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Effects of aging on T cell function

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Immunosenescence influences many components of the immune system. Most importantly, profound changes in T cell function are evident in older individuals. The impact of aging on specific T cell subsets has been difficult to examine, but recent advances in murine model systems and new insights into T cell function have allowed for the more precise examination of how T cell responses change with aging. Importantly, recent studies have shown that age-related enhancement of both Th17 generation and regulatory T cell function may contribute to significant changes in immune function. In this review, we summarize the current views on how aging influences the factors that impact T cell function and how this can affect the immune response to infections, vaccinations, and tumors.

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Introduction

Aging is a complex process of life that affects many aspects of mammalian biology, including the immune system. Age-related declines in immune function render older individuals more susceptibility to infectious diseases and tumors resulting in increased morbidity and mortality. In addition to increased susceptibility to infection, the efficacy of vaccination is significantly reduced in the elderly, limiting preventative prophylaxis [1–3]. Because a substantial percentage of the global population is approaching an advanced age, coupled with the threat of emerging diseases that can severely impact the aged, such as pandemic influenza (H5N1 and H1N1), West Nile virus (WNV), and severe acute respiratory syndrome (SARS), it is critical that we understand the mechanisms responsible for age-related declines in immune function and develop strategies for overcoming these defects.

Immune-mediated protection from infection is attributable to both circulating antibodies and antigen-specific CD8 T cells, which are elicited as a result of prior infection or vaccination. Antibody responses generated during youth, before the onset of immunosenescence, persist and function well into old age. An interesting example of this is the recent identification of protective antibodies from survivors of the 1918 influenza epidemic [4]. Similarly, T cell memory (both CD4 and CD8) generated during youth generally functions well into old age, whereas T cell memory generated later in life functions poorly [5,6]. Thus, it is the generation of novel immune responses against vaccines, tumors, or pathogens in the aged that is most significantly impaired. In addition, other changes in T cell populations, including increased presence of regulatory T cell populations, clonal expansion of T cells, and shifts in T cell receptor (TCR) repertoire usage, can negatively impact a new immune response in older individuals (summarized in Table 1). Recent advances in the understanding of T cell function have provided novel insights into how aging impacts T cells and how this influences immune function. Below, we focus on the most recent findings on how age-related changes in the immune system impact the generation new T cell responses.

Age-related changes in naive CD4 T cell function

The generation of a high affinity protective antibody response following vaccination or infection requires helper CD4 T cells [7,8]. Antigen-specific CD4 T cells interact with antigen-specific B cells, leading to B cell expansion and differentiation to a germinal center phenotype. Within germinal centers, affinity maturation of antibody responses occurs because of the induction of somatic hypermutation in immunoglobulin genes. Importantly, declines in the function of CD4 T cells with aging are thought to contribute to the decline in high affinity antibody production in older individuals, but age-related changes in the function of specific lymphocyte populations have been difficult to study in intact murine models. The use of T cell receptor transgenic (TCR Tg) mouse models has significantly enhanced the ability to examine the specific intrinsic defects found in naive CD4 T cells from aged mice both *in vitro* and *in vivo*. These models eliminate numerous variables that complicate interpretation of aging T cell studies, including the predominance of memory phenotype T cells in aged individuals, the enhanced presence of regulatory T cells, and changes in TCR repertoire. By examining TCR Tg T cells from young or aged mice, we can compare cells that have the same TCR specificity and the same antigenic experience with the only difference being the age of the mouse from which they were harvested

Table 1

Summary of age-related changes in T cells.

CD4 T cells
Reduced TCR signaling intensity
Reduced expansion in response to TCR stimulation
Reduced Th1 and Th2 effector differentiation
Reduced cognate helper function
Retain the ability to differentiate to Th17
CD8 T cells
Reduced TCR repertoire diversity
Development of clonal expansions
Reduced antitumor responses
Regulatory T cells
Increased numbers
Retain/gain function with age
Downregulate antitumor responses
May contribute to Th17 skewing

[9]. Thus, this model allows for direct comparison of very similar T cell populations.

