MOLECULAR CONNECTIONS OF AGEING AND CANCER

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Summary

Ageing is considered the most common risk factor for cancer. Meanwhile, ageing and cancer share a range of overlapping features, such as genomic instability, epigenetic alterations, and chronic inflammation. One mechanism that seems to link both is the accumulation of cellular damage over time. However, some ageing processes may also impede tumor development in a tissue-specific manner, including telomere attrition and stem cell depletion. In addition, since the elderly population is growing rapidly as life expectancy increases, older patients with cancer remain underrepresented in clinical trials, making it challenging for oncologists. The search for cancer and age-related molecular links could help provide optimal personalized treatment for them. Therefore, this chapter aims to review the literature on this topic to generate more attention and interest in the community and to conduct more research on the mechanisms of age-related cancers. Meanwhile, this chapter also proposes the inclusion of a section on drugs beneficial for both anti-aging and anti-cancer purposes, providing guidance for future research and human health.

1. Introduction

Life expectancy has increased dramatically in the last few decades due to dramatic improvements in medical technology, rapid economic growth, and enhanced opportunities for education. Older adults have become a rapidly growing part of the world's population. Ageing is the leading risk for cancer, with most tumors being diagnosed in older age groups compared to younger age groups (Berben, Floris, Wildiers, and Hatse, 2021).

The ageing process indicates the accumulation of molecular and cellular damage, resulting in decreased function, declined fertility and increased probability of death in adulthood (Kirkwood, 2008). Due to lifelong exposure to endogenous metabolic damage (e.g., free radicals) and exogenous factors (e.g., ultra-violet (UV) exposure, over-smoked and grilled meat, etc.), the accumulation of oxidative stress and DNA damage over the years eventually result in cell transformation and tumor initiation. The multi-step acquisition of cell-acquired genetic mutations results in cancer, particularly in stem cells (Solary, Abou-Zeid, and Calvo, 2022). The accumulation of mutated proto-oncogenes (e.g., PIK3CA) and tumor suppressor genes (e.g., p53, INK4, phosphatase and tensin homolog deleted on chromosome 10 (PTEN)), drive the expansion of mutant cells into clones (Solary et al., 2022). Significantly, the magnitude and amounts of these clones increase progressively with age. Moreover, almost all renewed tissue will become a collage of mutant clones over time, whose accumulations may constitute parts of the ageing process. Furthermore, the decreased production of T and B lymphocytes leads to a decline in the function of mature lymphocytes in secondary lymphoid tissue. (Franceschi and Campisi, 2014). As a result, older adults gradually accumulate more injured cells compared to younger people. They in turn have a higher risk of developing cancer.

Senescence and telomere shortening in young healthy tissues may protect against tumor formation (Shay and Wright, 2019). Telomere shortening restricts the maximum number of cell divisions. Since the telomeres can be shortened beyond the ability to achieve later replications, thereby initiating DNA damage signaling and senescence (Gorgoulis et al., 2019). Normal diploid cells will also enter senescence to cease responses to stressful insults (e.g., oncogenic stress) (Hayflick and Moorhead, 1961). Their senescence-induced mutated clones could be cleared substantially by the surrounding cells. However, the ability of ageing tissues to be cleared becomes insufficiently effective to allow the accumulation of increasing numbers of senescent cells. They persistently promote the generation of a pro-inflammatory and immunosuppressive microenvironment known as the senescence-associated secretory phenotype (SASP). Then, SASP further disrupts the extracellular matrix, promotes tissue vascular remodeling effects, and supports the cancer cell growth by secreting several inflammatory mediators, such as interleukin-6 (IL-6) and IL-8, vascular endothelial growth factors (VEGF) and matrix metalloproteinases (MMPs) (Shay and Wright, 2019). Additionally, in models of treatment-triggered senescence, cells undergoing senescence reacquire proliferation characteristics via the reversible nature of senescence or obtain senescence-related stemness through the mechanisms of reprogramming and become hyper-aggressive tumors, driving tumor relapse and development (Schmitt, Wang, and Demaria, 2022). Meanwhile, the incidence of cancer has been reported to be leveling off in older ages, with overall mortality due to cancer declining in the oldest age groups (De Magalhães, 2013). This may be explained that deaths due to cancer are skewed toward younger populations, with a resulting lower incidence of cancer-related deaths in the oldest age group (Vaupel, 2010). The increase in the incidence of age-related cancers also depends on the cancer type. For example, the incidence of testicular cancer peaks around the age of 30 and then drops off dramatically (De Magalhães, 2013). These suggest that the complex mechanisms of ageing in driving tumorigenesis.

