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Review

Can exercise-related improvements in immunity influence cancer prevention and prognosis in the elderly?

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ABSTRACT

Cancer incidence increases with advancing age. Over 60% of new cancers and 70% of cancer deaths occur in individuals aged 65 years or older. One factor that may contribute to this is immunosenescence – a canopy term that is used to describe age-related declines in the normal functioning of the immune system. There are multiple age-related deficits in both the innate and adaptive systems that may play a role in the increased incidence of cancer. These include decreased NK-cell function, impaired antigen uptake and presentation by monocytes and dendritic cells, an increase in 'inflammaging', a decline in the number of naïve T-cells able to respond to evolving tumor cells, and an increase in functionally exhausted senescent cells. There is consensus that habitual physical exercise can offer protection against certain types of cancer; however the evidence linking immunological mechanisms, exercise, and reduced cancer risk remain tentative. Multiple studies published over the last two decades suggest that exercise can mitigate the deleterious effects of age on immune function, thus increasing anti-cancer immunity. The potential ameliorative effect of exercise on these mechanisms include evidence that physical activity is able to stimulate greater NK-cell activity, enhance antigen-presentation, reduce inflammation, and prevent senescent cell accumulation in the elderly. Here we discuss the role played by the immune system in preventing and controlling cancer and how aging may retard these anti-cancer mechanisms. We also propose a pathway by which exercise-induced alterations in immunosenescence may decrease the incidence of cancer and help improve prognosis in cancer patients.

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1. Introduction

Cancer incidence increases with advancing age, which is a concerning fact in most Western countries where life expectancy is increasing and the elderly population is expanding [1]. The relationship between cancer and aging is not fully understood, although the natural passing of time may allow the accumulation of damage from free radicals, viruses, and carcinogens to cause mutated cellular proliferation that disrupts normal physiology and facilitates cancer development. Treatment options often entail some combination of surgery, radiation, and cytotoxic drugs although these are often limited by the incomplete elimination of cancer cells causing recurrence, and by severe side-effects. As cancer prevention is clearly the best option, it is important to

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understand how and why cancers develop in order to devise suitable therapeutic, pharmacologic, and/or holistic countermeasures for both prevention and treatment, especially in the aged.

One factor that may contribute to the increased incidence of cancer in the elderly is immunosenescence – a canopy term that is used to describe age-related declines in the normal functioning of the immune system. Known consequences of immunosenescence include increased infection occurrence, poor vaccine responses, and heightened levels of disease and mortality among the elderly [2]. As the immune system also plays a role in cancer prevention, declining immune function with age may contribute to lowered cancer defenses and facilitate poorer prognosis. Recent evidence indicates that regular physical exercise may help prevent or possibly reverse many aspects of immunosenescence [3] and, in doing so, may enhance cancer prevention and treatment in the elderly. Here we discuss the role played by the immune system in preventing and controlling cancer, how aging may retard these anti-cancer mechanisms, and how exercise appears to prevent age-related declines in immunity. Finally, we review the literature showing an inverse relationship between cancer and physical activity, and propose a pathway by which exercise-induced alterations in immunosenescence may decrease the incidence of cancer and help improve prognosis in cancer patients.

2. The immune system and cancer: elimination, equilibrium, and escape

The evolution of cancer involves three critical phases: elimination, equilibrium, and escape [4]. In the elimination phase, tumor cells are deleted by effector cells of both the innate and adaptive immune systems [5,6]. Natural killer (NK) cells are cytotoxic effectors of innate immunity that distinguish between healthy and malignant or virally-infected cells [7]. This process is tightly regulated by inhibitory killer-cell immunoglobulin-like receptors (KIR) on NK-cells which ligate with human leukocyte antigens (HLA) on healthy host cells [8]. When HLA becomes downregulated on transformed cells they are targeted for elimination by NK-cells [9]. Tumor infiltration by antigen presenting cells, such as dendritic cells (DCs) is required for the initiation of anti-tumor adaptive immune responses [10] and is associated with prolonged patient survival and reduced metastasis in patients with many different carcinomas [11,12]. Once initiated, effector cells of adaptive immunity play an important role in the elimination phase. Clonal expansion of tumor-specific T-cells has been observed to accompany spontaneously regressing melanoma lesions [13,14].

