CONNECTION BETWEEN AGEING AND CANCER

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ABSTRACT

The risk of many chronic diseases increases when the peoples get older. The chronic diseases are increases due to common theories of ageing, such as mutation accumulation, wear and tear, and antagonistic pleiotropism etc. However, the risk of some chronic conditions (e.g. asthma, arterial hypertension) declines in the old. At first glance, it doesn’t look like that ageing and cancer have any relationship. The scientists have intrigued the relationship between cancer and ageing for decades. It has long been widely accepted that ageing is the single greatest risk factor for developing cancer. Ageing may increase or decrease the susceptibility of various tissues to initiation of carcinogenesis and usually facilitates promotion and progression of carcinogenesis. A number of events at the molecular, cellular, and physiologic levels are associated with ageing that influence carcinogenesis and subsequent cancer growth. Here we review the main points to understand the connection between the ageing & cancer.

Keywords: Chronic diseases, ageing, cancer.

INTRODUCTION

Cancer is a disease of cells; their lives and behavior are controlled by genetic instructions that are present in every cell of the body. If those instructions get changed or destructive, a cell might start behaving and reproducing in an uncontrolled way. When that happens, uncontrolled growth of cell form tumor which cause cancer. All cancers start from a single cell that undergoes many changes. Some of those changes are permanent alterations to the DNA called mutations.\(^{(1,2)}\)

Luckily, our bodies have a host of defensive strategies for making sure damaged or mutated cells never get the chance to reproduce. It’s because a potentially cancerous cell has to make...
it past so many of these natural defenses that the process of cancer development can take a long time—years, even decades. Over our lifetimes, thousands and thousands of damaged cells get disposed of before they can cause any harm. \(^{(3,4)}\)

**Ageing Connection of Cancer**

Within the last century the mean life expectancy of humans in the industrialized world has increased dramatically and it is predicted that by 2050 about 5% of the population in developed countries will be older than 85 years of age \(^{(4)}\). Unfortunately, ageing is also linked to biological wear and tear leading to a variety of conditions including certain types of neoplasm. Thus, the risk for developing several types of cancers increases with increasing age. An explanation for this elevated cancer risk in older individuals has been attributed to the fact that progenitor cells from mature organisms accumulate molecular lesions which eventually evade the homeostatic control culminating into neoplastic situations. A number of abnormal epigenetic signals also contribute to tumor genesis such as DNA methylation and histone modifications.

Other biological changes of ageing that may support cancer development include proliferative senescence which may result in the loss of apoptosis and the production of tumor growth factors and proteolytic enzymes that promote the growth and the spread of cancer. \(^{(6)}\)

Another contributing factor is believed to be the functionality of the immune system as it influences not only the tumor's microenvironment, but the tumor itself. Immunosenescence has been associated with increased levels of interleukin-6 which is linked to tumors that elicit an immune response such as lymphomas and multiple myelomas. \(^{(5)}\) On the other hand, immunosenescence has also been suggested to create an environment that favors a less aggressive tumor which may be why the incidence of cancer levels off after a certain age. Additionally, one study found fewer tumor-infiltrating lymphocytes in tumor samples from older subjects compared to younger subjects, indicative of a reduced immune response; on the other hand a more robust immune response might drive tumor progression due to growth or angiogenic factors secreted from immune cells. \(^{(7,8)}\) Further, chronic inflammation has been reported to precede or accompany a number of cancers, adding further controversy. Although a definitive conclusion has yet to be drawn, strong evidence exists to suggest the activity level of the immune system plays a critical role in carcinogenesis.
The median age for cancer diagnosis in industrialized countries is approaching 70 years and it is expected to increase. The absolute number of cancer patients younger than 50 years of age is not expected to rise significantly over the next 50 years, but is expected to double in those over the age of 65. Because of these striking statistics, it is believed that a direct correlation between cancer risk and ageing exists.\(^{(10)}\)

An excellent example of an age-related neoplasm is prostate cancer (PCa). According to the Center for Disease Control and Prevention (CDC), PCa is one of the most common forms of cancer and is a leading cause of cancer deaths among men in the world. Further, according to recent estimates from the CDC, approximately 62% of all PCa cases are diagnosed in males 65 and older. Thus, it is now generally well accepted that ageing is a major risk factor for PCa in addition to race and family history. Further, a number of cancer types such as acute myeloid leukemia, breast, non-small cell lung cancer, and ovarian cancers tend to become resistant to chemotherapy and/or more indolent with increasing age\(^{(9,11)}\).