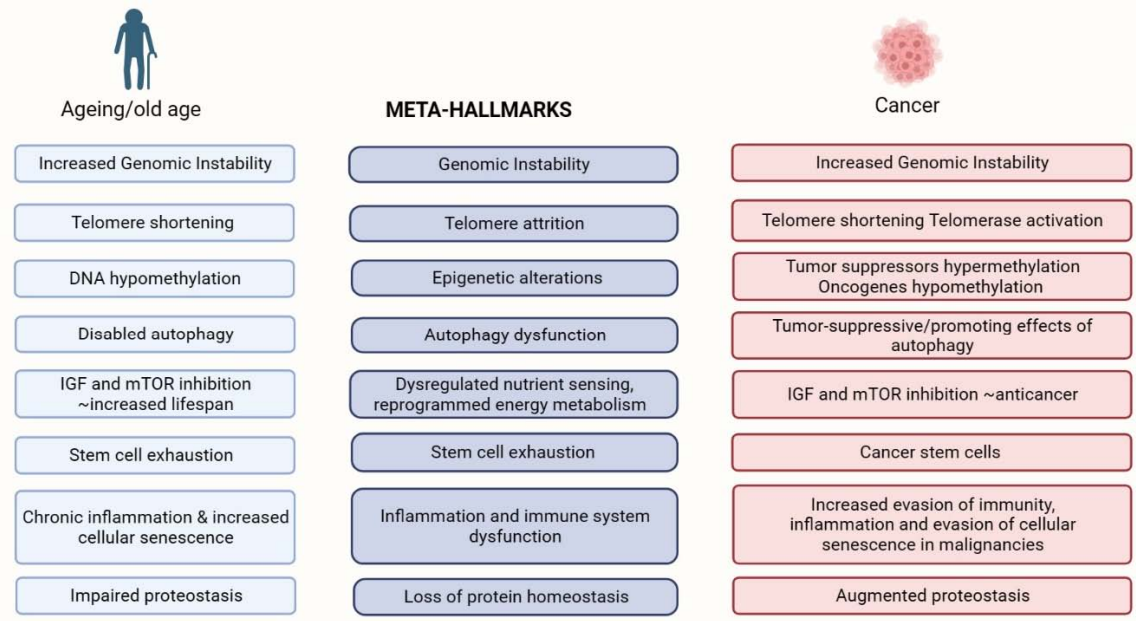

Figure 1. Common or Different Meta-Markers in Ageing and Cancer

Cancer and ageing are closely related, as shown in Figure 1 (De Magalhães, 2013; Finkel, Serrano, and Blasco, 2007; Rajput, Dwivedi, Sabarwal, and Singh, 2020; Serrano and Blasco, 2007). Although the incidence of cancer rises exponentially in humans during mid-life, it peaks at age 85 and shows a net decline in incidence and causes of death after age 90, falling to less than 5% of overall incidence and mortality above age 100 (Pavlidis, Stanta, and Audisio, 2012). It is hypothesized that this dual association is because certain mechanistic drivers or features associated with ageing will stimulate carcinogenesis and subsequent tumor progression, whereas additional age-related processes will restrict carcinogenesis (López-Otín, Pietrocola, Roiz-Valle, Galluzzi, and Kroemer, 2023). The identified molecular mechanisms of ageing include genomic instability, telomere attrition, epigenetic alterations, loss of protein homeostasis, autophagy compromise, and mitochondrial dysfunction (J. Guo et al., 2022; López-Otín, Blasco, Partridge, Serrano, and Kroemer, 2013; Shannon et al., 2021). The steadily accumulated mutational processes in cancer are defined as the molecular clock (Alexandrov et al., 2013), including genome instability and mutation, cell death resistance, cellular energy deregulation, sustaining proliferative signaling, evasive growth suppressors, immune destruction avoidance, replicative immortality induction, tumor-promoting inflammation, invasive and metastatic activation, and angiogenesis induction (Alexandrov et al., 2013; De Magalhães, 2013; J. Guo et al., 2022; López-Otín, Pietrocola, et al., 2023). As shown above, ageing and cancer are quite similar in character and show strong molecular equivalence. Therefore, this chapter aims to review the molecular connections between ageing and cancer.

