Immunology of Aging and Cancer Development

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Abstract

The incidence and prevalence of most cancers increase with age. The immune system is a unique mechanism of defense against pathogens and possibly cancers, however there is a body of evidence that the immune system of the aged is eroded, a phenomenon termed immunosenescence. Each arm of the immune system, innate and adaptive, is altered with aging, contributing to increased tumorigenesis. Related to immunosenescence, a low-grade inflammation also develops with aging contributing also to increase carcinogenesis. Understanding the contribution of immunosenescence to cancer development and progression may lead to better interventions in the elderly.

With aging the incidence and prevalence of cancer increase [1–3], which suggests a close association between aging and cancer [4, 5]. Although this relationship is not always well understood, most of the experimental data seem to sustain an essential role for time in the multihit development of cancer [1] due to accumulation of damages. Damages are induced either by free radicals or viruses rendering the oncogenes more active or the gatekeepers inactive [6]. There are well-known alterations occurring in the immune response with aging [7, 8], collectively designated as immunosenescence. However, it is still unclear to what extent immunosenescence may contribute to the development, progression and treatment of cancer in elderly subjects [9, 10]. Recently, it has been demonstrated that aging is accompanied by a low-grade inflammation, inflamm-aging, due to a disequilibrium of the immune response with aging [11, 12]. The occurrence of inflamm-aging may underline the putative contribution of immunosenescence to the increased incidence of cancer with aging.
Does the Immune System Play a Role in the Prevention of Tumorigenesis?

There are still many questions to be resolved before this question can be answered definitively. However, a variety of intrinsic tumor-suppressor mechanisms are recognized as leading to senescence and/or apoptosis to prevent the acquired capability of cells to proliferate uncontrolled [13]. It is also recognized that there are cell extrinsic tumor-suppressor mechanisms by which cancer cells are stopped from invading and spreading to other tissues. There are three major mechanisms including the limitation of specific trophic signals, the modulation of the interaction between polarity genes and proliferation, and the immune response. The immune system may play a role in tumor prevention at various levels such as eliminating the cancer-inducing viral infections, by resolving the inflammation and finally directly fighting the emerging cancer cells [14, 15]. Classically, the latter is called the immunosurveillance by which process the immune cells track modified and non-self antigens and destroy the target upon recognition. For cancer, an efficient immunosurveillance is reached when cancer cells are eliminated before formation of a clinically recognizable tumor. The immune system is controlling both tumor quantity and quality. This signifies that the immune system not only protects (quantity) against cancer formation but also influences the tumor immunogenicity (quality) [16]. Then, the concept of tumor surveillance complexified and became the cancer immunoediting hypothesis which states the dual role of the immune system toward cancer. The dynamic process of immunoediting is composed of three distinct phases: elimination, equilibrium, and escape [17]. The pre-malignant lesions appear at the stage when the immune system is able to eliminate the nascent cancer cells and this corresponds to the proper immunosurveillance. Mostly it consists of innate and adaptive immune responses against danger or stress signals originating from the pre-malignant lesion itself, e.g. DNA damage, apoptotic cells or the microenvironment. During the advanced oncogenesis there exists an immunoselection with an equilibrium status between the developing tumor and the immune system, as a consequence of the incomplete elimination of tumor cells during the previous phase. This remains still clinically unapparent. During this stage the immune system exerts a selective pressure on the evolving tumor cells and selects cells that become finally able to resist or suppress the immune response. The final stage of tumor growth corresponds to the escape phase where the tumor growth can be even favored by the immune system, the tumor growth [15] emerging ultimately as a clinically apparent disease. It also means that the tumor is actively suppressing the immune response by producing various inhibitory substances, e.g. NO, indoleamine-2,3-dioxygenase (IDO), PGE\textsubscript{2}. Thus, experimental data strongly support that the immune system plays an essential role in the tumor elimination at its early stage requiring its full functionality from most of cells building the effector immune response such CD8, Th1, NK and macrophages [18]. There are several mechanisms of escape from immunosurveillance, including the alterations related to immunosenescence.
What Is Immunosenescence?

With aging we assist to the erosion of the immune response called immunosenescence [8, 19, 20] (table 1). This deregulation particularly affects the T cell compartment of the adaptive immune response. 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.