**Mitochondrial Theory of Ageing**

Mitochondria are cellular energy factories that generate Adenosine tri phosphate (ATP) via the reaction of hydrocarbons with oxygen. Every human cell contains hundreds of mitochondria, and each mitochondrion contains multiple copies of mitochondrial DNA (mtDNA). The ancestry of the mitochondrial genome can be traced to early eubacteria, and it is therefore unexpected that this organelle may have a major role in governing the pace of human ageing.\(^{(11,12)}\)

Aerobic respiration in mitochondria have one of the main problem is that the electrons donated to the Electron transport chain (ETC) can often "leak out" and, rather than driving the creation of the pH gradient, can instead go on to form unstable molecules called reactive oxygen species (ROS). Unstable ROS are capable of damaging many types of cellular components, and it is thought that the damage that may accumulate over time from ROS generated from aerobic respiration may play a significant role in ageing. Given that mitochondrial DNA exists in the inner matrix and this is in close proximity to the inner membrane where electrons can form unstable compounds, mtDNA has a relatively high chance of getting damaged by ROS. This entails mutations to DNA (or straight out deletions of many base-pairs) that can result in the manufacturing of mutant ETC proteins that, in turn, can lead to the leaking of more electrons and more ROS. This so called "vicious cycle" is
hypothesized to play a critical role in the ageing process according to the mitochondrial theory of ageing. \(^{(13)}\)

**The Potential interplay between stem cells, stress, ageing & cancer**

During ageing, the stem cells proliferate within the tissue. On subsequent stress-dependent changes, the stem cell starts getting damaged. This results in increase of senescent cells within differentiated tissues. Incipient tumors, arises from stem cells or from more committed cells, undergo rapid proliferation. The pre-malignant tumour cells rapidly accumulate damage, in the presence of oncogenes. These will lead to a higher proportion of tumour cells, which becomes senescent. When tumour cells acquire mutation it impairs the senescence process leading to progression of tumour resulting in full malignancy. \(^{(14)}\)

**Genomic instability links cancer and ageing**

A fundamental and continuous challenge to every cell is the maintenance of DNA. Genomic instability is the cause of most cancers; many of the factors that have been implicated in sensing and responding to DNA damage are altered in human tumors. \(^{(15)}\)
By studying the various common forms of familial breast and ovarian cancer the link between the maintenance of genome integrity and cancer susceptibility have been developed. These conditions are caused by germline mutations in the genes for P53, the ataxia-telangiectasia mutated (ATM) kinase and breast cancer 1 (BRCA1), these three proteins are essential in the surveillance of DNA damage. All these three proteins have also been linked to cellular ageing. (16)

Another family of genes has found to play a role in ageing, thus an important function in maintaining genomic stability. This family of protein is known as sirtuins.

There are mainly seven sirtuin enzymes which are found in mammals that act as either a mono-ADP-ribosyl transferase (ART), a NAD+ dependent deacetylase (DAC), or both. An NAD+-dependent catalytic core domain is present in each sirtuin, the N- and/or C-terminal sequences are of variable lengths giving rise to specific sizes. Each sirtuin has a specific localization and function. (17,18)

Table 1. Localization and functions of sirtuins (19)

