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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. Copyright © 2016, Chongqing Medical University. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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>

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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 mice⁶ 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

(e.g. predators, harsh weather, etc), thus it makes sense for an organism to develop and then reproduce as quickly as possible before external factors kill the organism, and natural selection may have adapted animals for this; even though there seems to be pieces of evidence that conflict with this line of thought.²

One of the interesting paradoxes in the oxidative damage theory was created by recent experiments which showed that the lifespan of certain organisms (such as Yeast and *Caenorhabditis elegans*) is lengthened even in the presence of increased ROS.¹⁰ This observation obviously contradicts the oxidative damage theory, although scientists explained that the increased lifespan was as a result of an increased stress resistance; a phenomenon known as *hormesis*.¹⁰

Other experiments have brought about mixed results—while some have shown that antioxidants (which ought to combat ROS and therefore increase lifespan) shortened the lifespan of worms, others have shown that antioxidants increased worm lifespan.³ At present, the conclusion is that there is no convincing correlation between lifespan and levels of ROS.¹⁰

Contradictions like this inspired Blagosklonny to put forward a new theory — the theory of hyperfunction. In this theory, the unnecessary stimulation of the TOR pathway post-development, gives rise to the accumulation of unneeded proteins as well as unnecessary growth. Since the TOR pathway inhibits autophagy, these unwanted proteins accumulate because they are not being degraded. The TOR pathway also inhibits apoptosis, so the cell does not die; it just keeps growing.^{10,12} Importantly, Blagosklonny noted that, in the event that the DNA acquires a mutation that inhibits the cell from dividing, then the cell enters into a senescent 'hyperfunctional' state in which it just keeps growing and growing actively, without dividing and without undergoing apoptosis.¹² Also, these senescent cells tend to secrete proteins (such as growth factors and matrix metalloproteinases) that induce the growth of other cells in their environment and worse still, degrade the stroma, thereby creating an environment that enables pre-malignant cells (epithelial cells with oncogenic mutations) to thrive and become malignant. This is what gives rise to cancer in old individuals.

In summary, Blagosklonny¹² proposes that as a person gets older, the TOR pathway becomes hyperactive—since its effects are only needed in small amounts once development is completed; but because an adaptation for switching off or downregulating the TOR pathway post developmentally has not evolved yet, the products (proteins) of the TOR pathway accumulate in the cell, and if a mutation causes that cell to be arrested from dividing, then the cell becomes senescent and hyperfunctional — using its secretory phenotype to make its environment suitable for the development of cancer.¹²

There is evidence to show that mTOR is indeed involved in organismal ageing; and an increasing number of studies have demonstrated that rapamycin (an inhibitor of mTOR) extends lifespan in mice and prevents age-related pathologies including cancer.^{13,14} Rapamycin has also been shown to slow ageing and improve the health of obese mice.¹³ New evidence has also come up that shows that Rapamycin

suppresses geroconversion, maintaining quiescence instead of senescence.¹⁵

According to Blagosklonny, the hyperfunction theory explains why dietary restriction increases lifespan and postpones the development of age-related diseases (because ingesting a lower amount of nutrients — e.g. when undergoing dietary restriction— leads to a lower amount of TOR activity, thus unnecessary proteins do not accumulate any longer, since these proteins are no longer made in excessive amounts and can now be degraded through autophagy).¹⁰ He also proposes that the protein accumulation that arises due to hyperactive TOR signalling causes protein aggregation diseases such as Huntington's disease.

In the opinion of the authors of the present paper, both the oxidative damage theory and the hyperfunction theory are plausible. In fact, they should be integrated to form one theory, because they are not mutually exclusive. For instance, the hyperfunction theory cannot be explained without mentioning molecular damage (even though Blagosklonny argues that ageing is as a result of cellular damage and not molecular damage). Also, the oxidative damage theory does not have logical explanations for some of the observations that have been observed experimentally, therefore it needs to encompass the hyperfunction theory (see Fig. 1).

A synergy between the hyperfunction and oxidative damage theories of ageing

The hyperfunction theory is impossible to explain without incorporating molecular damage; the oxidative damage theory is only logical if it includes the concept of hyperfunction!

The point we are making here is that the process by which hyperfunction of the TOR pathway gives rise to age-related diseases (using cancer as a case study) actually involves molecular damage! According to Blagosklonny, for a cell to become senescent, it has to be arrested from the cell cycle.¹² This arrest is usually due to **mutations** in the DNA that are beyond what the DNA repair enzymes can repair, hence gatekeepers (including checkpoint proteins) arrest the cell and stop it from dividing. Thus the cell continues to grow, but cannot divide. The cell also begins to secrete proteins that make the environment suitable for **pre-cancerous cells** to grow and become cancers (Note that these 'pre-cancerous' cells are so-called, because they have acquired a number of **DNA mutations** and are thus prone to develop into cancer cells). From this explanation, it is obvious that **DNA mutations** are *critical* to explaining the hyperfunction theory, and this is what the molecular damage theory is all about.