2. Genomic Instability Response

Genomic instability refers to small structural changes in the genome due to altered physiological conditions, including (1) chemical damage to genomic DNA involving single and double-strand breaks in the DNA backbone, cross-linking between bases (both intra- and inter-strand), and depurination or depyrimidination of sugars and modified bases; (2) mutations, which are the addition/deletion/replacement of genetic code positions; and (3) epistatic mutations, i.e., heritable changes in DNA or protein modifications that control gene expression but do not affect the actual base pair sequence of DNA (Vijg and Suh, 2013). Genomic instability is associated with several different environmental and endogenous factors, such as reactive oxygen species (ROS), reactive nitrogen species (RNS), and UV radiation, which may in turn contribute to ageing and cancer (Schumacher, Pothof, Vijg, and Hoeijmakers, 2021).

During ageing, somatic mutation gene copy number variants and chromosomal aneuploidy occur in nuclear DNA, which may affect functionally fundamental genes and then induce cellular mutations, tissue malformations and organismal abnormalities that trigger ageing and age-related pathologies (Huang et al., 2022). Similarly, the manifestation of genomic instability in several cancers refers to a range of DNA alterations, from point mutations and deletion insertions to chromosomal rearrangements and numerical changes throughout the chromosome, which irreversibly alter the information content of the genome (Vijg and Montagna, 2017). This condition increases and accumulates with age, which may predispose cells to malignant transformation (Freitas and De Magalhães, 2011). As age advances, DNA repair pathways targeting mechanisms, such as base excision repair (BER), nucleotide excision repair (NER),

mismatch repair (MMR), homologous recombination (HR), and non-homologous end joining (NHEJ), that minimize inevitable genetic damage and maintain cellular homeostasis are progressively compromised, resulting in damage to multiple genes that control cell division and tumor suppressors (Y. Yao and Dai, 2014). This build-up of irrepressible cellular genome damage increases the risk of cancer (Miller et al., 2021). For example, alterations in DNA repair mechanisms induce ageing in mice and potentially premature ageing syndromes in humans (Hennekam, 2020). Also, these ageing-accelerating syndromes, for example, patients with Fanconi anemia have a 500-700-fold increased risk of developing squamous cell carcinoma (SCC) of the head and neck relative to the general population. (Carbone et al., 2020). Female with inherited BReast CAncer gene 1 (BRCA1) or BReast CAncer gene 2 (BRCA2) mutations have breast epithelial cells that are prone to breast cancer partially because of an absence of DNA repair (Shalabi et al., 2021). Furthermore, research among humans and other long-lived animals has reported that improvements in DNA repair processes have co-evolved with increases in lifespan (Quesada et al., 2019).

Both nuclear and mitochondrial DNA (mtDNA) are susceptible to external or internal stresses, leading to genetic mutations and deletions that can further result in ageing and carcinogenesis (Sanchez-Contreras and Kennedy, 2022). Mice lacking DNA polymerase γ showed acceleration of ageing as well as shortened longevity primarily related to mtDNA deletion (Macken, Vandrovcova, Hanna, and Pitceathly, 2021). Moreover, the damages on mitochondria promotes tumor development through genetic mutations and the generation of integrative metabolites, which promotes cancer development by metabolic re-programming and altered mitochondrial dynamic (López-Otín, Pietrocola, et al., 2023).

3. Telomere Attrition

During the ageing process, DNA damage may further damage the ends of chromosomes, termed telomeres, which is a repetitive region consisting of TTAGGG repeat sequences and associated proteins (Berben et al., 2021). Since replicative DNA polymerase is unable to complete the replication of the telomeric region in time (Blackburn, Epel, and Lin, 2015). As a result, consecutive cell division cycle lead to gradual shortness of telomere and ultimately genomic instability, culminating in the permanent arrest of cell cycle (senescence) or cell death and systemic inflammation (Artandi and DePinho, 2010). In zebrafish larvae with very short telomeres, melanomas appear more frequently, propagate more rapidly and become more aggressive (Lex et al., 2020). Furthermore, a reduction in leukocyte telomere length is considered a biomarker of biological ageing and plays an essential role in carcinogenesis (Brouwers et al., 2015). Nevertheless, there were inconsistent researches on associations between blood telomere length (BTL) and the risk of cancer (Hou, Zhang, Gawron, and Liu, 2012; Willeit et al., 2010). That may be because most studies which reported shorter BTL in cancer patients relative to controls were retrospective studies where BTL was measured after diagnosis (Hou et al., 2012). Unryn et al. (2006) reported that 8 weeks of chemotherapy resulted in a more than 100-fold increase in telomere attrition in 20 patients with neck and head tumors. When responding to treatment, the elderly was shown to have a greater telomere attrition. There was a mean loss of 400 bp of telomeric DNA in patients aged less than 55 years, compared to 880 bp in patients older than 55 years of age (Unryn, Hao, Glück, and Riabowol, 2006).

