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Translational Article

Special Issue on The Aging Lung

Translational

T-Cell Biology in Aging, With a Focus on Lung Disease

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T cells are essential for defending hosts against microorganisms and malignancy as well as for regulating the development of immune-mediated inflammatory diseases like autoimmunity. Alterations in T-cell immunity occur with aging, affecting the function and proportions of T-cell subsets. Probably, the most noticeable age-associated change in T-cell immunity is an alteration in the frequency of naive and memory CD4+ and CD8+ T cells. In fact, the frequency of naive CD4+ and CD8+ T cells decreases with aging, whereas the frequency of memory CD4+ and CD8+ T cells increases. Also, changes in T-cell proliferation, cytokine production, memory response, and cytotoxicity as well as in regulatory T-cell number and function have been reported with aging. Such alterations could contribute to the development of infections, malignancies, and inflammatory diseases that rise with aging. Of interest, T cells are closely involved in the development of inflammatory airway and lung diseases including asthma and chronic obstructive pulmonary disease, which are prevalent in the elderly people. In addition, T cells play a major role in defending host against influenza virus infection, a serious medical problem with high morbidity and mortality in the elderly people. Thus, it is conceivable that altered T-cell immunity may account in part for the development of such respiratory problems with aging. Here, we will review the recent advances in T-cell immunity and its alteration with aging and discuss the potential effects of such changes on the lung.

Key Words: T cells—Lungs—Aging.

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ALTERATIONS in the immune system occur with aging (1). These alterations likely contribute to the development of an array of clinical entities such as infections, malignancies, and inflammatory diseases that come across with aging. Although the increased frequency of infections and malignancies in the elderly people suggests an age-associated decline of the immune system (1–4), aging could be regarded as a condition with dysregulated inflammation (inflam-aging; (5,6)). The latter notion is supported by the observation that the elderly people had increased circulatory levels of the inflammatory cytokines interleukin (IL)-6 and tumor necrosis factor-α, which predicted mortality risk independently of other risk factors (7,8). Clinically, the elderly people have an increased incidence of some chronic inflammatory diseases including polymyalgia rheumatica, giant cell arteritis, and chronic obstructive pulmonary disease (COPD; (9,10)). In addition, atherosclerosis and type 2 diabetes, which are prevalent in the elderly people, are now considered chronic inflammatory conditions associated with an imbalance among proinflammatory and antiinflammatory cytokines (7,11).

Age-associated changes of the immune system are found in both innate and adaptive immunities (6,12). T cells, a component of the adaptive immunity, play a critical role in the immune system. T cells are essential for defending hosts against microorganisms and malignancy as well as for regulating the development of immune-mediated inflammatory diseases like autoimmunity. T cells are divided into CD4+ and CD8+ T cells based on the capacity to recognize the antigenic peptide presented in the context of the major histocompatibility complex class I and II molecules, respectively. CD4+ T cells provide help to other immune cells such as B cells and macrophages for their activation through producing cytokines and expressing costimulatory molecules (13,14). The primary function of CD8+ T cells armed with cytotoxic molecules is to kill host cells infected with pathogens or transformed into tumors (15). Indeed, CD4+ T cells and CD8+ T cells are referred to T helper (Th) and cytotoxic T cells, respectively. Here, we will review the latest findings on how aging affects T-cell immunity and discuss the potential effects of such changes on the lung.

Overview of T-Cell Biology

Over the past two decades, our understanding of T-cell biology has substantially advanced. These include the identifications of new CD4+ T-cell subsets as well as the discovery

of the mechanisms involved in memory T-cell homeostasis. Thus, it would be imperative to start the review by refreshing the general biology of T cells, focusing on the recent findings.

