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Review

Is cancer vaccination feasible at older age?

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ABSTRACT

Age-related defects of the immune system are responsible for T cell unresponsiveness to cancer vaccination at older age. Major immune defects at older age are lack of naive T cells, impaired activation pathways of T cells and antigen-presenting cells (APCs), and age-related changes in the tumor microenvironment (TME). This raises the question whether cancer vaccination is feasible at older age. We compared various cancer vaccine studies at young and old age, thereby focusing on the importance of both innate and adaptive immune responses for cancer immunotherapy. These analyses suggest that creating an immune-stimulating environment with help of the innate immune system may improve T cell responses in cancer vaccination at older age.

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1. Introduction

Cancer is an age-related disease. Since the elderly population is increasing, we can expect an increase in the number of cancer patients and mortality. In contrast to primary tumors which can often be removed by surgery, followed by radiation, chemo- or adjuvant therapy, for metastases there is no cure (Pardal et al., 2003). It has been shown in mice and humans that cancer vaccines expressing tumor-associated antigens (TAAs) target metastases with high specificity (Kim et al., 2008; Kruit et al., 2005; Marchand et al., 2003). However, vaccines are less effective at old than at young age (Gravekamp, 2009; McElhaney et al., 1994; Miller, 1996). This is caused by major age-related defects in immune responses resulting in short lasting and weak T cell responses to TAA. Ironically, the importance of the age factor in cancer vaccination is totally ignored in human clinical trials. Analysis of various vaccine studies in preclinical cancer models at young and old age showed that vigorous anti-tumor most innate responses could be obtained by tailoring vaccination to older age, while T cell responses were hardly detectable. Therefore, we questioned whether T cell responses by cancer vaccination could be improved at older age. To answer this question, we reviewed adaptive and innate immune responses in elderly and cancer patients, and compared vaccine studies in preclinical models at young and old age. In this review, we propose new approaches to improve innate and adaptive immune responses against cancer at older age through immunotherapy.

1.1. Immune deficiencies in elderly

Major immune defects at older age are lack of naive T cells, impaired activation pathways of T cells and antigen-presenting cells (APCs), and age-related changes in the tumor microenvironment (TME). While T cell unresponsiveness is the most significant defect in the immune system at older age, also innate immune responses are affected by aging although this seems less abundant than the adaptive immune responses.

1.1.1. Adaptive immune system

Lack of naive T cells (react for the first time to new antigens) and an increase in the number of memory T cells (react to previously exposed antigens) are two of the most significant changes in the immune system at old compared to young age. It has been suggested that continual activation of the immune system by new antigens during the life span would lead to a depletion of naive T cells from the thymus, and a clonal expansion of memory T cells (Utsuyama et al., 1992). With the involution of the thymus almost complete at the age of 60 years, new naive T cells at old age are now generated at a much lower frequency than at young age (Grubeck-Loebenstein, 1997). The host is then dependent on the pool of naive T cells generated earlier in life. Analogous to the situation in humans, a decrease of naive T cells and an increase of memory T cells have also been described for aging mice (Grubeck-Loebenstein, 1997). Other possible causes for diminished T cell responses in aged humans and mice have been described, such as defects in

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TCR/CD3-mediated phosphorylation events or aberrant regulation of tyrosine kinases associated with the TCR (Tamir et al., 2000) and a decrease in αβ repertoire of the TCR (Effros, 2007). The TCR is expressed by T cells, and is required for recognition of foreign antigens in association with self-major-histocompatibility complex (MHC) molecules, presented by APC to the immune system, and for subsequent activation of T cells. Another molecule important for T cell activation is CD28. CD28 is expressed at the cell membrane of T cells, and is the ligand for co-stimulatory molecule B7, expressed on APC. Clinical studies have documented that high proportions of CD8 T cells that lack CD28 are correlated with reduced antibody response to influenza vaccination (Effros, 2007). Also in mice, CD8 T cells lacking CD28 expression have been reported (Effros, 2004). Moreover, it has been shown that CD28-lacking CD8 T cells can suppress antigen-specific cytotoxic T lymphocyte (CTL) responses (Filaci et al., 2004).

In addition to the problems at the level of T cells, defects in cytokine production have been observed in aged humans. An example is a human vaccine study in which significantly lower interleukin (IL)-2 was produced by T cells of older individuals stimulated with an influenza vaccine in vitro compared to those of young individuals (McElhaney et al., 1994). Similarly, significantly lower IFNγ was produced by peripheral blood nuclear cells (PBNCs) from elderly individuals immunized with an influenza vaccine compared to young individuals. IL-2 promotes T cell activation and proliferation, as well as release of interferon (IFN)γ by T cells. The lower IL-2 production following in vitro stimulation with the influenza vaccine may explain the lower IFNγ production. IFNγ is involved in activation of dendritic cells (DCs). These DCs are important for CTL priming.

1.1.2. Innate immune system

The innate immune system is affected by aging as well, although this seems less abundant than the effect on the adaptive immune system. This includes natural killer (NK) cells, natural killer T (NKT) cells, γδ T cells, dendritic cells, macrophages and neutrophils.

NK cell function has been extensively analyzed in relation to aging in human and mice. Although NK cell function and number is decreased at old compared to young mice, such as the production of IFNγ, IL-2 or perforin, in healthy human centenarians NK cell cytotoxicity by activation with IL-12, IFNα, and IFNγ is well preserved, but somewhat decreased in less healthy elderly (Gomez et al., 2008; Ogata et al., 1997). In our studies we found that the production IFNγ by NK cells induced by vaccination with an attenuated *Listeria monocytogenes* was almost as good in old as in young mice (Chandra et al., 2013).

