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The Effect of Immune System Aging on Cancer Progression: A Review Article

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Abstract

Cancer is largely a disease of older people; the median age for cancer diagnosis in industrialised countries is approaching 70 years of age and is expected to increase. The morbidity and mortality rates of various tumors increase with age, and thus, malignant tumors are generally defined as aging diseases. The immune system has an ambiguous role in cancer, as it plays an important immune surveillance role in the antitumor response but is also closely associated with the initiation and progression of tumors. With aging we assist to the erosion of the immune response called immunosenescence. This deregulation particularly affects the T cell compartment of the adaptive immune response. In addition to the accumulation of genetic mutations, many researchers believe that immunosenescence may also play an important role in the tumoral process. In the future, targeting immune senescent cells may be a novel interventional opportunity in cancer patients.

INTRODUCTION

Cancer is largely a disease of older people; the median age for cancer diagnosis in industrialised countries is approaching 70 years of age and is expected to increase (1). It is definite that the occurrence and development of many diseases, including cancers, have been shown to be associated with aging. With aging the incidence and prevalence of cancer increase, which suggests a close association between aging and cancer (2). The morbidity and mortality rates of various tumors increase with age, and thus, malignant tumors are generally defined as aging diseases. Despite many studies considering aging as a tumor-suppressor mechanism, most senescent cells behave abnormally, which may eventually lead to serious outcomes, such as the development of tumors (3).

A Cancer and aging can be regarded as two different manifestations of the same underlying process, specifically, the accumulation of cellular damage 1. There are several genetic or pharmacological manipulations that are capable of modulating the effects of both cancer and aging (4). Another mechanism responsible might be reduced immune function, “immunosenescence”, in the elderly. The immune system has an ambiguous role in cancer, as it plays an important immune surveillance role in the antitumor response but is also closely associated with the initiation and progression of tumors (5). The importance of the immune system in preventing tumor formation, termed immune surveillance, has been repeatedly shown in animal models and is supported by epidemiological evidence, such as increased frequency of certain cancer types in immunosuppressed individuals (6). There is no question that there is a measurable decline in immune function with advancing age. Defects arise in both the humoral and cellular arms of the adaptive response, implicating defective T-cell function with age (7). As the thymus is the major site of Tcell development and maturation, thymic involution and the gradual decline in thymic output is considered a primary event in the process of age associated immune senescence. Furthermore, there is an inverse relationship between immune function and the incidence of many forms of cancer; as immune function decreases with age, the incidence of cancer increases (5, 8). However, a causative link between age-associated immune senescence and increased incidence of cancer remains controversial. The concept of immunosenescence was first proposed by Walford in 1964 and is characterized by decreased adaptive immunity, decreased infection resistance, and increased autoimmune risk. In addition, a variety of factors can dramatically influence this

status, such as genetics, exercise, nutrition, previous exposure to microorganisms, sex, and human cytomegalovirus infection (9). Many studies have shown that the tumor response of innate and adaptive immune systems is different between young and elderly individuals, but its clinical impact and underlying mechanisms are still mostly not understood. For example, T cells are the main effectors of acquired immunity, and their compartment is heavily affected during aging, cumulating defects that can increase immune system damage, disease susceptibility, and the occurrence of malignant tumors in the elderly (10). Therefore, these lines of evidence indicate that the underlying mechanism of tumorigenesis is closely associated with immunosenescence. The composite effect of normal aging is therefore one of a mild to moderate deficiency in the cellular immune response, yet the clinical consequences of these changes have yet to be established (11). The obvious suggestion is that these ageassociated changes render an individual susceptible to infection and cancer, may even be related to the development of age-associated autoimmune phenomena (including diabetes), and, remotely, atherosclerosis and Alzheimer's disease. To further understanding the geriatric oncology, here we provide a brief overview on the relationship between aging, cancer and immunity. In this review, the importance of immune senescence on the development and biologic characteristics of cancer is explained (12, 13).

