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REVIEW ARTICLE

Characteristic Hallmarks of Aging and the Impact on Carcinogenesis

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Abstract: Evidence shows that there is a synergistic, bidirectional association between cancer and aging with many shared traits. Age itself is a risk factor for the onset of most cancers, while evidence suggests that cancer and its treatments might accelerate aging by causing genotoxic and cytotoxic insults. Aging has been associated with a series of alterations that can be linked to cancer: *i) genomic instability* caused by DNA damage or *epigenetic alterations* coupled with repair errors, which lead to progressive accumulation of mutations; *ii) telomere attrition* with possible impairment of telomerase, shelterin complex, or the trimeric complex (Cdc13, Stn1 and Ten1 - CST) activities associated with abnormalities in DNA replication and repair; *iii) altered proteostasis*, especially when leading to an augmented proteasome, chaperon and autophagy-lysosome activity; i*v) mitochondrial dysfunction* causing oxidative stress; *v) cellular senescence*; *vi) stem cells exhaustion*, *intercellular altered communication* and *deregulated nutrient sensing* which are associated with microenvironmental modifications which may facilitate the subsequential role of cancer stem cells. Nowadays, anti-growth factor agents and epigenetic therapies seem to assume an increasing role in fighting aging-related diseases, especially cancer. This report aims to discuss the impact of age on cancer growth.

Keywords: Aging, cancer, epigenetic, genomic instability, microenvironment, oxidative stress.

1. INTRODUCTION

While worldwide cancer is considered the second most common cause of death, especially in older people, tumor incidence and mortality are rapidly growing as a consequence of both aging and the growth of the population, as well as changes in the prevalence and distribution of the main risk factors (often associated with socioeconomic development) [1-4].

Evidence shows that there is a synergistic, bidirectional connection between cancer and aging with many shared hallmarks (epigenetic modifications, altered intracellular communication, variations in proteostasis, mitochondrial dysfunction and cellular senescence) [5-9]. Both cancer and aging are characterized by accumulation of cellular and molecular damage leading to system dysregulation; furthermore, age itself is a risk factor for the onset of most cancers, while evidence suggests that cancer and its treatments (by causing genotoxic and cytotoxic insults) might accelerate aging [10-14]. Similarly to carcinogenesis, the aging process of an organism results from a combination of stochastic events, including both genetic and environmental factors (*e.g.,* diet, smoking, obesity, stress, alcohol abuse), which, at the molecular level, can impair gene expression initiating the decline of the physiological functions [15]. Though the subsequent patterns of aging cannot be changed, it has been suggested that preventive medicine should focus on the several age-related risk factors that contribute to cancer onset [16,17]. In particular, during midlife, the prevalence of numerous cancer risk factors is elevated, while incidence rates increase for many types of tumors; however, it has been suggested that if the environmental factors that influence these aging biologic mechanisms can be modified on time, the rate of aging may be slowed, and the onset of cancer delayed or even prevented [18,19]. Because of the concurrent increase in the number of both adults reaching older ages and the incidence of cancer, there is an urgent need to convert the available evidence into practice to promote cancer prevention and therapy (Fig. **1**).

This report aims to provide a summary and subsequent review of literature evidence, which highlights the impact of aging on cancer growth.

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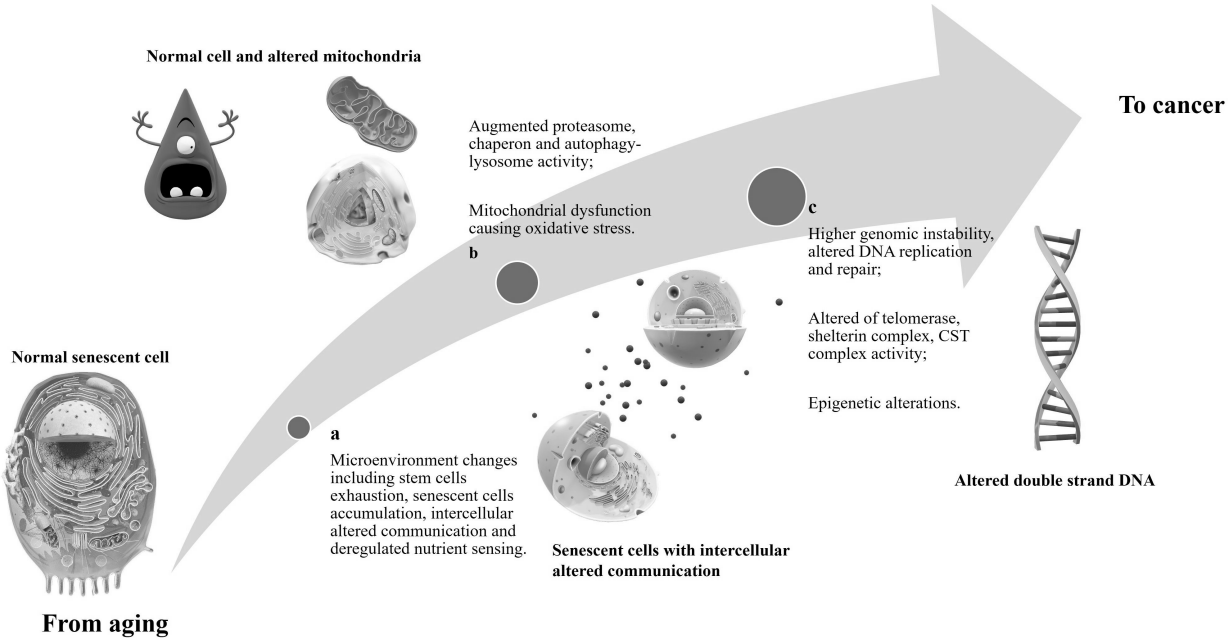

