicals. The most common source of free radicals in biological systems is oxygen (Halliwell and Gutteridge, 1989). There are many types of free radicals which are formed by different reactions with oxygen. Some other examples of these are hydroperoxyl radical (HPR), alkoxy radical (AR), peroxy radical (PR) and nitric oxide radical (NOR).

Successive research has uncovered that SOR are formed within cells during oxidative metabolism and SOD enzymes are existent within a variety of organisms ranging from bacteria to humans. Three isoforms of SOD are present within cells; these are cytosolic, mitochondrial and extracellular types of isoforms. Roughly 1-2 per cent of the oxygen within the mitochondria cell changes into hydrogen peroxide rather than water, which is the actual end product during respiration. The significance of SOD is revealed through studies carried out on mutant bacteria and yeast, lacking the SOD enzyme. In the presence of oxygen these cells are unable to grow. Equally the lack of SOD2 mitochondrial enzymes in mice, were incapable of surviving for a week after birth. However, genetically engineered mice that have been altered with higher hydrogen peroxide-destroying enzymes are able to live 20 per cent longer than the controls. These results observed in 2005, shows that enhanced antioxidant defences can increase life span.

While the high potential of free radicals especially SOR and Hydroxyl radicals, these agents are an important factor linking to aging yet still remains a debatable topic. Harman's predications relating to the fact free

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radicals are joined to the notion of aging. Then we can expect that mammals with a longer lifespan possibly produce a small number of free radical, this links to the better ability to destruct free radicals, or the facility to repair cellular damage due to free radical reactions far better than a mammal with a shorter lifespan. These believes are supported by many studies, one in which the growth of mouse and human fibroblasts were compared under standard (20 per cent) and reduced (3 per cent) oxygen levels. Mouse fibroblasts grown under reduced conditions suffered up to a third of DNA damage and experienced many cellular divisions eventually till it stopped compared to those cells grown in normal conditions. Whereas mouse fibroblasts grown in standard conditions suffered up to 3 times more oxidative DNA damage compared to human fibroblasts under the same conditions. This study shows that human cells are far better in repairing and preventing oxidative DNA damage than mouse cells.

The animal life spans can be increased by restricting the amount of calories within their diet (Perez et al. 2009 and Ristow, 2010). At first the study on mice in the 1930s, which maintained a strict diet, showed they typically lived longer by 30 to 40 per cent associated to mice that ate a normal calorific diet. Findings on the metabolic rates of these mice have shown inconsistent facts, but these studies show an overall agreement that animals that were fed with restricted calorific diets contain a visible decrease in O_2 and hydrogen peroxide formation, which could possible explain the increased longevity. Longitudinal studies on the rhesus monkeys are currently being carried out with calorie- restricted diets to see if they live longer healthier lives. Though, this study has not been analysed over a long enough period to

see if the top figure of lifespan which is 40 years in these monkeys, is increased. These animals have minimal levels of blood glucose levels, insulin and triglycerides making them less prone to age-related disorders for instance diabetes and coronary artery disease. Reduced blood- insulin levels may possibly important in promoting longer life span, experiments on nematodes (Kenyon et al., 1993) and fruit flies (Clancy et al., 2001) suggest that the lessened activity of insulin-like hormones can spectacularly boost the lifespan within these vertebrates. Hormonal signalling pathways are very powerful controllers of lifespan, possibly since they match the longevity of several key organs by acting in an organised manner. Research on mice with growth hormones (GH) defected by which the inability of the pituitary gland to secrete then showed that these mice had an extended life span by roughly 21- 40 per cent (Coschigano et al., 2003). Whilst transgenic mice that over expressed the GH hormone lived a shorter life span compared to wild mice (Wolf et al., 1993).

The first genetic component of ageing by gene regulation was identified by the budding of yeast. The number of daughter cells reproduced from the mother cells via cell division is known as the replicating cell aging. Calorie restriction in yeast cells results in increased life span with the presence of the gene Sir2. Here more mother cells undergo cell division rapidly to reproduce more daughter cells. This gene is programmed to carry out certain processes during cell division, if repeats occur cellular senescence occurs which slowly degrades the cell away from its essential nuclear factors. According to the gene regulation theory we are pre-programmed in our genes when to self-destruct, which cause ageing and eventually death.

Diet plays an important part in the formation of radicals on a molecular basis. Metal ions especially in foodstuffs contain high levels and diverse profiles of metals. Metal ions in this instance therefore correlate to the formation of free radicals so share key elements of the FRTA (Naughton et al, 2008).

An interrelated area of research concerns the study of substances known as antioxidants that are able to destroy free radicals by the prevention of oxidation (Fusco, 2007). These substances can most commonly be bought over the counter in pharmacies and general stores. Familiar antioxidants in the body are glutathione, vitamin E and C, and beta-carotene. Even though these antioxidants may prove highly beneficial in the diet due to the ability to destroy free radicals, research on mice and rats has been unsuccessful in delivering realistic evidence that can stop the aging process or increase life span. An antioxidant that is receiving substantial interest is resveratrol, which is a polyphenolic compound found in elevated strength levels in the skin of red grapes. It is believed that the substance resveratrol has many health benefits characteristic of red wine. Instead of searching for free radicals in the body, resveratrol acts by activating the enzymes Sir2 that has shown to prove increased longevity in yeast cells.