T-Cell Homeostasis

The development site of T cells is the thymus. The progenitor cells of T cells migrate from the bone marrow to the thymus where immature T cells or thymocytes undergo complicated selection processes to generate cells with the optimal affinity for the major histocompatibility complex molecules while avoiding the recognition of self-antigens (16). Cells that have survived the selection processes are exported into the circulation as naive but mature T cells. Naive T cells migrate to the secondary lymphoid tissues where they survey antigens presented by antigen-presenting cells, such as dendritic cells (14,15,17). When the naive T cells encounter the appropriate antigen, they become activated, proliferated, and differentiated into effector T cells, with the help from cognate interactions through costimulatory molecules and cytokines. The effector T cells move to the sites of infection and/or inflammation to control the source of antigens, such as pathogens. Upon the clearance of the source of the antigens, most effector T cells undergo activation-induced cell death, although a small number of cells survive and become memory T cells providing long-term immune protection against the same pathogens. The memory T cells can turn into effector cells, even in the absence of the help of costimulation and cytokines when they encounter the antigen again. At this time, the development speed and the quantity of this secondary immune response are much faster and greater than those of the primary immune response in the secondary lymphoid tissues.

CD4+ T-Cell Subsets: Th Cells and Regulatory T Cells

The concept of the existence of different CD4+ T-cell subsets with distinct functions was developed more than two decades ago. Indeed, CD4+ Th cells can be categorized into Th1, Th2, and Th17 cells with unique cellular characteristics based on the cytokines primarily produced by them. Although Th1 and Th2 cells predominantly produce interferon (IFN)-γ and IL-4, respectively, recently identified Th17 cells produce IL-17 (13,14,17,18). These cell subsets have distinctive roles in defending hosts against pathogens. Th1 cells are essential for controlling intracellular microorganisms such as mycobacteria by activating macrophages with IFN-γ. Parasites are effectively controlled by Th2 cells that produce the cytokines IL-5 and IL-13 with the capacity to activate eosinophils. Th17 cells are involved in eradicating extracellular microorganisms, including fungi, by activating neutrophils with IL-17. Although the proper immune responses by Th1, Th2, and Th17 cells are obviously beneficial for the host, any aberrant response can lead to the development of pathological conditions. For instance, allergy and asthma have been associated with increased Th2 cell response while dysregulated Th17 cell response is found in some autoimmune diseases, such as multiple sclerosis and systemic lupus erythematosus (14,19,20).

The differentiation of Th1, Th2, and Th17 cells from naive CD4+ T cells is critically dependent on cytokine milieu (13,14,17,18). IFN-γ and IL-12 induce Th1 cell differentiation, although IL-4 promotes Th2 cell development. In the differentiation of Th17 cells, multiple cytokines including IL-1β, IL-6, IL-21, IL-23, and transforming growth factor-β are known to enhance Th17 cell polarization. Along with the cytokines, transcription factors are also involved as the master regulators in the differentiation of Th cell subsets (13,14,17,18). The T-box transcription factor T-bet regulates Th1 cell differentiation. GATA3 and retinoid orphan receptor (ROR)γt are essentially involved in the development of Th2 and Th17 cells, respectively. These transcription factors and cytokines operate reciprocally (13). The expression of GATA3 and RORγt can be suppressed by T-bet (21,22). Similarly, the differentiation of Th17 cells is repressed by the Th1 and Th2 cytokines IFN-γ and IL-4 (23).

In addition to Th cells, CD4+ T cells also have cell subsets with the immune regulatory function. In fact, the concept of suppressor T cells or regulatory T cells that could control immune responses was conceived in the early 1970s (24). However, it was nearly forgotten until the 1990s when several groups demonstrated the existence of T-cell subsets, which were able to regulate inflammatory immune responses in mice (25–27). The best known one is naturally occurring $CD4^+$ $CD25^+$ regulatory T cells (Treg) that express the forkhead family transcriptional factor FOXP3 (28,29). The FOXP3 expression is essential for the regulatory of function. FOXP3 transfection to $CD4^+$ $CD25^-$ T cells, which did not have regulatory function, conferred the immune regulatory property (30–32). Also, mice and humans with mutations in the *Foxp3* gene have immune-dysregulated phenotypes (28). Of interest, FOXP3 can be induced in CD4+ T cells without expressing FOXP3 by T-cell receptor (TCR) triggering, IL-2, and transforming growth factor-β (29). These cells also appear to have immune regulatory function and are called induced Treg cells as opposed to naturally occurring Treg cells that are developed in the thymus.