Fig. (1). Aging has been associated with a series of alterations that can lead to cancer:

a) cellular senescence, stem cells exhaustion, intercellular altered communication and deregulated nutrient sensing are associated with microenvironmental modifications which may facilitate the subsequential role of cancer stem cells;

b) altered proteostasis, especially when leading to the augmented proteasome, chaperon and autophagy-lysosome activity and mitochondrial dysfunction causing oxidative stress;

c) genomic instability caused by DNA damage or epigenetic alterations coupled with repair errors lead to progressive accumulation of mutations; telomere abnormalities due to impairment of telomerase, shelterin complex, or CST (Cdc13, Stn1 and Ten1) complex activities; epigenetic alterations that cause a higher frequency of transcriptional changes. Images have been created by using the functionalities of Microsoft PowerPoint 365 Version 2112 https://www.microsoft.com/microsoft-365.
(A higher resolution / colour version of this figure is available in the electronic copy of the article).

2. AGING

2.1. General Mechanisms

Aging is an unavoidable time-dependent variable decline in all physiological functions, driven by a genetic program and linked to increased risk for numerous pathologies (*i.e.,* cardiovascular and cerebrovascular diseases, tumors). It has been suggested that one of the possible causes of aging is the activation of multiple pathways due to the altered function of quality control systems monitoring the performance of the genomic and proteomic repertoire of the cells [20]. In 2013, a total of nine biological hallmarks of aging were identified, while successive studies linked these common assets to various pathological conditions associated with aging itself; the hallmarks are: genomic instability, epigenetic alterations, telomere attrition, loss of proteostasis, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication and deregulated nutrient sensing [7,21,22].

Human aging consists of a series of changes that, over time, may involvediseases in a structured organization at the molecular (*e.g.,* homeostatic altered mechanisms), cellular (and intercellular biological alterations), physiological (*e.g.,* body structure, energetics, homeostatic control mechanisms, and neuronal plasticity), and functional (with physical, cognitive, emotional, and social functions deficiency) levels [6]. Being these alterations mostly inevitable, it has been suggested that the main objectives of medical interventions for elders should focus on maximizing the ability of an individual to function in his environment, maintaining autonomy and maximizing quality of life [6]. Interestingly it has been demonstrated a connection between the biological mechanisms of aging, aging phenotypes and functional aging, where the major aging phenotypes can be grouped into four domains, namely: body composition variations, energetics and homeostatic mechanisms, and neuronal control and plasticity [23,24]. These various aspects have been considered the fundamentals of studying aging-related diseases and should always be taken into consideration when analyzing the complex biological mechanisms at the base of these conditions.

3. CARCINOGENESIS

3.1. General Mechanisms

Similar to aging, there are some recognized cancer hallmarks. In fact, the most important biological capabilities acquired during tumorigenesis are sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis [25]. These characteristics are acquired in a complex multistep process called carcinogenesis [26,27]. Usually, the process is associated with genome instability. Cancer hallmarks are supported by numerous pathways simultaneously and the “primum movens” may differ vastly. In consideration of the location and the charac-

teristics of the original tissue, as well as the intricate genomic alterations and microenvironmental attributes, every cancer must be considered different.

Fundamentally, during carcinogenesis, the cell loses the ability to self-regulate its proliferation without being intercepted by the normal regulators that should bring it to death. In this situation, the cell duplicates without restrains, and it must confront two major limits to originate a tumor: the immune system of the host, which should kill the aberrant cell and the lack of nutrients that cannot keep up with the increased demand due to the higher energy requirement. Unfortunately, tumors may use various methods to survive in the immune system rendering it ineffective, while it can also stimulate neoangiogenesis to obtain new nutrients. So, inflammation, in this case, is not the synonym for immune response, often further promoting cancer growth. Finally, the tumor may acquire the capability to migrate and survive in other locations of the body, causing a more dangerous and resistant disease.

3. GENOMIC ALTERATIONS

3.1. Genomic Instability

Increased genomic instability is characterized by the high occurrence of the genome and cellular mutations, which may include alterations of nucleic acid sequences, chromosomal rearrangements and microsatellites [28]. These changes are common elements of both tumors, the aging process and aging-related diseases [29]. Genomic instability may be caused by DNA damage or epigenetic alterations coupled with repair errors, which lead to progressive accumulation of mutations [30]. Accumulation of genomic instability has been associated with malignant progression and worse prognosis and correlates with aberrant transcriptional and post-transcriptional regulation, indicating that genomic instability may be measured by the molecular signature [31]. Recently it has been suggested that genomic instability promotes tumor progression by influencing the immune microenvironment [31]. Many DNA-repair gene family mutations have been identified in hereditary cancers, while in sporadic (non-hereditary) cancers, mutations in DNA repair genes are less frequent, and the mechanism proves to be more complex [28]. Genome instability is one of the hallmarks of aging, and, as demonstrated in various organisms, it is deleterious for maintaining a long lifespan [32]. The maintenance of genomic integrity is critical for the prevention of aging: unrepaired genomic damage gives rise to mutations that can be transferred to new cells during cell division, causing the development of dysfunctional tissues or tumors. Therefore, as a protective measure, the DNA damage triggers a switch in biological pathways to a phenotype supporting the preservation of the organism ("survival response") often leading to apoptosis and cellular senescence [33]. However, this shift is believed to further contribute to the distinctive changes that occur during aging [33,34]. In particular, senescent cells experience cell cycle arrest maintaining a minimal metabolic activity waiting to be "re-awakened" but sometimes acquiring an immunogenic phenotype consisting of interleukins, pro-inflammatory cytokines, and growth factors resulting in faster aging of the organism and increased susceptibility to age-associated disease, including cancer and cardiovascular diseases [35,36]. So, senescence is both a mechanism inhibiting genomic instability during diseases, as well as the cause of the increased aging rate of the organism associated with several diseases, including cancer.