One of the major defects in the responsiveness of aged naive TCR Tg CD4 T cells has been shown to be owing to the reduced ability of these cells to form highly functional immunological synapses upon stimulation with peptide antigen and antigen presenting cells (Ag/APC) [10]. Because of reduced synapse formation, the initial signaling cascades generated in the aged naive CD4 T cells are less intense than those in young T cells. This then contributes to the well-documented reduced proliferation of CD4 T cells from aged mice. The ultimate result of this defect is that aged naive CD4 T cells do not expand, produce cytokines, and differentiate as well as those from young mice. The most striking phenotype with regards to aged naive CD4 T cells is their inability to produce significant levels of IL-2 upon TCR stimulation. This subsequently leads to the generation of poorly polarized T helper (Th) subsets (both Th1 and Th2) [11].

This age-related defect in CD4 T cell differentiation also results in the generation of a population of Th cells with significantly reduced B cell helper activity [12]. Using an adoptive transfer model, naive CD4 T cells from young and aged mice were shown to localize similarly to B cell follicles and germinal centers following transfer to young immunized hosts. While they appear to be in the appropriate location, the aged CD4 T cells were not able to help generate a robust humoral response in this model. The antibody response was not only quantitatively reduced when aged CD4 T cells provide help, but also qualitatively reduced with lower IgG titers and reduced frequencies of somatic hypermutation in the immunoglobulin heavy chain genes [13••]. This ultimately results in the generation of a less robust and protective antibody response, as has been described for older individuals following vaccination [1–3].

While aged naive CD4 T cells do not differentiate well to Th1 and Th2 effector subsets, recently it has been shown that they have retained the ability to generate functional Th17 effectors, which can be found readily in older individuals. In addition to the greater prevalence of Th17 effectors in the aged, naive CD4 T cells from older animals more readily differentiate to a Th17 phenotype [14•]. Consequently, this propensity to skew toward Th17 polarization appears to be an intrinsic property of the aged naive CD4 T cells. Not only can aged Th17 effectors produce high levels of IL-17 family cytokines (IL-17, IL-21, and IL-22), but they are also potent helper T cells in an adoptive transfer model, leading to extensive antigen-specific B cell expansion and germinal center formation [13••]. In addition, this study also demonstrated that aged CD4 T cell effectors generated in the presence of proinflammatory cytokines or an adjuvant that induces these cytokines, such as Poly I:C, also produce high levels of IL-17 and IL-21 and exhibit significantly enhanced B cell helper activity. Thus, while the ability to respond to IL-12 (for Th1) and IL-4 (for Th2) declines with aging, naive CD4 T cells do retain the ability to respond well to IL-1, IL-6, TGFβ, and IL-23 to generate Th17 effectors. This is an important point and may lead to further insights into how vaccine efficacy can be enhanced for the aged.

Because it has been hypothesized that Th17 effectors may be a more primitive T cell subset, bridging the innate and adaptive responses and contributing to innate immune functions such as the generation of antimicrobial peptides [15], it may be that this particular T cell function is more highly preserved with aging. These observations also suggest that aging has very specific effects on CD4 T cell populations and does not just lead to an overall downregulation of T cell function.

One other change in CD4 T cells with aging involves the development of clonal expansions (TCE). While not as well characterized as CD8 TCE, which are discussed in the next section, CD4 TCE could potentially impact the generation of a robust T cell response. In aging mice, CD4 TCE were found to occur in all mice over the age of 16 months as evidenced by skewing of TCR-Vβ spectratypes [16]. In aging humans, CD4 TCE were found in 70% of people over the age of 65 years and were found to be stable over a two-year period [17]. Importantly, these TCE were found to be predominant in only four Vβ families and, thus, could potentially impact CD4 TCR repertoire diversity.

Age-related changes in CD8 T cells

The ability to generate a CD8 T cell response to a viral infection also changes significantly with age. One of the most important changes described recently is a decrease in CD8 TCR repertoire diversity. This is critical because a highly diverse repertoire is vital for protection from viral infections. While little is known about age-related