Effector CD8+ T Cells

Naive CD8+ T cells acquire cytotoxic function rapidly in the presence of antigenic stimulation and costimulation (33). This process is further enhanced by inflammatory cytokines including IL-12 and IFN-α (33). The acquisition of cytotoxic function with the expression of perforin and granzyme B is regulated by several transcription factors (34). The best known ones are T-bet and Eomesodermin that belong to the T-box transcription factor family. As discussed earlier, T-bet is the master transcription regulatory for Th1 cell differentiation. In CD8+ T cells, T-bet expression is upregulated in response to TCR, IFN-γ, and IL-12 stimulation

(35,36). Similar to CD4+ T cells, T-bet is involved in IFN-γ production by CD8+ T cells, although it may not be critically required (37). Eomesodermin can also upregulate the cytotoxic molecules perforin and granzyme B as well as IFN-γ in CD8+ T cells (34). Although both T-bet and Eomesodermin are involved in inducing effector function in CD8+ T cells, they may have different roles in the development of memory CD8+ T cells. Although increased T-bet expression was associated with the generation of short-lived effector CD8+ T cells, the expression of Eomesodermin was required for the development of memory cells with the long-term survival capacity (35,38).

Memory T-Cell Subsets

Memory T cells are not a single population. Based on the capacity to migrate secondary lymphoid tissue and infected or inflamed peripheral sites, memory T cells can be categorized into central and effector memory (EM) T cells. Central memory T cells that express lymphoid tissue homing chemokine receptor 7 (CCR7) can migrate to secondary lymphoid tissues like the lymph nodes and spleen (39). In contrast, EM T cells can go to peripheral tissues such as the skin and mucosa through the expression of the receptors for the molecules expressed in inflamed tissues but not CCR7. In terms of functional capacity, naive and central memory cells produce IL-2 upon TCR triggering and have strong proliferative capacity. In comparison, EM cells can migrate to peripheral sites of inflammation via their expression of β1 and β2 integrins (40) as well as of receptors for inflammatory chemokines, such as CCR1, CCR3, and CCR5 (39,41). In addition, EM cells express cytotoxic molecules and produce effector cytokines, such as IFN-γ.

Development and Maintenance of Memory T Cells

Upon pathogen clearance, the majority of effector cells undergo activation-induced cell death, leaving behind a residual fraction of memory survivors that provide long-term protection against the same antigen. Memory T cells continue to divide at a slow rate in the absence of antigen, and IL-7 and IL-15 have emerged as the cytokines necessary for such homeostasis, as further discussed later (42–44). IL-7 is largely produced by thymic epithelial and bone marrow stromal cells while the major source of IL-15 is cells of myeloid origin, including monocytes, macrophages, and dendritic cells (44–46). IL-7 promoted survival of memory CD8+ T cells through upregulation of Bcl-2, an antiapoptotic molecule (42), whereas mice deficient of IL-15 or the IL-15 receptor had reduced numbers of memory CD8+ T cells with impaired cytotoxicity (43,44,47,48). In mice infected with virus, viral-specific $CD8^+$ T cells that expressed high levels of the IL-7 receptor alpha chain (IL-7Rα) had the increased ability to become memory cells compared with the same cells expressing low levels of IL-7Rα (49). Similarly, human IL-7Rα^{high} memory CD8+ T cells survived better in response to IL-7 compared with IL-7Rα^{low} memory CD8+ T cells (50). These findings suggest the role for IL-7 and its receptor in determining potential fates of effector CD8+ T cells. However, studies reported a redundant role for IL-7 and IL-7Rα in inducing and maintaining memory CD8+ T cells (51–54). Mice deficient of IL-7 were still able to generate viral-specific CD8+ memory cells with increased Bcl-2 (52). IL-15 is likely accountable for this phenomenon (53). In the development of memory CD8+ T cells, transcription factors are also involved. T-bet and Blimp-1, encoded by the *Prdm1* gene, were preferentially expressed in short-lived effector CD8+ T cells (35,55,56). In contrast, Eomesodermin expression was required for the development of memory cells with the long-term survival capacity (35,38). Analogous to CD8+ T cells, IL-7 is involved in the development and maintenance of memory CD4+ T cells (57,58). In addition, a recent study showed that IL-15 could maintain memory CD4+ T cells in mice with physiologically low levels of IL-7 (59). These findings indicate that IL-7 and IL-15 are involved in the maintenance of both memory CD4+ and CD8+ T cells.