3.2. Epigenetics

Epigenetics refers to the "study of heritable changes in gene expression that occur without a change in the DNA sequence" so that epigenetic mechanisms consent to an ulterior transcriptional control that regulates how genes are expressed [37-39]. In addition to genetic alterations, epigenetic changes, which include mainly DNA methylation and histone modifications (methylation and deacetylation), also play an important role in driving tumorigenesis. These modifications are dynamic and affect all cells and tissues throughout life, furthermore, the environment and lifestyle, as well as aging, can lead to remarkable epigenetic alterations [40]. Hence, alterations of the epigenetic mechanisms arising during aging cause a higher frequency of transcriptional changes responsible for aging-related diseases [15,41]. Among the aging-related diseases, cancer may be considered the result of the accumulation of genetic and epigenetic alterations, where perturbations in the genome resulting from changes in the cellular environment, inflammation, impaired immune function and accumulation of DNA damage lead the cells through carcinogenesis and malignant transformation [42-44]. Epigenetics (involving DNA methylation, histone modifiers and readers, chromatin remodelers, microRNAs, and other components of chromatin) and genetic alterations drive the cancer phenotype causing mutations in genes, and, conversely, mutations are frequently observed in genes that modify the epigenome [45,46].

The epigenetic study is a very difficult and actual topic, in fact, recently, genome-wide association studies identified 137 genetic loci (of which 113 are originals) for DNA methylation biomarkers of aging [47]. DNA methylation is the most abundant epigenetic modification that occurs by transferring a methyl group to the 5th carbon of the cytosine, however, DNA methylation does not always indicate a lower gene expression [48,49]. Methylation in gene promoters is generally associated with poor transcription factor (TF) binding and reduced transcription, while methylation removal by methylation-insensitive factors enables occupancy of methylation-sensitive factors, a principle that rationalizes hypomethylation of regulatory regions [50,51]. Among the various factors which affect the DNA methylation profile (biological sex, genetic background, environmental factors, age), age-dependent methylation is very well-characterized, with advancing age being mostly associated with a progressive loss of methylation marks on DNA (even though abnormal hypermethylation patterns are also observed in some gene promoters) [40,52-54].

It has been demonstrated that histones and epigenetic marks on histones undergo transitions with aging, while post-translational modifications of histones alter the gene transcription, alternative splicing, DNA replication and repair [55,56].

Epigenetics therapies, with the goal of reversing epigenetics changes, have been employed for several age-related diseases (*e.g.,* cancer, Alzheimer's disease) and are now one

standard of care for preleukemic disorders and lymphoma, also emerging for solid tumors [57,58]. Interestingly, the first hint that the body's biological age may be reversed has been shown in an intriguing study where regenerating the thymus by using dehydroepiandrosterone (DHEA) for 1 year resulted in a 2.5-year younger epigenetic profile that persisted six months after discontinuing treatment [59,60]. It has been suggested that methods that transiently erase the DNA methylation pattern of somatic cells may reset this aging hallmark with potentially profound effects on lifespan if DNA methylation-based epigenetic drift really plays a primary role in aging [61]. Furthermore, a contemporary study on rhesus monkeys showed that age-related methylation drift correlates with lifespan, moreover 40% caloric restriction in mammalians resulted in attenuation of age-related methylation drift, slowing down the aging process [62].

In line with this, small-molecule targets of various pathways have emerged in the hunt for caloric restriction mimetics. Resveratrol, oleuropein and its derivates, metformin, and rapamycin are the most extensively studied [63-67]. Interestingly, resveratrol and other polyphenols extracted for the olive possess similar antioxidant and anti-inflammatory properties [68-71]. Aging and obesity have common epigenetic changes (histone modification, DNA methylation, noncoding RNAs, and chromatin remodeling) that are also impacted by exercise [72,73]. The caloric restriction seems to affect the epigenetic profile causing decreased histone acetylation (mediated by increased SIRT1 expression), higher DNA methyltransferase activity, and hypermethylation of specific regulatory genes, such as Ras [74] [340]. An interesting recent study demonstrated that cumulative stress is also associated with epigenetic aging in a healthy population, and these associations may be modified by biobehavioral resilience factors [75].