Conversely, Hou et al. (2012) conducted a min-review (Hou et al., 2012), which reported an increased cancer risk in participants with shorter BTL when measured prior to diagnosis (Hosgood III, Cawthon, He, Chanock, and Lan, 2009; McGrath, Wong, Michaud, Hunter, and De Vivo, 2007; X. Wu et al., 2003), whereas other studies have shown the opposite result, i.e., longer BTL (Lan et al., 2009; Juan Liu et al., 2011; Svenson et al., 2008). Hou et al. (2015) (Hou et al., 2015) further conducted the longitudinal studies of BLT with multiple pre-diagnostic measurements and indicated that the attrition of age-associated BTL was accelerated in patients with cancer than in participants without cancer ($p = 0.017$). However, all participants had comparable age-adjusted BTL 8-14 years prior to diagnosis, with subsequent decelerating attrition of cancer cases leading to significantly longer BTL 3 years ($p = 0.003$) and 4 years ($p = 0.012$) prior to diagnosis. Thus, since early oncogenic effects lead to accelerated shortening of BTL, cancer subsequently hijacks the telomere lengthening machinery at some stage of its development (Hou et al., 2015).

Furthermore, the limited replicative potential of most somatic cells suggests that they do not have sufficient capacity to turn normal cells into malignant cells, as this requires substantial genetic and epigenetic alterations. Therefore, telomere attrition may contribute to the prevention of tumor formation and progression (Gao and Pickett, 2022). Apparently, cancer cells need to reactivate the mechanisms that maintain telomeres, either by telomerase (in 80-85% of cancers) catalyzing the synthesis of telomeric repeats, adding telomeric sequences to the ends of chromosomes, or by alternatively lengthening telomeres (ALT) (in 10-15% of malignancies) to avoid telomere degradation (Jang et al., 2008). These finally achieve replicative immortality (i.e., indefinite tumor cell proliferation and growth) and thus acquire one of the major hallmarks of malignancy (Forrester et al., 1990).

Telomerase is a large (>1 MDa) ribonucleoprotein particle with a catalytic core composed of telomerase reverse transcriptase (TERT) and RNA subunits (TR) (Cristofari and Lingner, 2006). Various mechanisms have been suggested to be engaged in telomerase activity. This is described in detail below. (1) The human TERT (hTERT) expression is tightly regulated at the transcriptional level, which closely correlates with telomerase activity. The hTERT over-expression in human fibroblasts is adequate to cause their immortality but not transformations (López-Otín, Pietrocola, et al., 2023). In contrast, mutations in the promoter of the gene encoding hTERT(-124C>T and -146C>T) override the silencing of hTERT through the recruitment of erythroid transformation specific (ETS) family transcription factors (Forrester et al., 1990). In melanoma, TERT expression was increased by an average of 4-fold, showing highly recurrent TERT promoter mutations (Horn et al., 2013). The primary glioblastoma also showed that TERT promoter mutations are present in more than 80% of cases (Killela et al., 2013). Li et al. (2020) (X. Li et al., 2020) used clustering regular interval short palindromic repeats (CRISPR)-mediated correction and achieve −124C>T TERT promoter mutation to −124C, which significantly prevented the E26 transcription factor family members from binding to the TERT promoter, reducing TERT transcription and TERT protein expression, inducing senescence and proliferative arrest in cancer cells, and ultimately prolonging the survival of glioma mice. (2) The hTERT protein also functions in mitochondria to suppress the intrinsic apoptotic pathways, and preserves its genome integrity in mtDNA (López-Otín, Pietrocola, et al., 2023). (3) The interactions of hTERT