Table 1. Alterations in T-Cell Immunity With Aging

Thymus and T-Cell Subsets	
Thymus	Atrophy
Frequency of naive CD4+ and CD8+ T cells	Decrease
Frequency of memory CD4+ and CD8+ T cells	Increase
CD4+ T cells	
Cell proliferation in response to PMA/ionomycin or PHA	Decrease
IFN-γ and IL-4 production from CD4+ T cells	Variable (no change, decrease, and increase)
Frequency of IL-17–producing Th17 cells in memory CD4+ T cell	Decrease
Frequency of FOXP3+ Treg cells	No change to increase
CD8+ T cells	
Proliferation	Decrease
Cytotoxicity	Decrease
Frequency of IL-7Rα^{low} effector memory CD8+ T cells	Increase
Frequency of CD28− (antigen experienced) and CD57+ CD8+ T cells	Increase
T-cell receptor repertoires	Decrease with oligoclonal CD8+ T-cell expansion

Note: PMA= phorbol myristate acetate; IFN = interferon; IL = interleukin; PHA = phytohemagglutinin.

Aging and T-Cell Immunity

Alterations in T-cell immunity occur with aging, affecting the function and proportions of T-cell subsets (Table 1; (12,60–64)). In studying the effect of aging on T-cell function, it is important to consider the fact that aging affects the frequency of naive and memory T cells. The thymus, the development site of T cells, undergoes atrophy with aging (12). This has a direct impact on the proportions of naive and memory T cells. In aged animals and humans, the frequency of naive CD4+ and CD8+ T cells decreases, whereas

the frequency of memory CD4+ and CD8+ T cells increases (12,60–63). As discussed in the T-Cell Biology section, naive and memory T cells are clearly distinct populations with unique cellular characteristics. Thus, any age-associated change in T-cell function including proliferation and cytokine production could be secondary to the alteration in the frequency of naive and memory T cells.

Age-Associated Changes in CD4+ T Cells

Age-associated changes in the function and the frequency of CD4+ T-cell subsets are found in humans and mice (61,65,66). The elderly people have an increased frequency of memory CD4+ T cells and a decreased frequency of naive CD4+ T cells compared with the young (66). Age-associated alterations were also reported in CD4+ T-cell functions including TCR signaling, cognate helper function, vaccine response, cell proliferation, and cytokine production (66,67). However, the results of studies are not always uniform. In particular, some studies reported an age-associated decrease in CD4+ T-cell proliferation in response to strong T-cell stimulations, such as phytohemagglutinin, phorbol myristate acetate, and ionomycin (68–70). In contrast, no altered proliferation of CD4+ T cells was reported when cells were stimulated with relatively low-dose anti-CD3 Abs (71,72). In consistence with these studies, we also noticed that young and elderly people had similar levels of CD4+ T-cell proliferation in response to low-dose anti-CD3 antibody stimulation, whereas the elderly people had decreased CD4+ T-cell proliferation in response to high-dose anti-CD3 antibody stimulation (73). Thus, it is likely that the proliferative capacity of CD4+ T cells from the young and the elderly people is comparable as these cells encounter relatively weak T-cell stimulation, even though such capacity is lower in the elderly people than in the young in response to strong and prolonged T-cell stimulation. A possible explanation for these findings is that the maximum proliferative capacity of CD4+ T cells in the elderly people is lower than that in the young, which likely stems from the shortening of a telomere length with aging (74,75).