3.3. Telomere Attrition

Telomeres, the protective DNA-protein structures at the ends of eukaryotic chromosomes, are essential for genome integrity and stability [32]. Telomeres are regions composed of thousands of hexameric nucleotide repeats of the sequence TTAGGG (initially double-stranded DNA but ending with a single-stranded DNA overhang) that lie at the ends of chromosomes, usually bound by the shelterin complex to prevent telomeres from being recognized as DNA double-strand breaks (DSBs) and enabling DNA replication at the telomeric repeats, which is critical for genome stability and cell survival [76]. The extended 5′ to 3′ strand contains the G-rich telomeric repeats and is referred to as the G-strand, while the 3′ to 5′ strand is defined as the C-strand. Although telomeres are heterochromatic, transcription still happens from the subtelomeric regions towards the end of chromosomes [77]. Currently, two types of telomere-associated RNA have been reported, telomeric repeat-containing G-rich RNA (TERRA, which induces the formation of stable R-loops - homology-directed repair-promoting RNA-DNA hybrids) and the complementary C-rich transcripts (ARIA) [78,79]. These RNAs play a central role in telomere stability and cellular replication control, where TERRA and R-loops may be a major source of telomere fragility [80]. During the cell division cycle, the eukaryotic DNA polymerase is unable to completely replicate the sequences at the chromosomal ends because RNA primers attach to the lagging strand during the synthesis of Okazaki fragments resulting in a loss of approximately 50-200 bases from the terminal sequence of chromosomes each time a cell divides causing every time telomere shortening. This "end replication problem" leads eventually to cellular senescence, cell cycle arrest and finally apoptosis so that telomeres may be considered a genetic time clock, leading to cellular aging. De facto, apart from the shedding RNA and the generation of the 3′ overhang by the sequence-specific exonuclease activity to resect back the 5′end of telomeres, telomere shortenings can also occur, regardless of cell replication, due to accumulative oxidative stress, age, gender, sex hormones, and lifestyle factors, such as the lack or presence of exercise, alcohol abuse, obesity and weight loss, smoking, and unhealthy diets [81-84]. The consequences of having short telomeres are genomic loss, shorter lifespan, genomic instability and sometimes elevated telomerase activity leading to a potential cancer predisposition factor. Early studies tried to explain cellular mechanisms of aging as mainly caused by telomere shortening at each duplication, nowadays the subtelomere-telomere theory overcomes various shortcomings of telomere theory by highlighting the essential role of subtelomeric DNA in aging mechanisms [85]. Telomeres act as caps that protect the internal regions of the chromosomes, and they worn down a small amount in each round of DNA replication and are indispensable chromatin structures for genome protection and replication. The telomere length maintenance has been attributed to several functional modulators, including telomerase, the shelterin complex, and the trimeric complex comprised of Cdc13, Stn1 and Ten1 (CST) complex, synergizing with DNA replication, repair, and the RNA metabolism pathway components [86-88]. Interestingly, a recent study concluded that cellular aging and senescence of the whole organism is substantially dependent on epigenetic modifications regulated by the subtelomere-telomere-telomeric hood-telomerase system [89]. These phenomena appear to be not random, inevitable, and irreversible but rather induced and regulated by genetically determined mechanisms, and modifiable and reversible by appropriate methods, supporting the thesis that aging is a genetically programmed and regulated phenoptotic phenomenon [89].

Dysfunctional telomere maintenance and telomerase activation are associated with several human diseases, including cancer. Cancer cells exhibit telomerase activation, causing cellular proliferation and enabling replicative immortality [90]. Hyperactivity of telomerase reverse transcriptase, the catalytic subunit controlling enzyme activity in telomerase, plays a key role in cancer development, furthermore, mutations in genes encoding shelterin and CST complexes can result in cancers because of a loss of regulation and maintenance of the telomere length [83]. Different from developing embryos and reproductive cells, typically in healthy adult somatic cells, telomerase is inactive to avoid uncontrolled cellular proliferation, however, in approximately 90% of human tumors, telomerase is up-regulated or reactivated to help tumor cells survive and multiply [91].

Interestingly, some drugs seem to cause accelerated biologic processes related to aging partially explained by the shortening of telomeres. In a recent study, morphine and dependency on heroin have been shown to increase oxidative

stress in drug-dependent persons causing an imbalance between oxidative stress and antioxidant defense mechanisms that can accelerate the shortening of telomere length [92]. On the other hand, melatonin alleviates age-associated endothelial injury of atherosclerosis by regulating telomere dysfunction-related vascular aging [93].

An optimal model to study aging and the related reduced resistance to stress and augmented risk of disease is the Werner syndrome (WS), a genetic disease caused by mutations in WRN, a gene involved in DNA replication and repair, characterized by accelerated aging, increased risk of cancer and metabolic diseases [94,95]. WRN mutations contribute to multiple hallmarks of aging, including genomic instability, telomere attrition, and mitochondrial dysfunction [96].

Another interesting pathological model associated with both aging and cancer is systemic sclerosis (SSc), a chronic connective tissue disorder characterized by immune dysregulation, chronic inflammation, vascular endothelial cell dysfunction, progressive tissue fibrosis of the skin and internal organ, increased cancer incidence and accelerated aging associated with chromosome instability [97]. Accelerated cellular senescence has been confirmed by the shortening of telomere length due to increased DNA breakage, abnormal DNA repair response, and telomerase deficiency mediated by enhanced oxidative/nitrative stresses [98]. Furthermore, both cancer and cellular senescence in these patients seem to be elicited by the interactions among excessive oxidative stress, pro-inflammatory cytokines, and autoantibodies. In fact, the immune dysfunctions of SSc patients are manifested by excessive production of proinflammatory cytokines, which can stimulate tissue inflammation followed by tissue fibrosis [99,100], as shown for other pathologies [101-103]. Data from these patients may provide a foundation for the development of treatments for similar diseases.