Unfortunately, such targeting of tumor cells leads to the selection of cells with the least immunogenicity [15], resulting in a dynamic equilibrium where tumor cells are contained, but not fully eradicated by the immune system [16]. During this phase of equilibrium, the growth of weakly immunogenic tumor cells is abated by the immune system [17], but complete destruction of the tumor is not achieved. Tumor cells decrease immunogenicity in several ways. Incomplete down-regulation of HLA expression by some tumor cells [18] prevents their killing by KIR-matched NK-cells [19]. Metastatic tumors evade detection by DCs by inducing apoptosis of DCs and their precursors [20], leading to reduced DC numbers in malignant tumors [21]. This results in a marked reduction in clonal expansion of tumor-specific T-cells [22]. The importance of T-cells in maintaining the equilibrium phase has been shown in murine models, where depletion of T-cells leads to rapid and uncontrolled tumor growth [23,24]. Clinical evidence also suggests a critical role for adaptive immunity in the equilibrium phase in humans as several studies have shown that the presence of tumor-specific T-cells is correlated with remission in leukemia patients [25]. Similarly, the presence of tumor-infiltrating CD8+ T-cells and a high blood CD8+/CD4+ T-cell ratio have been shown to be associated with improved survival and prognosis in epithelial ovarian cancer [26,27].

While the equilibrium phase represents a balance between tumor cell division and clearance that may be long-lasting [28,29], it is often not permanent. As a result of selective honing of tumor immunoevasive mechanisms [30], malignant cells escape containment, resulting in uncontrolled tumor growth. In addition to mutations in cancerous cells leading to their evasion of the immune system, normal functioning of the immune system may be hijacked by tumor cells, leading to a favorable microenvironment for tumor growth [31]. For example, cancer is associated with disrupted infiltration of tumors by NK-cells [32], as well as a decreased cytotoxicity per NK-cell [33] due in part to overexpression of inhibitory receptors [34] and decreased expression of activating receptors [35]. The tumor microenvironment also elicits downregulation of monocyte expression of tissue-homing receptors leading to impaired migration and adhesion [36], and can decrease monocyte anti-tumor cytotoxicity [37]. Certain tumors [38] are able to hijack macrophage function and switch their phenotype from a pro-inflammatory state to an immunosuppressive state [39]. Additionally, tumor-infiltrating macrophages have been shown to support tumor growth by stimulating angiogenesis [40]. Multiple phenotypic and functional alterations are observed in the DCs of cancer patients, including low expression of co-stimulatory molecules [41] and inhibited antigen processing [42]. The tumor microenvironment also favors polarization of DCs toward a tolerogenic phenotype that stimulates the generation of regulatory T-cells and myeloid-derived suppressor cells [43]. All of this impairs tumor-specific T-cell responses and encourages tumor escape [44].

3. Decreased cancer surveillance in the aging immune system

Many of the immunosuppressive effects of aging are similar to those observed in cancer patients, and are associated with the escape of malignant cells from immune control and the development of cancer [45]. Much like cancer, aging is associated with decreased NK-cell function [46], and cancer and aging are both associated with a decline in NK-cell expression of activating receptors [46] and an increase in inhibitory KIR expression [47]. Aging also alters monocyte, macrophage, and DC function in a number of ways that facilitate tumor progression. Increases in pro-inflammatory monocytes lead to elevated levels of local and circulating pro-inflammatory cytokines, which contribute to "inflammaging" [48]. DCs also exhibit amplified baseline NFκB activation and thus amplified unstimulated production of pro-inflammatory cytokines and increased reactivity to self-antigens [49]. This chronic, low-grade inflammation resulting from the aging process creates a tumor-promoting environment and is associated with increased cancer risk [48]. Furthermore, aging is associated with decreased antigen presentation by monocytes and macrophages [50], and decreased antigen presentation and migratory capacity of DCs [51], resulting in decreased cytotoxic T-cell responses to emergent tumors [52].

Maintenance of equilibrium requires vigorous T-cell responses to contain a constantly evolving pool of potentially malignant cells [53]. Unfortunately, aging is associated with an accumulation of functionally exhausted and suppressor CD8+ T-cells that are incapable of undergoing clonal expansion [54] and interfere with the immune response to tumors [55]. Increases in the proportion of senescent CD8+ T-cells are associated with increases in the incidence of both solid tumors [56] and blood borne malignancies [57]. One reason senescent cells may lack a sufficient anti-tumor