More and more experimental evidence shows that besides the changes in the adaptive immune response the innate immune response is also altered with aging. Each cell participating in the innate immune response is touched. Thus, natural killer cell...
functions are altered such as IL-2 production and cytotoxicity [21]. Phagocytic cells which are important in recognition and clearance through their Toll-like receptors (TLR) are also impaired with aging [22–24]. The functions of dendritic cells, being the main antigen-presenting cells, are also altered with aging [25].

The causes of these changes are not yet fully understood, but three main reasons can explain these changes. The first is the thymic involution with aging [26], the second are intrinsic changes because of the membrane damages leading to altered signaling [27] and thirdly the chronic antigenic stimulation occurring during life [28]. This antigenic stimulation can be of various nature – (i) from a viral source such as cytomegalovirus (CMV) of the herpes virus family, (ii) from constantly emerging tumor antigens, and (iii) from cell intrinsic sources [29]. This chronic antigenic stimulation leads with time to a low-grade inflammation characterized by the increased level of CRP, IL-6 and TNF-α [19, 30]. This low-grade age-associated inflammation was called ‘inflamm-aging’ by Franceschi et al. [31]. In the end, this impacts the development of age-associated chronic diseases such as atherosclerosis, diabetes, Alzheimer’s disease and cancer.

Experimental evidence suggests more and more that one of the driving forces in immunosenescence is the chronic, continuous antigenic stimulation [28]. Several groups have shown an increased frequency of CD8+ T cells bearing a T cell receptor (TCR) specific for the pp65-HCMV (495-503) epitope with aging. These CD8+ T cells are highly differentiated cells from the effector memory and the effector compartment characterized by changes in their surface markers CD45RA, CCR7, CD28, and CD27. These changes in T cell phenotypes may also be induced by tumor antigens, as CD8+CD28– cells can be purified from several human tumors such as lung, colorectal [32, 33]. T cell homeostasis maintains constant numbers of T cells in the periphery and even if naïve cells continue to some extent to be generated from the thymus, the T cell repertoire will be shrunken because of the clonal expansion of these CMV-specific CD8+ T cells, contributing to increased susceptibility to infectious diseases and cancer.

These findings were confirmed in two longitudinal studies of naturally aging (>85 year) populations: the Swedish longitudinal OCTO study (donors selected for good health) and NONA (donors not selected for good health; only 9% SENIEUR-compatible (i.e. of exceptional good health) completed by Wikby’s group [34, 35]. These investigations aimed at identifying factors predicting 2-, 4-, and 6-year mortality and resulted in the emerging concept of an ‘immune risk profile’ [36]. The immune risk profile consists of a cluster of parameters including high CD8+, low CD4+ and poor T cell proliferative response predicting higher mortality at follow-up. Other, experimental studies also suggested a special role for CMV in the loss of naïve CD8 T cells, Th1 polarization and increase of CD8+ memory T cells [37–39]. Recently, two epidemiological studies supported the data that CMV may be a primary driving force in immunosenescence by showing a correlation between CMV seropositivity, increased inflammatory markers and morbidity in elderly subjects [40, 41].
Although these experimental data clearly suggest a role for CMV, it is clear that other viruses can be implicated such as EBV [42]. Moreover, other experiments are clearly needed to understand further the effects of CMV on immunosenescence.

Furthermore, with aging we assist also to a decrease in the signal transduction of T cell surface receptors such as TCR, CD28 or cytokines. This manifests as a decrease of the phosphorylation cascade following receptor ligation, from the membrane to the nucleus (e.g. NF-κB, NFAT). Altered tyrosine kinases activation such as Lck, Fyn and adaptor molecules phosphorylation such as LAT or SLP76 at the very early stages of the receptor signal transduction are responsible for the overall reduced T cell signaling with aging [27]. These alterations originate from changes in the physicochemical properties of the membrane leading to malfunctions of lipid rafts in the membrane [43] as well as from the inability to relieve the negative signals provided by tyrosine kinases such as SHP-1.