3.4. Proteostasis

Proteostasis regulation and proteome integrity are essential for physiological cellular function. The proteasomes are multisubunit protease complexes that selectively catalyze the degradation of short-lived regulatory proteins and damaged peptides may directly affect the substrate selectivity regulating proteostasis maintenance in response to certain intracellular and extracellular conditions [104,105]. Thus, the proteasome contributes to controlling key processes that affect the cellular state, such as adaptation to environmental cues, growth, development, metabolism, signaling, senescence, pluripotency, differentiation, and immunity. Function abnormalities in this system are related to physiological processes like aging (with impairment of proteasome, chaperon and autophagy-lysosome activity) and pathological conditions such as neurodegeneration and cancer (with the augmented proteasome, chaperon and autophagy-lysosome activity) [106].

Since advanced glycation end products accumulate during aging and age-associated diseases, a recent study demonstrated, by using quantitative proteomics, that protein glycation triggers a proteotoxic response and indirectly affects the protein degradation machinery regulating the cellular function compromised during aging [107]. An interesting article demonstrated that FOXO (forkhead box, class O) transcription factors regulate metabolic homeostasis as well as longevity using *Drosophila* transgenic lines expressing high and relatively low *foxo* levels and overexpressed *foxo*, either ubiquitously or in a tissue-specific manner [108]. Ubiquitous *foxo* overexpression accelerates aging inducing the early onset of age-related phenotypes, increasing the sensitivity to thermal stress, and deregulating metabolic and proteostatic pathways. In particular, *foxo* overexpression counteracts the proteostatic pathways in an Nrf2/cncC dependent-manner, ameliorating the aberrant *foxo* overexpression-mediated toxicity [108].

An interesting kind of chaperone with a highly conservative primary structure is the Heat Shock Proteins (HSPs) group, which plays a central role in the processes of protein folding to obtain the most energetically advantageous conformation to maintain their stability. As demonstrated in *Drosophila* models, HSPs are up-regulated in tissue-specific patterns during aging, and their expression correlates with, and sometimes predicts, life span, making optimal biomarkers of aging [109,110]. The HSPs and their co-chaperones have key roles in regulating proteostasis within the cell, controlling protein folding/unfolding, aggregation and transport and in modulating protein degradation [111]. So HSPs reduce the toxicity of abnormal proteins by facilitating protein refolding and turnover, and through other mechanisms, including the inhibition of apoptosis.

On the other hand, when overexpressed, HSPs play a crucial role in cancer growth, disrupting the apoptosis process of transformed cells, and promoting the processes of proliferation, invasion, and metastasis with important practical perspectives as chemotherapeutic targets [112,113]. It seems particularly important to be HSP70 and HSP90 that are consistently overexpressed in numerous cancer types facilitating tumorigenesis by ensuring cancer cell proliferation, survival and invasiveness and predicting worse outcomes in cancer patients [114-116]. Specifically, to prevent protein degradation and cellular apoptosis, it has been shown that HSP90 prevents the degradation of mutated p53, encouraging the uncontrolled proliferation of cancer cells [112].

Recent studies suggest that ribosome ADP-ribosylation in cancers maintains proteostasis by reducing protein synthesis and preventing toxic protein aggregation [117,118]. Ribosomal mono-ADP-ribosylation (MARylation) may promote cancer cells' growth by regulating polysomes assembling or functioning through the 3'-untranslated region (3'-UTR) stem-loop secondary structures in mRNAs. It has been demonstrated that when poly(ADP-ribose) polymerase 16 (PARP-16 - a mediator of ribosomal proteins MARylation) or nicotinamide mononucleotide adenylyltransferase 2 (NMNAT-2 - a cytosolic NAD+ synthase supporting the catalytic activity of PARP-16) are deleted, the stem-loop element in the 3'-UTRs of mRNAs increases polysome loading, enhances protein synthesis, promotes toxic protein aggregation, leading to inhibited cancer cell growth [117].

The process of autophagy, which degrades and removes long-lived or damaged cellular organelles and proteins, becomes defective by aging, causing impaired aggregate clearance and protein quality control machinery causing aging-

associated diseases [119]. Aging has been associated with gradual impairment of autophagy function, shown by the reduced formation of autophagic vacuoles and altered fusion of these vacuoles with the lysosomes, leading to disrupted responsiveness to oxidative stress, starvation and hypoxia and decreased expression of autophagy-specific proteins (Beclin 1, LC3, Atg5 and Atg7) [120,121]. On the other hand, increased autophagic activity serves as a tumor suppressor during the initial stages but later protects the tumor cells from the immune system defense mechanisms [122-124]. Higher levels of autophagy cause cell death, while inadequate autophagy can bring to cellular senescence, but both have roles in human diseases because cellular senescence and autophagy commonly cause several degenerative processes, including oxidative stress, DNA damage, telomere shortening, and oncogenic stress [125]. Interestingly, autophagy acts as either a pro-senescence or an anti-senescence way. Indeed, general autophagy seems to act as an anti-senescence mechanism by maintaining homeostasis under either normal or stress-induced conditions. In turn, it promotes, however, cellular senescence by facilitating the synthesis of senescence-associated secretory proteins when there are signals asking to decrease the burden of stresses that senescent cells must cope with [126,127].