As for the oxidative damage theory, it obviously has to include the hyperfunction theory, in order to be sound. ROS causes damage to cell components such as proteins, lipids and DNA. Damage to DNA can cause the cell cycle to be arrested and this leads to senescence since the cell can no longer divide; but then a closer look at the senescent phenotype, reveals that the cell is **hyperfunctional** — it is actively undergoing metabolism, it is growing, it does not undergo apoptosis and most of all, it has a very important secretory phenotype⁸ and this can all be traced to

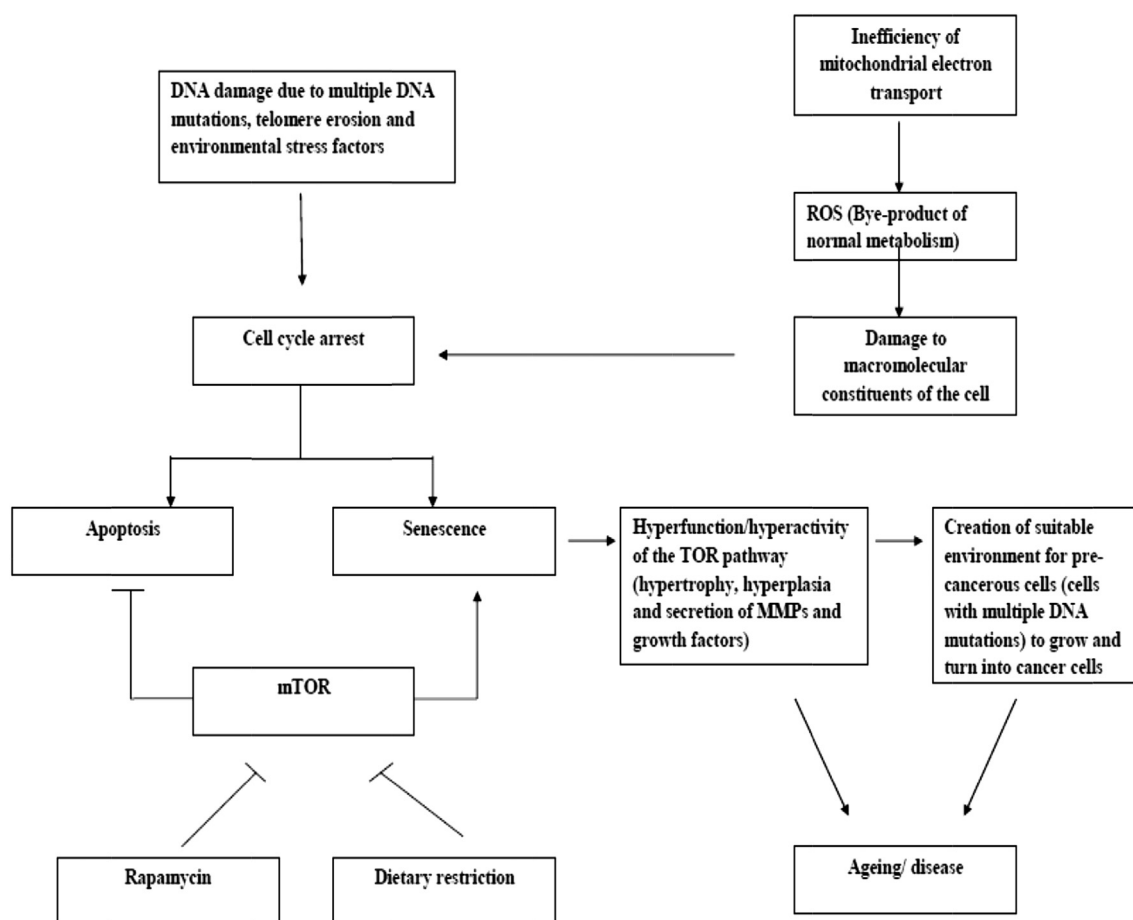


Fig. 1 The relationship between ROS, TOR, ageing and disease. Cells are arrested from participating in cell division when there is extensive DNA damage. This DNA damage can be caused by a variety of factors including but not limited to reactive oxygen species (ROS), telomere erosion, mutation and environmental factors. Cell cycle arrest can trigger apoptosis or senescence under different conditions. Senescence is characterised by hypertrophy, hyperplasia and creation of an environment suitable for pre-cancerous cells to thrive, due to the secretion of matrix metalloproteinases (MMPs) and growth factors. This leads to cancer as ageing proceeds. mTOR has been implicated in the ageing process. Its mechanism of action includes: aiding senescence and inhibiting apoptosis. Rapamycin administration and dietary restriction have both been shown to slow down ageing and disease progression as they both act to inhibit mTOR.

hyperactivity of the TOR pathway (because dietary restriction reduces TOR activity and therefore dramatically reduces cellular hyperfunction which has been implicated in accelerating the ageing process and the development of ageing-related diseases).¹² Thus, we conclude by reaffirming our point: the hyperfunction theory is incomplete without molecular damage, and the oxidative damage theory is not sound without mentioning the obvious hyperfunction of ageing cells!

Conclusion

In conclusion, we believe that the TOR pathway becomes hyperfunctional after the growth and development stages of life and this can lead to ageing and subsequently, ageing-related diseases. It is also true that as a human being advances in age, the body accumulates damage of all sorts (molecular as well as cellular), and these eventually lead to organ failure and subsequent diseases. Thus any

intervention that can slow down the onset of this damage-hyperfunction phenotype is most likely going to slow down the onset of ageing-related diseases as well. Only further laboratory experiments with model organisms and clinical trials with humans will be able to reveal the complex mechanism(s) of ageing and how ageing leads to the development of age-related diseases.

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Sylvia Oghogho Iseghohi*

Department of Biochemistry, University of Benin,
P.M.B. 1154, Nigeria

Kingsley Omege

Department of Biochemistry, College of Basic Medical
Sciences, Igbiniedion University Okada, Nigeria

*Corresponding author.

E-mail address: sylvia.iseghohi.13@ucl.ac.uk (S.O. Iseghohi)

19 January 2016