Not only is the adaptive immune response altered, but also the innate immune response [44]. Recently it became evident that most functions of the innate immune response are affected by the aging process. Neutrophils, the first cells to arrive at the site of an aggression, have decreased chemotactic and phagocytic activities and free radical producing capacity [23]. The dendritic cells seem also to be altered not only in their basic functions such as phagocytosis, chemotaxis and production of IL-12, but also in their ability to activate naïve CD4+ T cells via antigen presentation. In the mean time they retain the capacity to produce pro-inflammatory cytokines and to activate CD8+ T cells [45]. Moreover, experimental data suggest that most of the monocyte/macrophage functions are also changed with aging, leading to altered pathogen clearing, regulation of the adaptive immune response and the inflammatory process, contributing to the sustained low-grade chronic inflammation and increased age-related diseases such as infections, cardiovascular disease and cancers. More and more experimental data indicate that with aging there are phenotypic and functional changes in NK cells, such as cytotoxicity on a per cell basis [21].

**What Could Be the Link between Immunosenescence and Cancer?**

We have described that aging is one of the most important risk factors for cancer. As a consequence the prevalence and incidence of cancer increases and in the mean time, immunity is compromised. There is still a debate as to whether and how the immunosenescence may contribute to this increased cancer incidence, thus the specific question that is raised: Which changes in the immune response (innate or adaptive) are responsible for the inefficient immune response against tumors?

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. The immune stimulation of T cells by dendritic cells is critical for their efficient activation and this is altered in aging through the
following co-receptors: B7.1, B7.2, OX40, CD27, CD30, CD40, 4-IBB [46, 47]. This leads to a weakened T cell response and even to anergy.

One important discovery of the last few years more specifically in the innate immune system is the existence of the TLR. These receptors are pattern recognition receptors (pathogen-associated molecular patterns) and can sense almost all types of antigens [48]. There are currently ten receptors which are more or less specific to various substances from bacteria, viruses or destroyed cells, which subsequently activate the innate immune system via TLR signal transduction. A wide variety of TLRs are expressed in immature or mature dendritic cells, macrophages, monocytes and neutrophils, and these receptors control the activation of these phagocytic and antigen-presenting cells [49, 50]. With aging the TLR signaling is defective in the innate immune system resulting in altered activation of the phagocytic cells which become less able to destroy the invading organisms or the transformed cells [51, 52]. Besides affecting the functions of the individual innate cells, these alterations further render neutrophils unable to activate and recruit macrophages as the next cells at the site of aggression or acute inflammation via secretion of various chemokines. In turn the cytokines released by activated macrophages should prolong the lifespan of neutrophils which is also altered with aging [53]. The described neutrophil and macrophage functional changes may as such contribute to the development and progression of tumors [23].

Aging, via the immunosenescence, favors the development and amplification of a network of immune suppressions hallmarked by increased frequency of regulatory T cells (T\textsubscript{regs}: CD4+CD25+FoxP3+), myeloid-derived suppressor cells (MDSCs), IDO production, and B7 family molecules expression (B7-H1). T\textsubscript{regs} maintain and induce immune cell tolerance by directly inhibiting T cells, NK cells and DCs through direct cell-cell contact [54] or by soluble mediator secretion such as IL-10, TGF-β, as well as CTLA-4 and PD-L1 expressions [55]. There is more and more evidence that the number of CD4+CD25+FoxP3+ T cells is increased in aged humans [56]. This could largely contribute to tolerance towards cancers in elderly subjects. Furthermore, MDSCs are a heterogeneous population comprised of macrophages, neutrophils and dendritic cells. They are mostly expanded in response to various soluble factors secreted by tumors such as GM-CSF, IL-1β, VEGF or PGE\textsubscript{2} [57]. These cells can suppress the activation of CD4+ and CD8+ T cells and inhibit the generation of antitumor responses by various mechanisms such as TGF-β secretion, TCR nitrosylation and also by the induction of T\textsubscript{regs} formation and expansion [58–60]. It is of note that these cells are activated by various anti-inflammatory factors such as IL-10, TGF-β, and VEGF, which are known to increase with aging. This suggests that the increased anti-inflammatory response (Th2) or that secreted in the tumor environment favor the activation of these MDSCs which in turn can suppress the activation of an adequate immune response [61]. The IDO is an immunosuppressive molecule which is capable of inhibiting T cell activation by inhibiting CD8+ T cell proliferation and inducing CD4+ T cell apoptosis [62]. This was also shown to increase with age [63]. Thus, the increased level of IDO further