Studies that investigated the effect of aging on Th1 and Th2 responses in humans and animals were largely done in the 1990s by measuring serum cytokine levels as well as analyzing the cytokine gene or protein production by total T cells or $CD4^+$ T cells. The results of these studies were largely inconsistent. Although some studies reported an age-associated increase in IFN-γ production from T cells (76–78), others reported no change (79,80) or even a decrease in the elderly people (81–83). Similarly, the findings from studies comparing IL-4 production from T cells between the young and the elderly people are not consistent. In the elderly people, IL-4 levels were higher (84), lower (83), or similar (82) compared with the young. Recently, several studies investigated IL-17–producing Th17 cells in aging (85,86). The effect of aging on Th17 cells appears to be different between naive and memory CD4+ T cells in humans (86). In purified memory CD4+ T cells, the elderly people had a decreased frequency of Th17 cells compared with the young while both groups had similar frequencies of IFN-γ–producing Th1 cells. In contrast, the differentiation of IL-17–producing effector cells but not IFN-γ-producing cells from naive CD4+ T cells was enhanced in the elderly people compared with the young. The latter finding implies that the differentiation of Th17 cells from naive CD4+ T cells in response to new microorganism(s) may not be impaired in the elderly people despite the declined frequency of total naive CD4+ T cells. IL-1β is essential for the differentiation of Th17 cells. A recent study reported that naive CD4+ T cells with the expression of the IL-1 receptor 1 (IL-1R1) had increased differentiation of IL-17–producing $CD4^+$ T cells from naive CD4+ T (87). In fact, IL-1R1 expression on naive CD4+ T cells was increased in the elderly people compared with the young, suggesting that such altered IL-1R1 expression on naive CD4+ T cells could be a contributing factor to the increased Th17 cell differentiation from naive CD4+ T cells in the elderly people.

The effect of aging on the number and function of Treg cells has been studied. The results of these studies are somewhat inconsistent (88). A moderately increased frequency of FOXP3+ CD4+ T cells or CD25+ CD4+ T cells with aging was reported in humans (89–91). Also, a loss of the capacity to suppress target cell proliferation by CD4+ CD25+ T cells was found in the elderly people (92). In contrast, we found no difference in the frequency and phenotypic characteristics of FOXP3+ CD4+ T cells as well as their capacity to suppress inflammatory cytokine production and proliferation of CD4+ CD25− T cells between the young and the elderly people (93). However, the production of the antiinflammatory cytokine IL-10 from CD4+ CD25− T cells was more potently suppressed in the elderly people than in the young (93).

Age-Associated Changes in CD8+ T Cells

Age-associated alterations in CD8+ T cells have been extensively studied (2,94). These include impaired cellular functions like cytotoxicity as well as changes in the subsets of naive and memory CD8+ T cells. Aged hosts have a reduced ability to combat viral infections (95–97), which correlate with impaired cytotoxicity (98,99) as well as impaired proliferation and IL-2 production by virus-specific memory CD8+ T cells (100,101). With aging, the frequency of naive CD8+ T cell decreases, whereas the frequency of memory CD8+ T cells increases (102–104). In addition, oligoclonally expanded populations of CD8+ T cells appear in aged humans and mice (102,103,105), suggesting that the expansion of memory CD8+ T cells could be secondary to repeated exposures to microbial antigens over a lifetime. This notion is supported by the findings that expanded memory CD8+ T cells are typically CD28− (molecule downregulated

on antigen-experienced cells), CCR7−, and CD57+ (replication senescence marker) with decreased length of the telomere, which becomes shortened with each cell replication (106,107). Furthermore, several studies reported an association between the infectious status of cytomegalovirus, which establishes life-long latent infection, and the increased prevalence of CD8+ T-cell oligoclonal expansion in elderly humans (62,108–110). These observations suggest the potential role for chronic antigenic stimulations such as cytomegalovirus infection in expanding memory CD8+ T cells with aging (105,111,112). However, this may not be the only mechanism for such a phenomenon with aging. It is possible that the expansion of memory CD8+ T cells, including oligoclonally expanded cells, may occur independently of chronic antigenic stimulation via the alterations in IL-15- and/or IL-7-mediated CD8+ T-cell maintenance. This notion is supported by a study demonstrating the development of CD8+ T-cell clonal expansion in aged mice lacking a major histocompatibility complex class I molecule as well as in aged mice repeatedly injected with adjuvant alone, which stimulated many CD8+ T-cell clones nonspecifically (113). Of interest, my lab reported that human naive and central memory CD8+ T cells expressed high levels of IL-7Rα, whereas human EM CD8+ T cells (CCR7−CD45RA+/−) had two different subsets of cells expressing IL-7Rα^{high} and IL-7Rα^{low} with distinct characteristics (50). The expression of the *IL7Rα* gene was differentially regulated in the two groups as determined by DNA methylation, an important gene regulatory mechanism that is inherited from mother to daughter cells in the *IL-7Rα* gene promoter (114). The elderly people had an expansion of IL-7Rα^{low} EM CD8+ T cells compared with the young. IL-7Rα^{low} EM CD8+ T cells were highly antigen-experienced cells with limited TCR repertoire and increased expression of the replication senescent marker CD57. These cells had impaired survival and replication in response to IL-7 and TCR triggering, respectively. However, IL-15 induced substantial proliferation of IL-7Rα^{low} cells in the presence and absence of TCR triggering, which supports the potential role for homeostatic cytokines such as IL-15 in expanding memory CD8+ T cells with aging (115). Although it is yet to be determined how the age-associated expansion of memory CD8+ T cells exactly affects the host immunity, such phenomenon could be harmful to hosts in that it may impair the ability of $CD8^+$ T cells to properly develop immune responses to newly encountered microorganisms such as emerging strains of influenza virus by occupying "immunological space" (2,12,116–118).