Concept of Immunosenescence

Immunosenescence, which is the term given to age-associated impairments of the immune system at both cellular and serological levels, affecting the process of generating specific responses to foreign and self-antigens (14). In fact, the process of immunosenescence is regulated by many factors, including aging, chronic inflammation, and changes in the microenvironment (15).

With aging we assist to the erosion of the immune response called immunosenescence. This deregulation particularly affects the T cell compartment of the adaptive immune response (16). The most important changes in the cellular immune response with aging are (i) phenotypic, such as the decrease of naïve CD4+ and CD8+ T cells, as well as the reduced expression of CD28 with the concomitant increase of the more and more terminally differentiated memory CD4+ and CD8+ T cells characterized by surface markers such as CD95, CD45RA, CD57 and CCR7, and (ii) functional, such as a decreased proliferation, IL-2 production, telomere length with concomitantly increased DNA damage. There were three major theories which may explain immunosenescence, known as autoimmunity, immunodeficiency and immunodysregulation (8, 17).

T-cell function

There are three major trends in T-cell function that have been observed in the aging immune system. The first is a decrease in the number and proportion of naive T cells (18, 19). This is mainly caused by the progressive decrease in thymic output that begins in childhood and continues into advanced age. It has been well documented that the thymus is a lymphoid organ where T cells differentiate, develop, and mature. Thymus degeneration leads to a decrease in the number and proportion of CD8+ naïve T cells, which is one of the main manifestations of immunosenescence. It is therefore likely that T cells are important immune cells and play a key role in the occurrence and progression of tumors (20).

The second major trend is the increased proportion of memory T cells. These cells are still capable of proliferative memory responses, but include defects from normal function, including increased type I/ type II cytokine production profiles (21). The third major change in T-cell function is the accumulation of terminally differentiated T cells that are dysfunctional and have extremely limited T-cell receptor (TCR) repertoire diversity (22). Another hallmark of senescent T cells is telomere shortening (21, 44) (Fig. 1), which is caused by the continuous replication of T cells and the decrease in expression of the human telomerase RNA component (23).

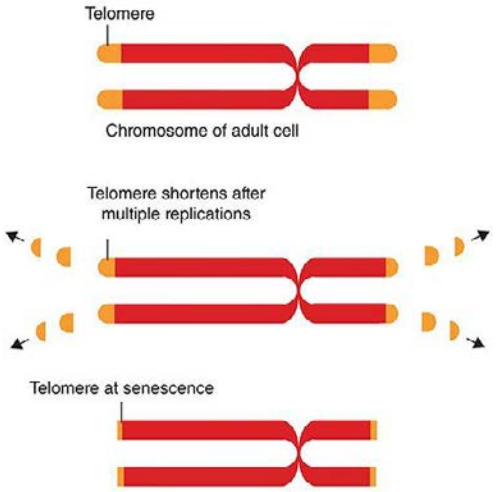

Fig.1. Telomeres form the ends of human chromosomes. Telomeres shorten with each round of cell division and this mechanism limits proliferation of human cells to a finite number of cell divisions by inducing replicative senescence, differentiation, or apoptosis. Telo-.mere shortening can act as a tumor suppressor

Naive T cells

Naïve T cells are a very relevant factor in immunosenescence research. A diverse TCR (T-Cell-Receptor) repertoire is critical for normal immune function and the recognition of a wide range of antigenic targets (23, 25). However, with age, the

thymus involutes and naive T-cell output decreases. As mentioned previously, this age-associated decrease in thymic output is the primary cause of immunosenescence (26). Their generation is completely dependent on the thymus function, so the degeneration of the thymus is of great significance to the study of human immunosenescence. Degeneration of the thymus leads to structural changes and declines in function, which ultimately leads to a significant reduction in the thymus output of naïve T cells, thereby reducing the T cell antigen receptor diversity pool and ultimately leading to the destruction of T cell homeostasis. Therefore, degeneration of the thymus is the cause of age-related failure of the adaptive immune system (27).