with chromatin remodeling factors (e.g., SMARCA4) can transactivate genes involved in tumor progression (López-Otín, Pietrocola, et al., 2023). In the chromosomally unstable high-grade prostatic intraepithelial tumors, telomerase with experimental reactivation resulted in malignant progression, acquiring new phenotypes (e.g., bone metastases). On the contrary, telomeres remained intact in controls without post-crisis reactivation of telomerase, showing only localized invasion (Ding et al., 2012). (4) Meanwhile, it also interacts with transcription factors (e.g., nuclear factor kappa B (NF-κB)) and binds with IL-6 and tumor necrosis factor-alpha (TNF-α) promoter elements to promote tumor cell proliferation and increase cellular resistance to programmed death (Ghosh et al., 2012).
ALT commonly occurs in osteosarcomas and glioblastomas and is usually associated with a poor prognosis (Heaphy et al., 2011). ALT uses a DNA homology-directed repair mechanism to lengthen telomeres where telomeric DNA templates are replicated from sister chromatids or non-homologous chromosomes (Heaphy et al., 2011). ALT-positive cells have large amounts of the extrachromosomal telomeric repeat (ECTR) DNA, and ECTR can also develop circular and double-stranded structures termed t-loops (i.e., the end product of telomere pruning), which has been proposed as the substrate for telomere elongation in ATL cells (Sommer and Royle, 2020). However, the presence and persistence of ECTR are associated with defects in the cGAS-STING cytoplasmic DNA sensing pathway, which triggers the IFN response. However, it is non-functional in some ATL-positive cell lines, indicating their defective ability in sensing cytoplasmic DNA (Y.-A. Chen et al., 2017). Therefore, sequential ECTRs products provide extra anti-proliferative barriers to ALT-adopting tumor cells, including induction of senescence and innate immune surveillance (Chakravarti, LaBella, and DePinho, 2021).

Additionally, ALT-positive cancers are not biologically equivalent to telomerase-positive tumors. ALT is essential in driving tumorigenesis even without reactivating telomerase, nevertheless, it cannot promote aggressive malignancies and metastasis efficiently. In comparison, the telomerase-positive cancer cells obtain metastatic potential followed by mTERC transduction (Y.-A. Chen et al., 2017).

Telomere attrition is not completely relevant to the suppression of tumorigenesis. Even though there are various drugs in development to suppress hTERT in direct, such as 2-[[(2E)-3-(2-naphthalenyl)-1-oxo-. 2-buten-1-yl]amino]-benzoic acid (BIBR1532). The inmetelstat and other antisense oligonucleotides, which are the RNA template molecules belonging to the telomerase complex, could indirectly prevent elongation of telomere by a nucleoside analogue or G-quadruplex stabilizing ligand, and/or induct specific immuno-reactivity targeting hTERT (Gao and Pickett, 2022). In addition to Imetelstat, whose efficacy in relapsed/refractory myelofibrosis remains to be proven (Kuykendall et al., 2022), and UV1, which is a DNA-based vaccine that encodes the inactivated ubiquitin-fused form of hTERT and it may evoke a therapeutic and significant immune response in a proportion of patients with melanoma (Aamdal et al., 2021), none of these approaches has been shown to be clinically active. The absence of any molecule inhibiting this process against ALT may indicate that it normally disrupts other DNA repair processes (Gao and Pickett, 2022). No particular ALT inhibitor has been applied to the clinic. Therefore, telomerase-depleted mice showed an increase in the incidence of spontaneous malignancies (Rudolph et al., 1999), particularly in the presence of p53 deficiency. Even though the deficiency of p53 did reduce the carcinogenicity of mice deficient in the Cdkn2a tumor suppressor gene (Greenberg et al., 1999). Similarly, the

prospective study involving a Danish population of 47,102 has shown a linear relationship between telomere length and increasing age ($P < 0.001$), and a reduction in quartiles of telomere length was related to decreased survival after cancer (log-ranked $P < 0.001$) (Weischer et al., 2013).

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William Cho specializes in cancer research, focusing on identifying biomarkers for cancer diagnosis, treatment prediction, and prognostication. With an H-index of 100, he has authored over 630 peer-reviewed papers in journals, including *Lancet*, *Lancet Oncology*, *Annals of Oncology*, *Advanced Science*, *Nature Communications*, *PNAS*, *Science Advances*, *Journal of the National Cancer Institute*, *Journal of Extracellular Vesicles*, *Clinical Cancer Research*, *Clinical Chemistry*, *Molecular Cancer*, and *Theranostics*, among others. Additionally, Dr Cho has authored over three dozen of books, including "MicroRNAs in Cancer Translational Research", "An Omics Perspective on Cancer Research", and "Drug Repurposing in Cancer Therapy: Approaches and Applications", to name a few. As one of the top 2% most influential scientists globally since 2017, Dr Cho has recently been included in the 2023 and 2024 Global Highly Cited Researchers list by Clarivate.

In addition, Dr. Cho has also served as a research grant reviewer for many international research funds, including the Hope Funds for Cancer Research (United States), Cancer Research (United Kingdom), National Medical Research Council (Singapore), etc.