NKT cells belong to the innate immune system because of their early response to infection and cancer. Although they have characteristics of T cells, they share some functional and phenotypical characteristics with NK cells (Emoto and Kaufmann, 2003). They represent a heterogeneous population of $CD4^+$, $CD8^+$ or $CD4^-CD8^-$ cells, but most characteristic of NKT cells is their invariant TCR Vα14Jα281/Vβ8.2, or Vβ7, or Vβ2 in mice and Vα24JαQ/Vβ11 in humans. While the number of NKT cells increases with age, their production of Th1 cytokines decreases with age (Mocchegiani and Malavolta, 2004). However, NKT cells bearing TCRγδ strongly increases with age and their functions are well preserved in very old mice and humans (Plackett et al., 2004). When activated with alphagalactosylceramide (αGalCer), NKT cells communicate with NK cells through the production of cytokines (Biron and Brossay, 2001).

DCs are affected by aging as well. They play an important role in T cell activation, but the age-related effects on DC described are variable. It has been reported that blood DC from old individuals can still function as powerful antigen-presenting cells when exposed to purified protein derivate (PPD) of *Mycobacterium tuberculosis* or influenza vaccine (Sprecher et al., 1990), while others have shown that DCs from aged individuals are more mature and have impaired ability to produce IL-12 (Della Bella et al., 2007), or that secretion of tumor necrosis factor (TNF)α and IL-6 significantly increased upon stimulation with lipopolysaccharide (LPS) and ssRNA in DC of aged compared to young individuals (Agrawal et al., 2007). Also, others describe that no major effects on the numbers of DC were observed by aging, but their capacity to phagocytose antigens and migration was impaired at older age (Agrawal and Gupta, 2011).

Macrophages play an important role in the clearance of infections. Crosstalk between innate and adaptive immune responses exists through shared receptors such as Toll-like receptors (TLRs). It has been reported that Toll-like receptor (TLR) signaling in macrophages is defective at older age (Dunston and Griffiths, 2010; Goral and Kovacs, 2005). Aging of mice has been associated with an increase in the number of bone marrow macrophages that have an impaired ability to respond to infections, while cytokines such as circulating IL-6 or IL-10 increases with age upon stimulation with LPS (Treuting et al., 2008; Wei et al., 1992).

Myeloid derived suppressor cells (MDSCs) are a heterogeneous population of myeloid progenitor cells, i.e., immature macrophages, granulocytes, and dendritic cells (DCs) that are endowed with a robust immunosuppressive activity (Gabrilovich and Nagaraj, 2009; Ostrand-Rosenberg and Sinha, 2009). They migrate from the bone marrow in to the blood circulation upon infections or cancer. Evidence exists that the number of MDSC in blood increases with age (Verschoor et al., 2013). Flu is a major problem in the elderly because their immune system is significantly impaired compared to young adults. It has been shown that accumulation of MDSC increases in the lung in response to Influenza A virus infections, in correlation with suppression of CD4 T cell responses, which negatively influences the course of the disease (Jeisy-Scott et al., 2011). The increase in the number of MDSC at older age might contribute to the lower capacity of elderly compared to young adults to clear the infection. We found that MDSCs play a central role in cancer immunotherapy and could be used to improve T cell responses by *Listeria*-based vaccination at young and old age (Chandra et al., 2013) (for more detail see "MDSC under the Cancer vaccination at older age section").

1.2. Immune deficiencies in cancer patients

We expect that these age-related defects in the adaptive and innate immune system also play a role in cancer vaccination, because cancer patients are usually old. In addition to the age related changes, also tumor-induced immune suppression, genetic instability, and expression levels of antigens/receptors involved in T cell stimulation/inhibition contribute to T cell unresponsiveness at all ages.

1.2.1. Adaptive immune system

CTL, recognizing tumor-associated antigens (TAAs) in association with major histo-compatibility complex (MHC) molecules on the tumor cells through their T cell receptor, and expected to destroy tumor cells when exposed simultaneously to both TAA/self-MHC complexes and co-stimulatory molecules, are often found at the site of the tumor, but have evidently been unable to destroy the tumor cells in cancer patients (Gravekamp et al., 1990). Multiple possible causes have been described for this unresponsiveness of the CTL in cancer patients (for a review see Gravekamp, 2009). This includes decreased expression of MHC, TAA, or co-stimulatory molecules by tumor cells, and immune suppression induced by the primary tumors. In humans and mice, many tumors secrete lymphokines or factors that inhibit vaccine-induced T cell and NK cell responses. Examples are transforming growth factor (TGF)β, IL-6, IL-10, cyclooxygenase-2 (COX-2) and its products prostaglandin E2 (PGE_2), PD1-ligand, or indoleamine 2,3-dioxygenase (IDO) (Gajewski et al., 2006).

Inducible T_{regs} play an important role in suppression of the immune system in cancer patients, through the production of soluble factors such as IL-10 and TGFβ or through direct cell–cell contact, resulting in the inhibition of T cell and NK cell responses (Bluestone and Abbas, 2003; Chen et al., 2007; Gregg et al., 2005; Mahnke et al., 2007;