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Aging and Cancer: a Long-Term Relationship

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Abstract
Cancer and aging, despite seemingly opposite characteristics, are tightly linked. Indeed, cancer incidence and mortality dramatically increases with age. This review discusses some of the hallmarks of the two processes and tries to offer an explanation on why the degenerative pathology of aging is at least partly linked to the hyperplastic diseases of cancer.

Keywords: aging, cancer, hallmarks, homeostasis, immune system, microenvironment, oncogenic mutations, senescence

Introduction

Aging is a complex multidimensional process which is characterized by a decline into the ability to respond to stress, an increased loss of homeostasis and an increased risk of developing diseases. In contrast to the loss of function that characterizes degenerating cells and tissues, cancer is a process throughout malignant cells acquire new functions that allow them to grow uncontrolled and often to colonize distal tissues. Despite this clear difference in fitness between this two biological processes, the relationship between aging and cancer is strong. What are the hallmarks of aging and cancer and how we explain this strong connection?

Hallmarks of aging

Aging is characterized by a time-dependent decline of different physiological functions. Many molecular and cellular aspects of aging are conserved during evolution, and common hallmarks of aging can be observed in different organisms [1]. These hallmarks are identified as processes that are sufficient to accelerate aging when experimentally aggravated [2].
One common feature of aging is the accumulation of genomic instability [3]. Some diseases of premature and accelerated aging are the consequence of excessive accumulation of DNA damage [4]. The loss of DNA integrity is due to either extrinsic, such as physical or chemical perturbations, or intrinsic, such as DNA replication errors or Reactive Oxygen Species (ROS), damages [4]. According to the mitochondrial free radical theory of aging, age-associated mitochondrial dysfunction is responsible to increase the production of ROS, which then causes massive cellular damage [5]. Unexpectedly though, mice with high mitochondrial ROS do not accelerate aging, arguing if oxidative damage *per se* can cause aging [6]. The mitochondrial dysfunction is also accompanied by a reduction in ATP production and with a substantive alteration of cellular metabolism. Cellular metabolism with age is also affected by changes in nutrient sensing, and genetic or chemical interventions aimed to decrease nutrient signaling have been shown to promote longevity [7]. Another important contributor to the DNA damage is telomere shortening. Indeed, these chromosomal regions that protect the end of the chromosomes appear to be deteriorated with age and to cause a persistent DNA damage response [8,[9].

The quality control mechanisms to preserve the stability and functionality of the proteome are deregulated with age [10]. This is further supported by the fact that unfolded or aggregated proteins lead to age-related pathologies, such as Alzheimer's disease and Parkinson's disease [11].

In general, the age-associated decline is associated by an increased risk to develop several other pathologies, including cancer.

One of the most intuitive phenotypes of aging is the decline of the regenerative potential due to stem cells exhaustion [12]. Almost every adult stem cell compartment encounters a decline with age, including the immune system [13].

Importantly, this defect in regeneration is also strongly associated with the accumulation of cells in an irreversible growth arrested state called cellular senescence. Indeed, senescent cells increase with age, and are evident at sites of numerous age-related pathologies and pre-cancerous lesions [14,[15,[16,[17,[18,[19]. Senescent cells are characterized by the overexpression of cell cycle inhibitors such as p16INK4A, which expression increases with age in mouse and human tissues [20,[21]. A striking characteristic of senescent cells is the secretion of inflammatory cytokines, proteases and other molecules that can alter the tissue microenvironment (a phenomenon termed the senescence-associated secretory phenotype or SASP) [22,[23,[24,[25,[26]. Senescent cells might then contribute to aging in 2 distinct ways: in cell-autonomous fashion, reducing the capacity to regenerate tissues; in a non-cell autonomous fashion, causing a low level of chronic inflammation which may contribute to the onset and progression of several diseases.

Hallmarks of cancer

Cancer refers to a wide variety of different diseases characterized by abnormal cells able to infiltrate and destroy different tissues. Cancer is a major concern in wealthy countries, since it represents the second leading cause of death after heart disease.

The most evident phenotype of cancer cells is the capacity to grow without control, thus escaping the fine tuning that regulates tissue homeostasis. The uncontrolled growth is often due to constitutive activation of mitogenic pathways, either through somatic mutations or chronic support of growth factors by the surrounding microenvironment [27], or by the disruption of inhibitory mechanisms, such as mutations in the tumor suppressor genes p53, p16INK4A or PTEN [28]. The enzyme that allows to maintain telomeres length, called telomerase, is also often over-expressed in immortalized cells conferring a potentially unrestricted capacity to divide [29]. Moreover, the uncontrolled growth requires a higher supply of nutrients. This supply is sustained by the induction of angiogenesis, which provides the formation of new vasculature [30].

Another important feature of cancer cells is the resistance to death signaling. This resistance arises from the induction of anti-apoptotic factors, such as members of the bcl family [31], or by inactivating mutation of important inducer of apoptosis, such as the DNA-damage sensor p53 [32].

