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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.

**Addresses**

1. Trudeau Institute, 154 Algonquin Ave, Saranac Lake, NY 12983, United States
2. SUNY Upstate, Department of Microbiology and Immunology, 2204 Weiskotten Hall, 750 E Adams Street, Syracuse, NY 13210, United States

**Corresponding author:** Haynes, Laura (lhaynes@trudeauinstitute.org) and Maue, Alexander C (mauea@upstate.edu)

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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.
bulin heavy chain genes [13]. This ultimately results in the generation of a less robust and protective antibody response. This has been described for 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.

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           |

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.

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 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
design appropriate strategies for overcoming these defects and enhancing immune responses in the elderly.

References and recommended reading

Papers of particular interest, published within the period of the review, have been highlighted as:

* of special interest
** of outstanding interest

1. Burns EA, Lum LG, L’Hommedieu G, Goodwin JS: Specific humoral immunity in the elderly: in vivo and in vitro response to vaccination. *J Gerontol* 1993, 48:B231-236.

2. Cook JM, Gualde N, Hessel L, Mounier M, Michel JP, Denis F, Ratinaud MH: Alterations in the human immune response to the hepatitis B vaccine among the elderly. *Cell Immunol* 1987, 109:99-96.

3. Musher DM, Chapman AJ, Goree A, Jonsson S, Briles D, Baughn RE: Natural and vaccine-related immunity to *Streptococcus pneumoniae*. *J Infect Dis* 1986, 154:245-256.

4. Yu X, Taibane T, McGraw PA, House FS, Keefer CJ, Hicar MD, Turney TM, Pappas C, Perrone LA, Martinez E et al.: Neutralizing antibodies derived from the B cells of 1918 influenza pandemic survivors. *Nature* 2008, 455:532-536.

5. Haynes L, Eaton SM, Burns EM, Randall TD, Swain SL: CD4 T cell memory derived from young naive cells functions poorly. *Proc Natl Acad Sci U S A* 2005, 100:15053-15058.

6. Roberts AD, Ely KH, Woodland DL: Differential contributions of central and effecter memory T cells to recall responses. *J Exp Med* 2005, 202:123-133.

7. MacLennan IC: *Germinal centers*. *Annu Rev Immunol* 1994, 12:117-139.

8. Tsiagbe VK, Inghirami G, Thorbecke GJ: The physiology of germinal centers. *Crit Rev Immunol* 1996, 16:381-421.

9. Linton P-J, Haynes L, Klinman NR, Swain SL: Antigen independent changes in CD4 T cells with aging. *J Exp Med* 1996, 184:1891-1900.

10. Garcia GG, Miller RA: Age-dependent defects in TCR-triggered cytoskeletal rearrangement in CD4+ T cells. *J Immunol* 2002, 169:5021-5027.

11. Haynes L, Linton P-J, Eaton SM, Tonkonogy SL, Swain SL: IL-2, but not other common γ chain (γc)-binding cytokines, can reverse the defect in generation of CD4 effector T cells from naive T cells of aged mice. *J Exp Med* 1999, 190:1013-1023.

12. Eaton SM, Burns EM, Kusser K, Randall TD, Haynes L: Age-related defects in CD4 T cell cognate helper function lead to reductions in humoral responses. *J Exp Med* 2004, 200:1613-1622.

13. Maue AC, Eaton SM, Lanthier PA, Sweet KB, Blumerman SL, Haynes L: Proinflammatory adjuvants enhance the cognate helper activity of aged CD4 T cells. *J Immunol* 2009, 182:6129-6135.

14. Huang MC, Liao JJ, Bonasera S, Longo DL, Goetzl EJ: Nuclear factor-kappaB-dependent reversal of aging-induced alterations in T cell cytokines. *FASEB J* 2008, 22:2142-2150. The authors demonstrate that naive CD4 T cells from aged animals differentiate into Th17 effectors and that proinflammatory cytokines can enhance the helper function of aged CD4 T cells.

15. Kolis JK, McCray PB Jr, Chan YR: Cytokine-mediated regulation of antimicrobial proteins. *Nat Rev Immunol* 2008, 8:829-835.

16. Mosley RL, Koker MM, Miller RA: Idiosyncratic alterations of TCR size distributions affecting both CD4 and CD8 T cell subsets in aging mice. *Cell Immunol* 1998, 189:10-18.