<table>
<thead>
<tr>
<th>Member</th>
<th>Activity</th>
<th>Localization</th>
<th>Size (kDa)</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sirt1</td>
<td>DAC</td>
<td>Nucleus</td>
<td>62</td>
<td>Chromatin modulation, gene expression, senescence, apoptosis, insulin secretion, neuronal differentiation, adipogenesis, development, glucose metabolism</td>
</tr>
<tr>
<td>Sirt2</td>
<td>DAC and ART</td>
<td>Cytoplasmic</td>
<td>41.5</td>
<td>Cell cycle progression, adipocyte differentiation</td>
</tr>
<tr>
<td>Sirt3</td>
<td>DAC and ART</td>
<td>Mitochondria</td>
<td>43.6</td>
<td>Cellular metabolism, apoptosis</td>
</tr>
<tr>
<td>Sirt4</td>
<td>ART</td>
<td>Mitochondria</td>
<td>35.2</td>
<td>Regulation of insulin secretion, mitochondrial NAD(+) salvage</td>
</tr>
<tr>
<td>Sirt5</td>
<td>DAC</td>
<td>Mitochondria</td>
<td>33.9</td>
<td>Regulation of urea cycle</td>
</tr>
</tbody>
</table>
The potential role of autophagy in cancer and ageing

According to cell biology, autophagy is a catabolic process which involves the degradation of a cell's own components through the lysosomal machinery. This process plays a important part in cell growth, development, and homeostasis which help in maintaining a balance between the synthesis, degradation, and subsequent recycling of cellular products. It is a major mechanism by which a starving cell reallocates nutrients from unnecessary processes to more-essential processes. (20)

In Ageing

So we can compare Autophagy as recycling garbage which collects and recycling process in healthy cell. As we get older, the process becomes slows or becomes less judgmental. Consequently, haphazard agents are accumulated in the cells, haphazard agent are accumulated which may be damage the various parts of cells and tissues and lead to some ageing-related diseases. (21)

For example
- Failure to clear protein aggregates in neurons of the central nervous system causes dementia;
- Failure to clear ROS (reactive oxygen species)-producing mitochondria leads to nuclear DNA mutations and cancer.

Collectively, these pathological conditions contribute to, or even define, the process of ageing. (22)

In Cancer

Autophagy has the potential of being useful for cancer suppression but also for cancer promotion. The maintaining the equilibrium is very important, too little can cause cell death when the cell cannot produce things it needs by reusing parts of itself. Too much of it can also cause cell death since the cell can eat itself. Altering this balance in a tumors cell could be the source of a new therapy although as usual it is important to remember that cells might

<table>
<thead>
<tr>
<th>Sirt6</th>
<th>ART</th>
<th>Nucleus</th>
<th>39.1</th>
<th>Telomere maintenance, DNA repair</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sirt7</td>
<td>None</td>
<td>Nucleolus</td>
<td>44.8</td>
<td>rDNA transcription</td>
</tr>
</tbody>
</table>
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Evolve mechanisms to avoid the trouble of autophagy, maybe by inactivating the autophagy mechanism all together. Even in that case the tumors cell would be less capable of surviving in situations of stress since it would not be able to recycle material. \(^{23,24}\)

**Stem cell perspective on cancer and ageing**

The long-lived cells (such as stem cells) accumulate DNA damage from a number of stresses including intracellular oxidants generated from normal metabolism in the lifespan of an organism. Such as prolonged exposure to Reactive Oxygen Species has been contributed in ageing \& also cause the default pathway for damaged stem cells which is undergo growth arrest, apoptosis or senescence. As more and more stem cells withdraw from the proliferative pool, there is a decrease in the overall number and/or functionality of both stem and progenitor cells. This decrease predisposes the organism to impaired tissue homeostasis and regenerative capacity and could contribute to ageing and age-related pathologies. Some rare cells adapt additional mutations \& escape the normal default pathway that allows them to continue to proliferate even in the setting of damaged DNA. The seeds for future malignancies might be provided by proliferating damaged cell. \(^{25}\)

In this scenario, both cancer and ageing result primarily from accumulating damage to the stem and progenitor cell compartment. Mutations that allow stem cells to continue to grow rapidly in the setting of normal growth arrest signals such as DNA would temporarily expand the stem cell pool and hence delay age-related pathologies. Over the long term, these mutations would also increase the likelihood of cancer. \(^{26}\)

**CONCLUSION**

So, we can’t stop people to get became older i.e. we can’t stop ageing. Ageing is a natural process but we can minimize the chronic diseases related to ageing like cancer, diabetes, asthma, arterial hypertension etc. by the help of understanding the mechanism of ageing and their connection with chronic diseases like cancer etc and then it easy for us to find out the exact treatment of ageing related diseases.

**REFERENCES**

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