3.5. Microenvironment

The tumor microenvironment (TME) is composed of various cell types embedded in an altered extracellular matrix (ECM). ECM not only serves as a support for tumor cells but also regulates cell-cell or cell-matrix cross-talks [128]. Alterations in ECM may be induced by hypoxia and acidosis, by oxygen free radicals generated by infiltrating inflammatory cells or by tumor- or stromal cell-secreted proteases. A poorer diagnosis for patients is often associated with ECM alterations. Tumor ECM proteome, also named cancer matrisome, is strongly altered, and different ECM protein signatures may be defined to serve as prognostic biomarkers [128]. Collagen network reorganization facilitates tumor cell invasion. Proteoglycan expression and location are modified in the TME and affect cell invasion and metastatic dissemination. ECM macromolecule degradation by proteases may induce the release of angiogenic growth factors but also the release of proteoglycan-derived or ECM protein fragments, named matrikines or matricryptins [128]. Solid tumors are complex organ-like structures that consist not only of tumor cells but also of vasculature, ECM, stromal, and immune cells [129]. Often, TME comprises the larger part of the overall tumor mass. Like the other components of the TME, the ECM in solid tumors differs significantly from that in normal organs [129]. Intratumoral signaling, transport mechanisms, metabolisms, oxygenation, and immunogenicity are strongly affected if not controlled by the ECM. Exerting this regulatory control, the ECM does not only influence the malignancy and growth of the tumor but also its response to therapy [129]. Understanding the particularities of the ECM in a solid tumor is necessary to develop approaches to interfere with its negative effect. Most cancers arise in individuals over the age of 60. As the world population is living longer and reaching older ages, cancer is becoming a substantial public health problem. It is estimated that, by 2050, more than 20% of the world's population will be over the age of 60 — the economic, healthcare and financial burdens this may place on society are far from trivial. In this Review, we address the role of the ageing microenvironment in the promotion of tumour progression. Specifically, we discuss the cellular and molecular changes in non-cancerous cells during ageing, and how these may contribute towards a tumour permissive microenvironment; these changes encompass biophysical alterations in the extracellular matrix, changes in secreted factors and changes in the immune system. We also discuss the contribution of these changes to responses to cancer therapy as ageing predicts outcomes of therapy, including survival. Yet, in preclinical studies, the contribution of the aged microenvironment to therapy response is largely ignored, with most studies designed in 8-week-old mice rather than older mice that reflect an age appropriate to the disease being modelled. This may explain, in part, the failure of many successful preclinical therapies upon their translation to the clinic. Overall, the intention of this Review is to provide an overview of the interplay that occurs between ageing cell types in the microenvironment and cancer cells and how this is likely to impact tumour metastasis and therapy response.

Cancer cells acquire multiple genetic mutations contributing to tumor development and growth; cancer cells may also acquire numerous epigenetic changes with cancer-inducing effects [130]. Epigenetic changes are modifications that alter DNA accessibility and chromatin structure affecting gene expression [131]. Epigenetic alterations (methylation, acetylation, phosphorylation, ubiquitination) are important factors for cancer initiation and progression [132], since they impact multiple aspects of tumorigenesis, including the modulation of tumor-suppressor genes and oncogenes and regulation of signaling pathways that induce cancer cell growth, invasion, and metastasis [133]. Epigenetic changes in cancer cells have also been related to drug resistance and response to treatment [134]. Interestingly, there is developing evidence that epigenetic changes play crucial roles in modulating the expression of fibrous ECM glycoproteins and proteins [135].

Indeed, ECM proteins play a key role in regulating ECM-mediated signaling that promotes cancer growth and metastasis. Several therapeutic strategies have been developed to target both fibrous ECM proteins and glycoproteins for effective cancer therapy. Indeed, the inhibition of collagen/elastin/fibronectin/integrins combined with chemotherapy and radiotherapy has shown promising results in clinical trials [136].

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An interesting recent article analyzed the role of the aging microenvironment in influencing tumor progression [9]. Aging can affect the normal cells of the tumor microenvironment, promoting cancer progression and metastasis. The microenvironment plays a key role in aging and tumorigenesis. Aged people tend to have increased cellular senescence, exhausted stem cells, higher oxidative stress and stimulated insulin and mTOR signalings (indeed, the inhibition of these two seems to increase lifespan), while malignancies show increased cellular senescence only in premalignant tumors evolving in fully malignant cancers, in the presence of active cancer stem cells (CSCs), higher oxidative stress and stimulated insulin and mTOR signaling (inhibition of these two has antineoplastic effects) [8,137]. The CSCs are self-renewing cancer cells responsible for the expansion of the malignant mass in a dynamic process shaping the tumor microenvironment, impeding host immune surveillance [138]. Stromal cells (fibroblasts, immune cells, endothelial cells, etc.) of the tumor microenvironment play important roles in both supporting and limiting cancer growth, where the tumor-associated stromal cells phenotype seems to be mainly due to epigenetic dysregulation of gene expression (DNA methylation and histone post-translational modification-based gene expression regulation, and miRNA-mediated translational regulation) [139]. Different stromal tissue environments through the body may be specifically reprogrammed during aging, therefore affecting cancer growth and progression [9].

