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Debate

The free radical theory of ageing

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Abstract

The free radical theory of ageing hypothesizes that ageing is a consequence of incomplete inactivation of certain harmful toxins (called reactive oxygen species, or ROS) by the defence systems of the body. ROS are produced by the body as a direct consequence of its need for oxygen to survive. They are produced either accidentally, in the process of energy production, or deliberately, to annihilate bacteria and viruses. ROS produced in excess damage cell membranes, proteins and even DNA. It is hypothesized that the damage cannot always be reversed and hence causes the deterioration seen in the body during ageing.

The nature of the mechanisms underlying the ageing process is presently not well understood. A theoretical maximum lifespan of about 120 years for humans was proposed by Hayflick (1974), following his investigations of the potential capacity of cells to divide only a fixed number of times before dying. Several hypotheses have been proposed to identify mechanisms which are associated with longevity – one of which is the free radical theory of ageing.

Production of free radicals in the body

Oxygen is essential for energy production. Throughout the lifespan, oxygen is carried by red blood cells (erythrocytes) to all the cells in the body, where it is taken up by mitochondria. The latter organelles are the energy-producing units within the cell. Here the oxygen molecule (O_2) is activated and split into two oxygen atoms; during this process carbon dioxide and water are formed as final products, with the simultaneous production of adenosine triphosphate (ATP). ATP is the high-energy molecule (or "energy currency") which can then be utilized throughout the body by cells in reactions which require energy.

The activated oxygen molecule accepts electrons from the "electron chain" within the mitochondria. These electrons, originally obtained from food molecules (which is why we have to eat, to generate energy), are transferred to mitochondrial membrane proteins which have metal ions such as iron and copper as part of their structure. These metals, which have the ability to accept or donate electrons, eventually transfer the electrons onto the oxygen at the end of the "electron chain."

A small percentage of the electrons in the chain do not become attached to the oxygen which is coupled to the production of ATP, but instead escape from the chain prematurely to oxygen molecules which are not part of the energy chain. Such single-electron reduction of oxygen produces the superoxide anion radical ($O^{\cdot-}$), which is then rapidly converted to O_2 and hydrogen peroxide (H_2O_2) by superoxide dismutase. H_2O_2 is reduced to H_2O by other enzymes called peroxidases and catalases.

Superoxide and hydrogen peroxide are in themselves not very reactive chemically. However, on coming into contact with metal ions, especially iron and copper, they form a very reactive free radical species, the hydroxyl radical ($OH^{\cdot}$), which will attack and damage almost any molecule found in the human body. The hydroxyl radical has sufficient reactivity to abstract a hydrogen atom from a methylene group attached to lipid molecules in cell membranes. This process initiates a detrimental chain reaction in the membranes called lipid peroxidation. The hydroxyl radical may also react with protein molecules in the cell membrane causing fragmentation, increased susceptibility to proteolysis and crosslinking (Smith, Sayre, Monnier & Perry, 1995). Nuclear DNA and mitochondrial DNA are also susceptible, and a number of researchers are of the opinion that the ageing process is abetted by this mitochondrial deterioration (Halliwell, 1997).

A free radical is thus a molecule rendered reactive by an unpaired electron, and it is this molecule which results in damage to cells and tissue, an integral part of degenerative processes. Free radicals form part of reactive oxygen species (ROS), a collective group of oxygen compounds that can potentially cause cell damage. Hydrogen peroxide is a ROS but not a free radical. Interestingly, environmental influences such as smoking and pollution can also increase the production of free radicals by the body.