Aging, Lung, and T Cells

The lung and immune system are closely coupled. The lung is constantly exposed to microorganisms and environmental irritants that can trigger the immune system. Any under or over immune responses to these stimuli could result in pathological conditions, such as pneumonia, asthma, and COPD. In fact, aging has been associated with an increased risk of influenza, pneumonia, and COPD (10,119). T cells are essential for the development of immune responses to influenza virus and vaccine (64). Studies reported age-associated alterations in T-cell immune responses to primary influenza virus infection and influenza vaccine. A decreased memory CD4+ T-cell response to the influenza vaccine had been reported in the elderly people (120). Also, the CD8+ T-cell response to the influenza virus diminishes with aging (121,122). A recent study reported that EM and effector CD8+ T cells in the elderly people had decreased cytotoxicity against the influenza virus compared with the young (121). In mice, TCR repertoire of CD8+ T cells responding to the influenza viral infection was restricted with aging, although the numbers of CD8+ T cells in the airways and lungs of young and aged mice were similar (122). Such impaired T-cell response to influenza virus could be related to the age-associated decrease in the frequency of naive T cells with the thymic atrophy (122). In a separate study, influenza virus–infected aged mice had increased mortality and delayed recovery compared with young mice infected with the same virus (123). This could be related to decreased lung infiltration of CD4+ and CD8+ T cells with reduced numbers of activated influenza viral–specific CD8+ T cells (123). Overall, these findings suggest that aging is associated with impaired influenza viral–specific T-cell responses that may stem from a decreased frequency of naive T cells as well as impaired function of memory and effector T cells.

T Cells in COPD

COPD that affects more than 2 million people worldwide is the fourth leading cause of death (124,125). The prevalence of COPD increases with aging independently of cigarette smoking, the best known risk factor for COPD (126,127). This suggests that age-associated change(s) could contribute to the development of COPD. A body of accumulating data indicates a critical role for the immune system in the pathogenesis of COPD (reviewed in (125)). Both innate and adaptive immune cells are likely involved in the development of dysregulated inflammation and tissue damage in COPD. T cells were frequently found in the airways of patients with COPD, suggesting the role of T-cell immunity in the pathogenesis of COPD (10,128). In fact, overexpression of the T-cell cytokines IFN-γ and IL-13 induced massive emphysematous changes in mice (129,130). CD8+ T cells with the cytotoxicity were the predominantly infiltrating T-cell type in the airways and alveolar compartment of patients with COPD (125,131). Also, the frequency of IFN-γ–producing CD8+ T cells in peripheral blood correlated with disease activity in patients with COPD (132). Deleting CD8+ T cells improved lung inflammation and tissue destruction in a mouse model of cigarette smoke–induced emphysema (133). These observations clearly support the critical implication

of CD8+ T cells, which are armed with the capacity to produce cytotoxic molecules and inflammatory cytokines, in the pathogenesis of COPD.