3.6. Growth Factors

It has been demonstrated that diffusible molecules, such as growth factors and steroid hormones, play an important role in cellular senescence and cancer due to microenvironmental modifications and signal pathways stimulation. Evidence suggests that these molecules do not act as independent signals, but show reciprocal regulation and cooperative control over the aging process [140]. It was about three decades ago when it was demonstrated that genes encoding transcription factors (especially neurotrophins) and glucocorticoid receptors both play a key role in the cascade of events leading to environmentally induced cerebral changes in aging rats, also suggesting that environmental enrichment in adulthood, like neonatal handling, may have the potential to protect the aged hippocampus from glucocorticoid neurotoxicity [141]. Neurotrophins, and especially nerve growth factor (NGF), have also been implicated in the initiation and progression of many aggressive cancers [138,142-144], even though the NGF pathway plays a central role in oncogenic inflammation control and in promoting an immune response against cancer [145-147]. Another important growth factor is the vascular endothelial growth factor (VEGF) which is associated with important functions such as pro-angiogenic activity, having a mitogenic and an anti-apoptotic effect on endothelial cells, increasing vascular permeability and promoting cell migration, among the main functions [148]. The VEGF has been associated with tumorigenesis and tumor progression but also with other age-related diseases such as macular degeneration and Alzheimer's disease [149-151]. These findings suggest that more attention should be paid to the role of anti-growth factor agents and therapies for cancer and age-related diseases [150,152].

3.7. Inflammation

Inflammation may be triggered by exogenous pathogens (most commonly), but also DNA damage, UV radiation and physical trauma, which can cause low-grade sterile inflammation involving not only immune cells but also other types of cells such as epithelial cells and fibroblasts accompanying and modulating multiple biological processes, including cancer and aging-related pathologies [153,154]. Age-associated decline in immune function is mostly due to thymic involution, so it may be viewed as an unfortunate side effect of a selective process evolved to allow the peripheral selection of a T-cell repertoire during young-adult life. This process is optimized for fighting infections, reducing energy expenditure and minimizing autoimmunity while later in life, it contributes to immunosenescence which is an important factor that links tumorigenesis and aging [155-157].

3.8. Oxidative Stress

Despite being a well-known hallmark of aging, new findings have revealed novel cross-talk between histone epige-

netic modifications and oxidative stress during stem cell aging, which once more highlights the importance of this issue for aging and age-related diseases [158]. Evidence pinpoints a major role for mitochondrial dysfunction (Fig. **2**) in promoting aging and in supporting tumorigenesis and cancer progression, with a key part played by mutations and changes in the content of the mitochondrial genome, activation of mitochondria-to-nucleus signaling and mitochondria-telomere communication [159,160]. Mitochondria are intracellular organelles, equipped with their own circular genome (mtDNA) that maintain cellular homeostasis by producing adenosine triphosphate (ATP) and intermediate metabolites. Moreover, they regulate energy metabolism, cell survival and proliferation, and are also involved in Ca^{2+} signaling, mitophagy and mitochondrial transfer, fusion, and fission (known as mitochondrial dynamics) [161,162]. Mutations accumulate at a higher rate in mtDNA than nuclear DNA, resulting in mitochondrial dysfunction and diseases, and this is even more true in older people where a reduced mitochondrial efficiency and a degeneration of the antioxidant system coexist [163-165]. Studies in various species highlighted several alterations in mitochondria and mitochondrial DNA (mtDNA) associated with aging, including increased disorganization of mitochondrial structure; decline in mitochondrial oxidative phosphorylation function; accumulation of mtDNA mutation; increased mitochondrial production of reactive oxygen species (ROS); increased extent of oxidative damage to DNA, proteins, and lipids [166,167]. So, the decline in mitochondrial energy metabolism alters the quality control pathways. Also, it enhances mitochondrial oxidative stress, and the accumulation of mtDNA mutations is an important contributor to human aging. Since the efficacy of the respiratory chain diminishes, aging is associated with electron leakage, increased ROS production and reduced cellular ATP generation [168,169]. Mitochondria have also been related to multiple, often aging-related diseases, such as neurodegeneration and cancer [170,171]. Interestingly it has been suggested that novel mitochondrial quality control pathways that protect the cell may offer unique opportunities for disease therapy when ongoing mitochondrial damage takes place [172].

Some studies demonstrated the major role of oxidative stress in regulating lifespan so that reducing oxidative stress resulted in expanded life in murine models [173,174]. In a major study, to determine the role of reactive oxygen species in mammalian longevity and pathology, the authors generated transgenic mice that specifically overexpressed the human catalase localized in the peroxisome, nucleus, or mitochondria [173].

In mice overexpressing human mitochondria catalase, the median and maximum life spans increased on averages of 5 months and 5.5 months, respectively, while cardiac diseases and cataract development were delayed, oxidative stress damage was lessened, H_2O_2 production and H_2O_2-induced aconitase inactivation were reduced and incidence of mitochondrial deletions was lowered.

These results support the free radical theory of aging and reinforce the importance of mitochondria as a source of these radicals [173,174]. These results have been confirmed by another study that demonstrated how overexpression of the antioxidant enzyme catalase in mitochondria can extend mouse life span, highlighting the importance of mitochondrial damage in aging and suggesting that, when targeted appropriately, boosting antioxidant defenses can increase mammalian life span [174,175]. Unfortunately, some experiments on naked mole rats suggested that the role of oxidative stress parameters is limited and species-dependent, so the real extent of its influence on human aging processes still needs to be determined [176,177].

On the other hand, it has been observed an increased expression of genes encoding mitochondrial proteins in cancer stem cells, emphasizing the crucial importance of mitochondria for cancer cell survival, resistance, and spreading [178-180]. Mitochondria play a central role in tumor progression, as they can decide cell fate and promote cancer cells' ability to survive in adverse conditions such as hypoxia [181-183].