Cancer cells have the unique capacity to move around the body and invade other tissues, a process defined as metastasization [33]. Cancer cells are able to spread throughout the body following a complex mechanism articulated in four different steps: 1) local invasion of the surrounding tissues; 2) intravasation and transit into the blood and lymphatic vessels; 3) extravasation from the vessels into the target tissue; 4) growth into macroscopic tumor [33].

The relationship between cancer and aging

As described in the above sections, aging and cancer may seem to derive from opposite sides. Indeed, aging arises as a process of loss of fitness, with tissues lose some of their original functionality, whereas cancer is represented by an aberrant gain of fitness, with cells are characterized by new advantageous functions.

However, the correlation between age and cancer in humans is strong. Aging is the single biggest risk for developing cancer, and the incidence of cancer increases dramatically in populations where the advances in public health and the prevention of infectious diseases

extended the median lifespan. Around 60% of all malignant tumors occur in the age group 65 years and older, and the cancer incidence in this group is 11 times higher than in people under age 65 (SORUCES: http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2014/index; http://www.cancerresearchuk.org/cancer-info/cancerstats/).

The relationship between cancer and aging has been a topic of debate for decades. In particular, at the moment two main hypotheses are mainly supporting this relationship.

The first hypothesis considers the rise in the incidence of cancer with age as the time required by a cell to acquire multiple oncogenic mutations. Since with age we increase the time of exposure to environmental carcinogens, physical stresses, and physiological and pathological changes we then also increase the number of mutations that accumulate in the genome [34]. As discussed in the previous section, oncogenic mutations often provide a cell new and aberrant phenotypes, considered essential hallmarks of cancer [35]. In contrast with this view, the majority of the mutations are accumulated during ontogeny and not during adulthood, in part due to the lower rate of cell division after maturity. If cancer is caused when a cell acquires 5 or 6 mutations, then 20 years old should have high risks of getting cancer [36]. So, this hypothesis might not completely justify why cancer incidence and mortality exponentially increases with age (Figure 1).

The second hypothesis considers the changes in the tissue environment as an essential feature to support and drive cancer and other diseases of aging. As described in the first section, aging is indeed characterized by loss of tissue homeostasis and decrease capacity to regenerate [2]. A possible contributor to this phenotype is the decline of the immune system, which can become inefficient in clearing damaged host cells, for a process termed 'immunosenescence' that seems to be conserved in both short- and long-lived species [37].
Damaged cells, which might accumulate with age as a consequence of the immunosenescence, often react to stress insults by secreting factor to communicate their condition to the neighboring cells.
One example can be cellular senescence. Senescence is a potent tumor suppressive mechanism induced by several stresses including oncogenic mutations such as RAS [38].

However, some of the SASP factors can lead to the disruption of the tissue homeostasis and promote the formation of pro-cancer niche, rich of factors involved in different steps of tumourigenesis [39]. The SASP factors IL-8 and GROα can stimulate cellular proliferation of pre-malignant or malignant epithelial cells [23,[40,[41]. VEGF, MMPs and IL-1 can stimulate de-differentiation, adhesion to blood vessels, migration and invasion thus promoting tumor metastasis [25,[42,[43].

Chemotherapy-induced senescent cells have been proposed to reduce the effect of genotoxic treatments through the activation of the Wnt signaling in cancer cells, which promote survival and disease progression (Sun 2012). In a model of obesity-induced cancer (Yoshimoto 2013). Senescent hepatic stellate cells secrete various pro-inflammatory and pro-tumorigenic factors which, in turn, promote the development and progression of hepatocellular carcinoma.

Conclusion

Taken the strong relationship between age and cancer, we should consider how environmental changes contribute to promote oncogenic mutations and modify the tissue microenvironment thus favoring cancer formation and progression. As a preventive approach, maintaining healthier tissues, for example through a correct nutrition or physical activity, might lower cancer incidence with age. As an alternative therapeutic approach, it will be interesting to consider the development of drugs

that could 'fix' or eliminate seemingly normal cells that express aberrant but non-cancerous phenotypes, thus contributing to a pro-malignant tissue niche, and consider combinatorial treatments with drugs that target specific mutations in the cancer cells. One example of this alternative approach can be to target senescent cells. Senescent cells accumulate as a consequence of several stresses, such as aging, diet or chemotherapy treatments, and they might promote different stages of cancer progression through the SASP.

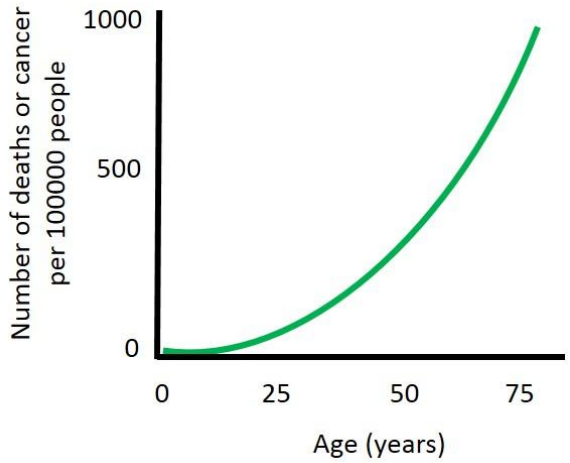

Figure 1. Exponential rise of cancer mortality with age.

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