Genes & Diseases (2016) 3, 105–109

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journal homepage: http://ees.elsevier.com/gendis/default.asp

PERSPECTIVES

How ageing increases cancer susceptibility: A tale of two opposing yet synergistic views

Available online 16 April 2016

KEYWORDS
Ageing;
Cancer;
Hyperfunction;
Oxidative damage

Abstract It is well known that with increasing age, the risk of acquiring certain age-related diseases – such as diabetes, cancer, cardiovascular disease and neurodegenerative diseases, increases. Several theories have been proposed to explain the reason why ageing leads to higher susceptibility to disease. Over time, many of these theories have been proven wrong. Currently, the two theories holding the interest of researchers in this field are the oxidative damage theory and hyperfunction theory of ageing. The former is an old theory which explains that ageing is as a result of oxidative damage (to macromolecular components of the cell) by reactive oxygen species produced as a normal part of metabolism. The hyperfunction theory is a much newer theory which explains that ageing is as a result of the unnecessary and unwanted continuation of certain metabolic processes at old age. In this review, we discuss the mechanisms which underlie the development of age-related cancer. We also discuss the aforementioned theories of ageing. We conclude by explaining the opposing views of proponents of both theories and provide a new viewpoint by revealing a point of synergy in the two theories.

Introduction

With increasing age, the body tends to accumulate damage and the functions of different organs begin to decline. Ageing has been shown to correlate with the onset of many terminal diseases such as: cardiovascular disease, type II diabetes, neurodegenerative diseases such as Huntington's disease and Alzheimer's disease and cancer.[1] Ageing can thus be said to be a major risk factor for these diseases. Several hundred theories of ageing have been put forward by researchers in the past, with nearly all of them being disproved with time. Currently, there are two highly prominent theories of ageing generating the interest of biogerontologists: the oxidative damage theory and the hyperfunction theory.[2]

Theories of ageing and mechanisms by which ageing leads to age-related disease.

The oxidative damage theory of ageing

From the oxidative damage point of view, ageing occurs as a result of the accumulation of molecular damage caused by reactive oxygen species (ROS) which are normally produced as a by-product of metabolism.[3,4] ROS are capable of damaging cellular constituents including proteins, lipids and DNA (where they cause double strand breaks and oxidative lesions). This damage then triggers the activity of

Peer review under responsibility of Chongqing Medical University.

http://dx.doi.org/10.1016/j.gendis.2016.04.002

cellular machinery involved in damage repair. Genes that code for proteins involved in rectifying damage to DNA are known as tumour suppressor genes. The tumour suppressors can be classified into two types based on their mode of action: caretaker tumour suppressors and gatekeeper tumour suppressors.

Caretaker tumour suppressors and cancer

Caretaker tumour suppressors are the first line of defence against DNA damage. They help to prevent DNA damage in the first place. Caretaker tumour suppressors also help to repair DNA in the event of damage. They can help in nucleotide-excision repair, mismatch repair, base-excision repair, as well as repairing double strand breaks.[4]

Caretaker tumour suppressors involved in preventing DNA damage by ROS, include antioxidant enzymes such as superoxide dismutase (SOD), catalase and glutathione peroxidase. These enzymes are responsible for clearing up free radicals before they cause damage to the body.[4]

The mitochondrial electron transport chain (ETC) is not 100% efficient in transferring electrons and an electron sometimes 'leaks out' as it is being transferred from one component of the ETC to another. This electron can accidentally be picked up by oxygen, forming superoxide (a very pertinent example of ROS).[5] In the process, ROS-induced oxidative damage to the genes encoding caretaker tumour suppressor proteins, leads to an insufficient amount of functional proteins that can act to prevent DNA damage as well as repair it whenever it occurs. Hence, more DNA damage occurs and this accumulates as one gets older. This may explain the increased risk of diseases in the elderly, such as cancer- as a result of mutation accumulation. Evidence is accumulating that shows that oxidative stress can cause DNA damage and mutations which lead to cancer in mice[6] also, protection from ROS has been shown to increase healthspan.[7]

Gatekeeper tumour suppressors and cancer

Gatekeeper tumour suppressors are responsible for clearing up cells that are prone to be neoplastic, i.e., cells in which the DNA has already undergone such extensive damage or mutation that it will be difficult to repair. An example of a gatekeeper tumour suppressor is p53. Gatekeeper tumour suppressors usually 'clear up' these cells by causing them to senesce or undergo apoptosis.[8]

Although this mechanism sounds good for tumour suppression and cancer prevention, it can have terrible consequences for ageing and longevity. This is due to the fact that when cells undergo senescence, they secrete certain substances such as growth factors and degradative enzymes including matrix metalloproteinases which affect their immediate surroundings. Thus as one ages, the environment around senescent cells becomes a fertile place for the development of pre-cancerous cells (cells which have undergone sufficient mutations) that have accumulated throughout the person's life and this is what leads to cancer as one increases in age.[8] This is a vivid example of the concept of **antagonistic pleiotropy** — a term used to describe the phenomenon in which the same genes that control 'good' phenotypes (such as senescence/cancer prevention) at young age, become responsible for provoking 'detrimental' phenotypes (such as tumour formation) in old age.[9]

Also, apoptosis has been linked to ageing because in adult humans, many of our cells are mitotic (capable of dividing) while some are post-mitotic. Thus if when the DNA in our cells undergoes extensive mutation, the cell's response is to cause apoptosis right away, then as a person gets older, the number of cells capable of regeneration, as well as non-renewable tissues of irreplaceable post-mitotic cells, gets depleted and this leads to ageing (as a person runs out of stem cells and irreplaceable cells) and subsequent diseases.[8]

The hyperfunction theory of ageing

From the **hyperfunction** point of view, ageing results as a quasi-programmed hyperfunction from youth. This means that processes contributing to growth and reproduction during development, continue to occur in later life (post-development) excessively and unwantedly, eventually giving rise to hypertrophy, hyperplasia as well as subsequent age-related diseases such as cancer and neurodegenerative diseases.[10,11]

The originator of the hyperfunction theory (M.V. Blagosklonny) argues that ageing originates as a result of hyperfunction and not molecular damage.[11] He argues that the hyperfunction of the TOR (target of rapamycin) pathway (a nutrient sensing pathway) is what gives rise to ageing and subsequently, diseases of ageing.

The pieces of evidence he used to draw this inference interestingly, are previously published data which were interpreted using older theories of ageing especially the oxidative damage theory and the trade-off theory. The conclusions of researchers using these theories were never really a hundred percent convincing; because there were still some observations that these theories could not explain; for instance 'why does dietary restriction increase lifespan and decrease reproductive ability'? The reason why this was a troubling question is because, from the point of view of the evolutionary theory, organisms survive in order to be able to reproduce; thus if they encounter something that could limit their life (e.g. starvation), the organism will likely adapt to it in a way that favours reproduction (even at the expense of their own lifespan). In the case of limited food, the organism may adapt by channelling nearly all the nutrients it gets into reproduction, while leaving just a sufficient amount to activate longevity mechanisms (such as somatic maintenance) in order to live long enough to reach the end of the reproductive period. This is known as the 'trade-off' theory.[2]

The paradox in the trade-off theory is that, if the trade-off theory were true, then dietary restriction ought to shorten lifespan, since most of the nutrients will be channelled away from somatic maintenance towards reproduction, but recent observations have shown that dietary restriction actually increases lifespan and decreases reproductive ability. It also postpones the onset of age-related diseases.[10,12]

From the evolutionary point of view, reproductive ability is more likely to be favoured compared to fitness/lifespan because in the wild, animals mostly die of external factors