Different types of CD4+ T cells appear to be associated with COPD. Numbers of CD4+ T cells, in particular IFN-γ–producing Th1 cells, were increased in the airways and parenchymal tissues of patients with COPD (134). In addition, increased expression of IL-17, a cytokine produced primarily by Th17 cells, was reported in bronchial mucosa and submucosa of patients with COPD (135,136). Furthermore, the increased number of IL-17–producing Th17 cells was found in the peripheral blood of patients with COPD (137). Of interest, the expansion of CD28− CD4+ T cells, which also increase with aging (138), was found in patients with COPD, correlating with impaired lung function (139). These cells had increased expression of natural killer–like T-cell receptors (CD94, CD158), intracellular perforin, and granzyme B (139). The results of studies measuring the frequency of Treg cells in bronchoalveolar lavage from patients with COPD were inconsistent, showing both increased and decreased numbers of this cell subset in patients with COPD (140,141). As discussed earlier, aging is associated with the altered numbers and functions of T cells including CD8+ T cells, Th17 cells, and Treg cells, which are likely involved in the pathogenesis of COPD. Thus, it is conceivable that such age-associated changes in T-cell immunity could contribute to the development and/or progress of COPD, which increases with aging. For instance, increased IL-17 production from naive CD4+ T cells in the elderly people could be an aggravating factor for COPD upon respiratory infection with a previously unexposed microorganism (86). Also, the expansion of EM CD8+ T cells with the expression of perforin in the elderly people could be detrimental to COPD (50) given the role of such cells in the pathogenesis of COPD. Further studies in basic and clinical science are warranted to address these intriguing questions, which will lead to better therapeutic interventions.

T Cells in Asthma

Although asthma has been considered a disease primarily affecting children and young adolescents, a substantial number of asthmatic patients develop the disease after the age of 40 (142). Furthermore, elderly asthmatic patients appear to have more severe disease (143). T cells are a major player in the pathogenesis of asthma (reviewed in (144)). Traditionally, asthma was thought to be a Th2 cell–mediated disease with the involvement of the cytokines IL-4, IL-5, and IL-13, which could promote IgE switching, eosinophilia, mast cell recruitment, mucus production, and airway hyperresponsiveness (144,145). However, recent studies indicate the involvement of other types of Th cells, Treg, and CD8+ T cells (144). Allergenic challenges promoted airway inflammation, hyperresponsiveness, and neutrophilia by inducing Th17-cell response (146,147). Th17 cells also enhanced Th2-mediated eosinophilic inflammation in mice (148). In addition, IL-9–producing CD4+ T helper cells (referred to Th9 cells) may participate in inducing airway inflammation and hyperresponsiveness, although its exact role is yet to be determined given the mixed results of the studies on IL-9 overexpression and IL-9 deficiency in a mouse model of asthma (149,150). Treg cells also appear to have a role in regulating airway inflammation in asthma. Transfer or induction of Treg cells reduced airway inflammation and airway hyperresonsiveness in mice and rats (151,152). CD8+ T cells are likely involved in the development of asthma. In the airways and sputum of patients with asthma, CD8+ T cells that produced IL-5, IL-13, and/or IFN-γ were found, correlating with disease activity (153–155). In mice, deleting CD8+ T cells reduced allergic airway inflammation while reconstituting CD8+ T cells in these mice with EM but not central memory CD8+ T cells increased airway hyperresponsiveness, eosinophilic inflammation, and IL-13 levels in bronchoalveolar fluid (156). Although data regarding the effect of aging on the pathogenesis of asthma are limited, aging may affect airway hyperresponsiveness. In a mouse model of asthma, aged mice developed greater airway and lung inflammation in response to ovalbumin challenge compared with young mice (157). In addition, the cytokine profiles were different between the two groups. Aged mice had increased production of IL-5 and IFN-γ in the lung tissues and spleen cell culture, whereas young mice had increased levels of IL-4 and IL-13. These findings support the notion that aging may affect airway hyperresponsiveness and inflammation. Aging is associated with alterations in T-cell immunity, which is a critical component in the development of asthma. However, additional investigations are required to determine whether and how such alterations could promote asthma in humans.

In summary, a range of immunologic alterations in T-cell immunity occurs with aging, encompassing from cell function to the proportion of T-cell subsets. Despite extensive investigations, the mechanisms for and biological significance of such alterations are still largely unknown. Further studies are warranted to address these critical issues, in particular focusing on the organs that are frequently affected by aging (eg, lungs).

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