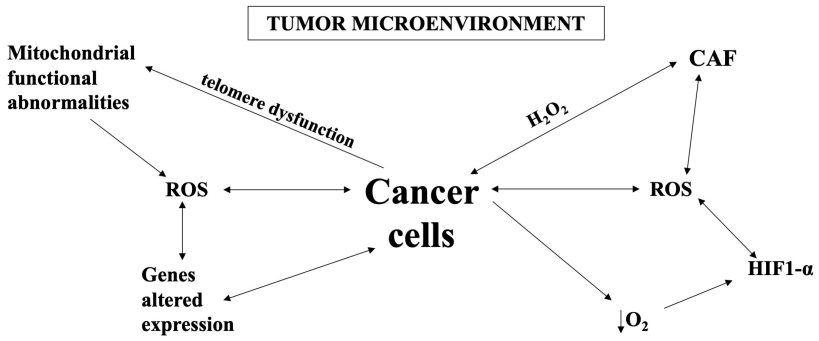

Fig. (2). Cancer and reactive oxygen species (ROS) production. Cancers produce high levels of ROS; however, tumor cells also express increased levels of antioxidant proteins, thus, maintaining elevated mitogenic signaling without experiencing significant oxidative stress damage [189]. The ROS are produced both by cancer cells and their microenvironment with self-sustaining loops: tumor cells produce and secrete hydrogen peroxide, increasing oxidative stress and stimulating cancer-associated fibroblasts (CAF) doing the same cross-talking; tumor microenvironment hypoxia activates various key regulators associated with oxidative stress such as hypoxia-inducible factor 1-alpha (HIF1-α), leading to ROS generation, which causes a feedback loop, upregulating HIF1-α in turn [191]. Oncogenes and the loss of tumor suppressors increase ROS production leading to genomic instability and cell growth. The major source of ROS in cancers is associated with mitochondrial functional abnormalities, often due to telomere dysfunction and tumor increased metabolic activity.

Given this, and because of their capability to adapt to stressful conditions, mitochondria have been considered critical targets for cancer therapy [184-186]. Another mechanism for tumorigenesis has been related to mitochondrial retrograde signaling that alters the expression profile of nuclear genes in response to dysfunctional mitochondria [187,188]. As several signaling pathways associated with carcinogenesis can additionally control ROS generation and regulate ROS downstream mechanisms [189], it has been demonstrated that the modulation of cancer initiation may be stimulated by nutrition-mediated elevation in ROS levels also triggering DNA mutations, damage, and pro-oncogenic signaling [190]. Mitochondria and oxidative stress are key elements in both tumorigenesis (especially chemoresistance) and aging, with potential implications in anticancer and antiaging research [191].

4. DISCUSSION

Beyond tumorigenesis and its correlation with the aging process, it should be noted that the link between aging and cardiovascular diseases has been extensively studied and should be mentioned to better understand the relationship between aging and health compromission. In fact, the cardiovascular system is vital for the health and longevity of the organism by delivering oxygenated blood and nutrients to all body tissues [192-194]. Aging has a remarkable effect on the heart and arterial system, leading to diseases like atherosclerosis, hypertension, myocardial infarction, and stroke [195]. Additionally, some pieces of evidence still have to be effectively explained and exposed to better clarify the practical consequences of harmful habits like a diet high in calories without physical or mental exercise that causes accumulation of cholesterol and fatty acids in tissues, which compromise tissue function and stimulate the production of inflammatory cytokines as well as ROS but also suppress the expression of "longevity genes" that promote cellular defenses against aging and age-related diseases [196,197].

As the initiating events in tumorigenesis cause DNA damage, the activation of this malignant response (one of the first lines of defense against malignant transformation) ultimately results in the stabilization of the tumor suppressor p53. Such events may induce temporary cell cycle arrest allowing damage repair or, in case of damage that cannot be resolved, cellular senescence or apoptosis. The accumulation of DNA damage and the activation of tumor suppressor signaling pathways is an important factor underlying the reduced ability of the stem cells to regenerate and repair damaged tissues characteristic of aging. One of the phenomena observed in the aging stem cell population, due to fundamental differences in the DNA damage response, is the drift in stem cell clones. This may be the result of increased or decreased DNA repair capacity in certain subpopulations, distinct checkpoint responsiveness, and variable up-regulation of 'eat me' signals in response to accumulating damage [198].

Recently, the frailty index to measure an accumulation of deficits has been considered a valuable method for identifying elderly people at risk for increased vulnerability, disease, injury, and mortality [199]. Indeed, several genes and pathways playing crucial roles in aging and age-related diseases [199] were identified. Furthermore, factors broadly expressed, related to several "hallmark of aging" pathways as well as used or predicted as biomarkers in other disease settings, particularly in age-related pathologies, were discovered [199,200]. In particular, PTX3 and LAMC1 in adhesion pathways may subtly regulate the aging processes and age-related diseases [199,200] .

CONCLUSION

In conclusion, cancer and aging share many hallmarks and have a synergistic, bidirectional association. Many recent studies have highlighted the role of age in carcinogenesis and tumor growth, also highlighting the key role of good lifestyle habits (healthy diet and physical activity *in primis*) in cancer prevention and suggesting that anti-growth factor agents and epigenetic therapies seem to assume an increasing role in counteracting aging-related diseases including cancer.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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