Efficient antioxidant defense systems mop up these harmful chemicals in order to achieve some balance and to protect, at least partially, against ROS damage. These defenses include metal chelators (e.g. transferrin and melatonin), enzymes (e.g. superoxide dismutase, glutathione peroxidase and catalase) and antioxidant nutrients, notably vitamins A, C and E, the carotenoids and bioflavonoids. The body does not

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manufacture any of these vitamins but rather extracts them from the diet. However, it is important to note that some anti-oxidants may also act as pro-oxidants. For example, beta carotene becomes a pro-oxidant in the presence of high oxygen concentrations (Fraser, 1985), while in the presence of free iron, vitamin C (ascorbate) exacerbates lipid peroxidation (Halliwell & Gutteridge, 1985). Hence, ascorbate acts as a pro-oxidant at low concentrations and as an anti-oxidant at higher concentrations *in vitro*.

A study comparing two strains of mice (the house mouse and the white-footed mouse) illustrates the role of ROS in the ageing process. The greater than two-fold longer lifespan of the white-footed mouse was associated with lower rates of mitochondrial superoxide ($O_2^{\cdot}$) and hydrogen peroxide (H_2O_2) production, higher activities of catalase and glutathione peroxidase, and lower levels of oxidative damage (Sohal, Ku & Agarwal, 1993).

Useful ROS production in the body

Apart from the accidental production of ROS as a byproduct of energy metabolism, these species are deliberately generated by phagocytes to kill bacteria and fungi, to inactivate viruses, and to destroy degenerating or dead tissue. This deliberate production of ROS by polymorphonuclear leucocytes (neutrophils, basophils and eosinophils) is a very important defense mechanism in the body. However, if inappropriately activated and left unquenched, the ROS produced becomes dangerous to the body. This situation arises in chronic inflammatory diseases, such as inflammatory bowel disease and rheumatoid arthritis. Here phagocytes accumulate, become activated and produce ROS, which damage the bowel or the joints, respectively (Halliwell, 1997).

Situations in which ROS levels are raised encompass:

- Tissue damage and the body's inflammatory response.
- Reduced uptake of antioxidants from the diet, as occurs in ageing (Davies, 1990).
- Reduced production of molecules by the body required to quench ROS, such as melatonin, a hormone secreted by the pineal gland, which is of interest in diseases associated with ageing, since it is known to decrease in concentration with age. The biological functions of melatonin include regulation of secretion of other hormones (i.e. regulation of the body's biological clock). Melatonin is secreted only in the dark (Brzezinski, 1997). Levels start to rise at 21:00, peaking between 02:00 and 04:00, whereafter they decline. In the presence of electric light of sufficient intensity at night time, melatonin secretion is reduced. Under experimental conditions melatonin has been shown to protect platelet membranes from lipid peroxidation (Daniels, Van Rensburg, Van Zyl, Van der Walt & Taljaard, 1997) and scavenges metal ions that could potentially produce free radicals (Limson, Nyokong & Daya, 1998).
- Genetic susceptibility. Transferrin is the protein that safely carries iron in an inactive form in the blood. A genetic isoform of transferrin (Tf C2) has been shown to have a decreased iron binding capacity, and appears to fail partially in carrying iron in this inactivated form (Wong & Saha, 1986). This allows active iron to react with oxygen species in the blood to form ROS. TfC2 has been shown to be present at a higher frequency in persons with Alzheimer's disease (65%), compared to controls (14%) (Van Rensburg, Carstens, Potocnik, Aucamp & Taljaard, 1993; Namekata, Imagawa, Terasha *et al.*, 1997), providing a possible link between ROS, the ageing process and Alzheimer's disease.

Protective strategies against free radicals

While genetic intervention is limited, environmental factors can be manipulated. Thus, ensuring optimal cellular functioning at all levels would induce and maintain good health, thereby negating the deleterious effects of ageing. A diet containing adequate amounts of antioxidants, such as are found in fruit, vegetables, meat, eggs and unrefined grain products, should go some way to meeting this goal. Apart from an adequate vitamin intake, supplementation with melatonin may be considered (Reiter, Guerrero, Escames, Pappolla & Acuna-Catroviejo, 1997). This strategy would theoretically combat the higher ROS production that occurs in the process of ageing.

Further studies on the role of free radical damage in the process of ageing are required to provide a better perspective on interventive strategies for the reduction of morbidity and increased longevity.

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