changes in CD4 T cell repertoire usage, a recent study by Yager *et al.* [18••] demonstrated that the CD8 TCR repertoire used in response to influenza infection is dramatically decreased in older mice. This study described a shift in both viral epitope immunodominance as well as the naive precursor frequency in the influenza-specific CD8 T cell population with aging. This ultimately results in 'holes' in the CD8 T cell repertoire in aging individuals, leaving them more susceptible to severe infection. It has been proposed that one cause of this shift in TCR repertoire usage is owing to an increasing dependence on homeostatic turnover in the absence of new thymic emigrants, leading ultimately to the generation of CD8 TCE. TCE have been defined as a population of T cells expressing perturbations in TCR-Vβ expression in which a particular TCR-Vβ occupies greater than two to three standard deviations from the mean of that particular Vβ in young mice [19]. Not only do these TCE take up space within the CD8 T cell compartment, but also the presence of these clonal expansions has been shown to negatively impact the TCR repertoire in response to both influenza infection [20••] and herpes simplex virus (HSV)-1 infection [21]. These studies demonstrate that TCE that develop with aging functionally impair the efficacy of antiviral CD8 T cell responses, signifying that TCE are a contributing factor to age-related immunodeficiency. In addition to these results in mouse models, the presence of CD8 TCE in older people has also been correlated with a reduced humoral response to influenza vaccination [22], indicating an even broader impact of TCE on the aging immune system.

The complexity of CD8 TCE populations is now only beginning to be understood. A recent study clearly delineated two separate populations of TCE in mice based on cell surface expression of integrin α4 (itgα4) [23••]. Each of these populations has specific characteristics including different cell surface phenotypes, responsiveness to stimulation, and persistence *in vivo*, suggesting that they are uniquely different subsets. Importantly, the authors hypothesize that each of these TCE populations has distinct origins. TCE that express high levels of itgα4 are thought to originate from T cells involved in an immune response, while those expressing low levels of itgα4 are thought to arise in an antigen-independent manner. Thus, it is becoming clear that TCE can develop under various conditions and specific TCE populations may have distinct impacts on the function of the aging immune system.

Regulatory T cells and aging

In addition to the above intrinsic changes in CD4 and CD8 T cell populations with aging, significant increases in regulatory T cell populations have recently been described in aged mice [24]. While regulatory T cells are important for maintaining homeostasis and limiting autoimmune responses, they also act to dampen the immune response to infectious agents and tumors, both of which also decline with age. Recently, it has been proposed that effector T cell populations generated during an immune response may have an active role in potentiating regulatory T cell mediated suppression, possibly via the production of regulatory cytokines [25]. Thus, it is not surprising that a lifetime of generating effector T cell populations in response to infections and vaccinations would also result in the generation of an expanded population of regulatory T cells. In fact, not only the number of regulatory T cells increased with age, the actual level of suppression per cell is higher in cells from aged mice compared to young mice [26•].

The age-related increase in regulatory T cells has been shown to reduce the ability of aged animals to respond to and reject transplanted tumors in two separate models [27•,28•]. This is problematic because these studies were examining antitumor immunotherapies that might be beneficial for older individuals, who exhibit an increase incidence of tumors. While young mice survive and develop robust antitumor responses, aged mice succumb and develop few tumor-specific cytolytic cells. In these studies, the regulatory T cells involved in the age-related reduced response to tumors were $CD4^+$ $CD25^+$ $FoxP3^+$ T cells and depletion with an anti-CD25 monoclonal antibody could restore antitumor responses to the level found in young mice. Interestingly, the antitumor responses in the aged animals could also be overcome by inducing expression of CD80 on the tumor cells, by the addition of IL-12 or by the use of CpG-oligodeoxynucleotide as an adjuvant. These results suggest that induction of inflammatory cytokines may enhance antitumor CD8 T cell responses in older animals, as has also been shown for the enhancement of CD4 T cell function with aging [13••,29].

It is important to note that regulatory T cells have been shown to be dependent on IL-2 signaling in order to maintain proper homeostasis and function [30]. In contrast, IL-2 inhibits the expression of IL-17 and blocking IL-2 promotes the differentiation of Th17 effectors [31]. Thus, it has been recently hypothesized that the presence of regulatory T cells during an immune response may favor the development of a Th17 polarized response because the regulatory cells consume IL-2, which is needed for the development of Th1 and Th2 but not Th17 effectors [32]. If this is the case, the increase in the numbers of regulatory T cells with age could be a responsible propensity for the development of Th17 responses in older individuals.

Conclusions

Recent studies have shown that aging has very specific effects on T cell function. The immune response to infection, immunization, and tumors in aged individuals is quite different from that found in the young. This is the result of several distinct factors including the propensity to generate Th17 effectors, changes in TCR repertoire, development of clonal expansions, and the increased percentage of regulatory T cells. Only when we fully understand these age-related changes, we can begin to

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