An alternative view, the evolutionary theories of ageing indicates that ageing is due to DNA programming that only the survival of the best genes are available to assure offspring have vital living conditions omitting any mutations. Senescence genes that have harmful effects on the vitality of the cells are nominated against using natural selection. The mutations in these genes delay harming effects of the gene in an individual to a later stage

reduce the ability to naturally select the best genes. The deleterious genes which may not be visible till after it has reproduced, the gene itself possibly escapes natural selection and is passed through to the next stage of replicating. Yet there is no actual evidence to prove this theory.

Although when we begin to age, is down to variation of our genetic inheritance. Recently, cellular senescence has become an interest to explain aging likewise. The continuous chromosomal shortening of the telomeres, where each cell cycle is considered to affect the vitality of the cell, hence contribute to aging. In 1973, Olovnikov proposed the telomere theory in that cells lose a bit of DNA followed by a round of replication because the lack of ability for DNA polymerase to fully copy telomeres (chromosome ends) and that eventually an acute deletion triggers cell death. A study on the yeast cells lacking a functional EST1 gene showed progressive shortening of the terminal G1-3T telomeric repeats and a parallel increase in the frequency of cell death (Lundblad and Blackburn, 1993). Similarly research on loss of telomeric DNA during cell proliferation may play a role in ageing and cancer. Telomere length, telomerase activity and chromosome rearrangements in human cells were measured; overall telomerase (enzyme) activity was not detectable in control or extended lifespan populations but was present in immortal populations (Counter et. al, 1992). Telomerase enzymes switch themselves on to which adds to the telomeres when cells divide. There have, then again also been accounts that cloning may perhaps vary the shortening of telomeres. For example Dolly the sheep died of progressive lung disease and severe arthritis. The common life expectancy of sheep is 11- 12 years however Dolly the sheep lived till she was 6 years. This could possibly be

because the sheep she was cloned from lived to 6 years. One understanding is that Dolly the sheep had short telomeres which are the result of the aging process (Campbell et al, 1999). This supports the telomere theory of aging as well as the FRTA.

A further notion of ageing is the mitochondria DNA theory. This theory suggests that the effectiveness of mitochondria; the power producing organelles found in every cell of each organ, surfaces age-related degenerative diseases. The mitochondria have their own genome (mtDNA), which is produced within the inner mitochondrial membrane close to locations of formation of extremely reactive oxygen species (Sanz, 2010). Mitochondrial DNA appears incapable to frustrate the damage inflicted by the by-products of respiration for the reason that distinctively the nuclear genome lacks advanced repair mechanisms. Consequently, the cell fails to produce energy and progressively dies. This concept is backed by observations verifying the genomic variability of mitochondria, on top of many mtDNA deletions and more types of injury to the mitochondrial genome.

In addition, children with the Progeria disease are naturally liable to premature aging. They have symptoms which involve progressive heart disease. Almost all Progeria patients die as of heart disease. Heart disease is moreover one of the directing triggers of death across the world. Children with Progeria commonly experience cardiovascular events, such as high blood pressure (hypertension), stroke, angina, enlarged heart and heart failure - illnesses linked to aging. Progeria has a mutation on the gene that codes for Lamin A, a protein that maintains the nucleus of the cell together.

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It is thought that the defective Lamin A protein makes the nucleus insecure. This variability appears to lead to the process of premature aging between Progeria patients. Yet it occurs without any cause so it is hard to relate this idea to support the FRTA in anyway.

Another idea that does not support the FTRA is anoxic animals. According to BMC report deep under the Mediterranean Sea small multicellular organisms are present (belonging to the group Loricifera) which are completely surrounded by poisonous sulphides and they live their entire life in the absence of oxygen, they are still able to reproduce without the existence of oxygen and are metabolically active. Electron microscopy shows that these animals own organelles as an alternative to aerobic mitochondria as well which resembles to the unicellular organisms (protozoan) having hydrogenosomes that occupy anaerobic environment. The discovery by Danovaro et al. offers the “ tantalizing promise of metazoan life in other anoxic settings, for example in the subsurface ocean beneath hydrothermal vents or subduction zones or in other anoxic basins,” (Levin). The incidence of anaerobic mitochondria and hydrogenosomes in other organisms showed the highlight to the evolutionary significance from the findings at Comenius and Dusseldorf Universities.

In conclusion, the FRTA is not dead and it alone is not the only explanation of how we age. Genetic data alone doesn't provide strong evidence for the FRTA; however in studies with oxidative stress being reduced or inhibited can play an effect in prolonging life span. Damages and accumulation of radicals are the highlight of many other theories. This implies that the FRTA provides a foundation for other theories and that radicals cause aging to an

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extent is still alive. However studies on anoxic animals proves that the FRTA can not support the idea for FRTA due to lack of mitochondria instead mitosomes are present. Also studies on antioxidants supported the notion that consumption of vitamins prevents free radicals from forming or being reduced. Further studies still need to be carried out in order to prove whether FRTA is actually dead.