Memory T cells

Some studies also documented that memory T cells gradually accumulate with age. In addition to the observed loss of naive T cells in old age, there is also a well-documented phenotypic transition from naive to memory T cells (28). Memory T cells with a naïve phenotype also accumulate with age , and the number and ratio of memory CD8+ T cells in the elderly are usually higher, affecting their immune function (29). The inability to generate an effective memory response to newly evolving antigenic targets may critically impair, in an age-dependent manner, the immune system's ability to prevent tumorigenesis (30).

Immunosenescence and cancer

We have described that aging is one of the most important risk factors for cancer (31). As a consequence the prevalence and incidence of cancer increases and in the meantime, immunity is compromised. In addition to the accumulation of genetic mutations, many researchers believe that immunosenescence may also play an important role in the tumoral process (32). Among the many changes in the immune response with aging are specific alterations in the innate and adaptive immune responses which contribute more specifically to the development of cancers. DeSantis et al. found a higher risk of tumorigenesis in the elderly group (33). By analyzing the age distributions of 100 different tumors, Palmer et al. concluded that the immune system may play an important role in tumor development . Aging, via the immunosenescence, favors the development and amplification of a network of immune suppressions hallmarked by increased frequency of regulatory T cells (Tregs: CD4+CD25+FoxP3+), myeloid-derived suppressor cells (MDSCs), IDO production, and B7 family molecules expression (B7-H1) (34). Tregs maintain and induce immune cell tolerance by directly inhibiting T cells, NK cells and DCs through direct cell-cell contact or by soluble mediator secretion such as IL-10, TGF-β, as well as CTLA-4 and PD-L1 expressions (35). According to these considerations, young and old individuals will most likely require different treatment approaches, which could solve some of the problems of treating geriatric cancer patients with other, more traditional, modalities. Cancer could be less responsive to chemo- and radiotherapy in the elderly, and this might be because the immune system is less effective in the elderly, following the notion that even responses to chemo- and radiotherapy require an intact immune system. Chemotherapy can also induce CD8+ T cell senescence in patients with breast cancer (36). In a preclinical mouse model of pancreatic ductal adenocarcinoma, T/P drugs induced senescence of pancreatic cancer cells and activated SASP-dependent vascular remodeling, which not only enhances the uptake and efficacy of chemotherapy drugs but also promotes the infiltration of T cells into tumor tissues. Altogether, these findings indicate that immunosenescence is linked to the occurrence and progression of tumors (37, 38).

Future perspective and Conclusion

Overall, immune parameters are different between the young and the elderly (39). Indeed, the aging process particularly affects the immune response: this imbalance of the immune system may be involved in the development of tumors. A causal link between declining immunity with age and increased incidence of cancer, although currently controversial, is suggested by some studies. Currently, there are relatively few systematic studies on immunosenescence (40). The impact of immunosenescence on tumor progression indicates that it is necessary to better understand its role in treating and driving tumor progression.

In some cases, tumors are able to limit the function of T cells, including those specific for tumor antigen. First, the reduction of T cell output caused by thymic degeneration can be achieved through the intervention with immune regulatory factors, i.e., by supplementing IL-7 thereby restoring T cell production and thymic function (41). As such, improving resistance to cancer in old age may depend on therapeutic options that restore thymic function. For example, IL-7, growth hormone, IGF-1 and KGF have been employed to improve thymopoiesis (41, 42). Substantial efforts have been made to improve homeostatic peripheral expansion for generating naive T cells outside the thymus in the context of immune reconstitution following bone marrow transplantation. Therefore, a more profound understanding of immunosenescence, especially of its underlying mechanisms and therapeutic targets in malignant tumors, is urgently needed to reduce this growing public health burden. In the future, targeting immune senescent cells may be a novel interventional opportunity in cancer patients (43). As research in the field progresses, from animal models to human clinical

trials, new therapeutic strategies to enhance immune function, especially T-cell induction in the aged, may become powerful tools to reduce cancer incidence (44).

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