17. Schwab R, Szabo P, Manavalan JS, Weiskler ME, Posnett DN, Pannetier C, Kourilsky P, Even J: Expanded CD4+ and CD8+ T cell clones in elderly humans. *J Immunol* 1997, 158:4493-4499.

18. Yager EJ, Ahmed M, Lanzer K, Randall TD, Woodland DL, Blackman MA: Age-associated decline in T cell repertoire diversity leads to holes in the repertoire and impaired immunity to influenza virus. *J Exp Med* 2008, 205:711-723.

The authors demonstrate that there are dramatic changes in TCR repertoire usage during influenza infection in aged mice.

19. Callahan JE, Kappler JW, Marrack P: Unexpected expansions of CD8-bearing cells in old mice. *J Immunol* 1993, 151:6657-6669.

20. Ahmed M, Lanzer KG, Yager EJ, Adams PS, Johnson LL, Blackman MA: Clonal expansions and loss of receptor diversity in the naive CD8 T cell repertoire of aged mice. *J Immunol* 2006, 172:784-792.

The authors show that changes in TCR repertoire usage are correlated with the occurrence of clonal expansions in aged mice.

21. Messacaud I, Lemaout J, Guevara-Patino JA, Metzner BM, Nikolich-Zugich J: Age-related CD8 T cell clonal expansions constict CD8 T cell repertoire and have the potential to impair immune defense. *J Exp Med* 2004, 200:1347-1358.

22. Saurwein-Teissl M, Lung TL, Marx F, Gschosser C, Asch E, Blasko I, Parsons R, Bock G, Schonitzer D, Tranroy E et al.: Lack of antiviral production following immunization in old age: association with CD8+CD28− T cell clonal expansions and an imbalance in the production of Th1 and Th2 cytokines. *J Immunol* 2002, 168:5893-5899.

23. Clamhcy ET, White J, Kappler JW, Marrack P: Identification of two major types of age-associated CD8 clonal expansions with highly divergent properties. *Proc Natl Acad Sci U S A* 2008, 105:12987-13002.

The authors demonstrate that there are at least two distinct kinds of clonal expansions that can be distinguished by several characteristics. They also speculate that each of these types of clonal expansions has distinct origins.

24. Nishioka T, Shimizu J, Iida R, Yamazaki S, Sakaguchi S: CD4+CD25+Fox3+ T cells and CD4+CD25−Foxp3− T cells in aged mice. *J Immunol* 2006, 176:6586-6593.

25. Vignali DA, Collison LW, Workman CJ: How regulatory T cells work. *Nat Rev Immunol* 2008, 8:523-532.

26. Lages CS, Suffia I, Veilla PA, Huang B, Warshaw G, Hildeman DA, Belkaid Y, Chounguet C: Functional regulatory T cells accumulate in aged hosts and promote chronic infectious disease reactivation. *J Immunol* 2008, 181:1835-1841.

The authors demonstrate that the numbers of regulatory T cells in aged mice and determined that these cells have a higher level of suppressive per cell when compared to regulatory T cells from young mice.

27. Ruby CE, Weinberg AD: OX40-enhanced tumor rejection and effector T cell differentiation decreases with age. *J Immunol* 2009, 182:1481-1489.

The authors demonstrate that regulatory T cells in aged mice impair antitumor responses and this can be overcome by adding exogenous IL-12.

28. Sharma S, Dominguez AL, Lustgarten J: High accumulation of T regulatory cells prevents the activation of immune responses in aged animals. *J Immunol* 2006, 177:8348-8355.

The authors demonstrate that regulatory T cells in aged mice impair antitumor responses and this can be overcome by the depletion of regulatory cells or by immunization with Cpg as an adjuvant.

29. Haynes L, Eaton SM, Burns EM, Rincon M, Swain SL: Inflammatory cytokines overcome age-related defects in CD4 T cell responses in vivo. *J Immunol* 2004, 172:5194-5199.

30. Fontenot JD, Raamsussen JP, Gavin MA, Rudensky AY: A function for interleukin 2 in Foxp3-expressing regulatory T cells. *Nat Immunol* 2005, 6:1142-1151.

31. Laurence A, Tato CM, Davidson TS, Kanno Y, Chen Z, Yao Z, Blank RB, Meylan F, Siegel R, Henningshaussen L et al.: Interleukin-2 signaling via STAT5 constrains T helper 17 cell generation. *Immunity* 2007, 28:371-381.

32. Stockinger B, Veldhoen M, Martin B: Th17 T cells: linking innate and adaptive immunity. *Semin Immunol* 2007, 19:353-361.