Rheumatoid Arthritis: A Role for Immunosenescence?

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Aging is accompanied by a progressive decline in the integrity of the immune system, a process known as immunosenescence. Pathological features typical of immune dysfunction in older adults, encompassing dysregulation of innate and adaptive immune responses, characterize rheumatoid arthritis (RA), an autoimmune disease whose incidence increases with age. Recent evidence suggests that certain features of immunosenescence, such as the decrease in T-cell generation and diversity, may contribute to the development of RA. Thus, physiological immunosenescence may render older adults susceptible to RA, and premature immunosenescence may contribute to the development of RA in young adults. In addition, other features of immunosenescence may result from the chronic immune stimulation that occurs in RA and lead to worsening of the disease. This article reviews the immunopathological features common to aging and RA and discusses the mechanisms by which immunosenescence may contribute to the development or progression of RA. **J Am Geriatr Soc 2010.**

Key words: immunosenescence; rheumatoid arthritis; aging; autoimmunity; CD28

A gradual deterioration of the immune system known as immunosenescence occurs with aging. The resulting failure to mount effective immune responses renders elderly individuals more susceptible to infections and to development of certain cancers. Aging is also associated with an increase in autoimmunity and in the incidence of certain autoimmune diseases, such as rheumatoid arthritis (RA).[1–4] Individuals with RA are immunocompromised,[5,6] and accumulating evidence suggests that premature aging of the immune system contributes to the pathogenesis of RA.[7–10] The progressive deterioration of the immune system with advancing age may therefore predispose to the development of RA late in life. In addition, the chronic immune stimulation characteristic of RA may itself age the immune system and lead to progression of the disease.[11–13] After a brief description of the regulation of the immune response and the pathogenesis of RA, this article discusses the mechanisms by which immunosenescence spawns autoimmunity and the evidence that immunosenescence is involved in the development or progression of RA.

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QUALITY CONTROL IN THE IMMUNE SYSTEM

The immune system can be broadly divided into an innate component, comprising natural killer (NK) cells, macrophages, dendritic cells (DCs), and complement factors, and an adaptive component, comprising T and B cells. The innate and adaptive immune responses act in concert to defend the body against infection. Innate immunity serves as an immunological sentinel poised to counteract pathogens in a rapid and nonspecific manner. Adaptive immunity, on the other hand, is a slow starter but, once activated, is exquisitely specific to the inciting antigen and results in the generation of immunological memory. The partition into distinct innate and adaptive responses is not black and white, because extensive crosstalk between the two systems occurs during an immune response. For instance, cytokines secreted by various immune cells modulate the activity of innate and adaptive immune cells. Moreover, the adaptive immune response springs into action only once it has received an alert from its innate counterpart, and cells of the innate system are summoned to eliminate incapacitated pathogens and to clear cell debris in the wake of an adaptive immune response.

Induction of a primary adaptive immune response usually relies on DCs of the innate immune system taking up pathogens and presenting the pathogen antigens to naïve T cells of the adaptive immune system (Figure 1). T-cell receptors (TCRs) on the surface of T cells recognize antigen only when it is bound to major histocompatibility complex (MHC) molecules on the surface of DCs or other antigen-presenting cells.[14] T cells that bear a TCR specific for the antigen presented are activated to proliferate (a process known as clonal expansion) and differentiate into effector T cells. Effector T cells include cytotoxic $CD8^+$ T cells, which destroy infected cells, and helper $CD4^+$ T cells,

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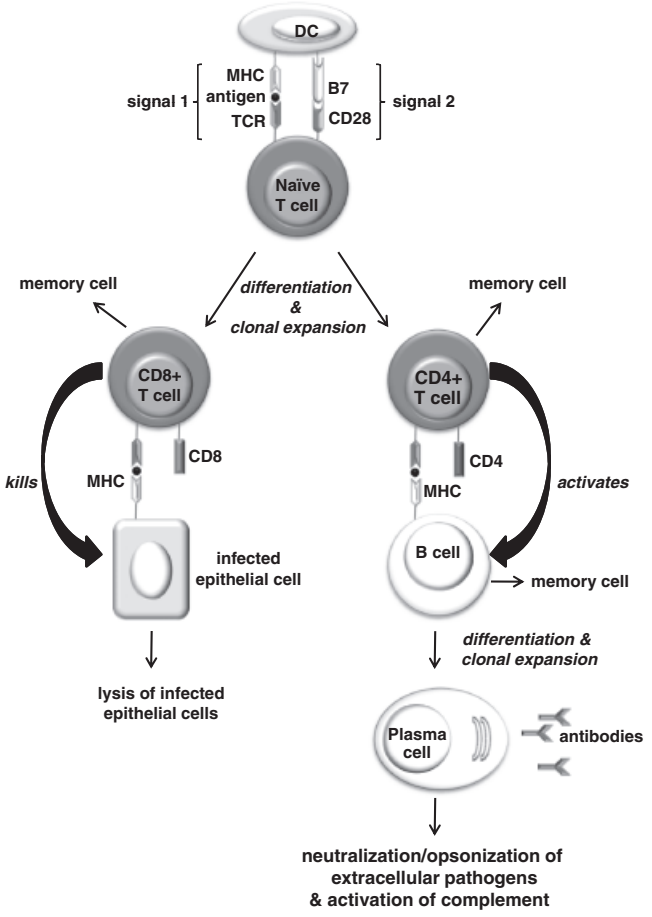

Figure 1. Induction of a primary adaptive immune response. Antigen-presenting cells such as dendritic cells (DCs) take up pathogens and present the pathogen antigens to naïve T cells. Those T cells that bear a T-cell receptor (TCR) specific for the antigen presented undergo clonal expansion and differentiate into $CD8^+$ and $CD4^+$ effector T cells. For this to occur, the T cell must receive two signals from the DC. The interaction between the TCR and the antigen–major histocompatibility complex (MHC) on the DC delivers Signal 1. Signal 2 is delivered upon binding of the B7 molecule on the DC to the CD28 receptor on the T cell. Cytotoxic $CD8^+$ T cells recognize the antigen–MHC complex on the surface of cells and are activated to destroy the infected cells. Naïve B cells bearing immunoglobulin receptors specific for the antigen internalize the antigen and present it to antigen-specific $CD4^+$ T cells, which in turn induce the B cells to clonally expand and differentiate into antibody-producing plasma cells. The antibodies produced target extracellular pathogens and their toxic products through the processes of neutralization, opsonization, or complement activation. A small proportion of activated T and B cells form long-lived memory cells, which are responsible for mounting a stronger, secondary immune response upon subsequent encounters with their cognate antigen.

which regulate other immune cells such as B cells. B cells can function as antigen-presenting cells and antigen-specific effector cells. B cells bearing immunoglobulin receptors specific for the antigen encountered take up the antigen and present it to antigen-specific $CD4^+$ T cells, which in turn induce the B cells to clonally expand and differentiate into antibody-producing plasma cells (Figure 1). The antibodies produced tackle extracellular pathogens by blocking a pathogen's access to cells (a process known as neutralization), by coating the pathogen and thereby targeting it for phagocytosis by innate immune cells (a process known as opsonization), or by activating the complement system, which promotes pathogen destruction. Whereas most activated T and B cells become effector cells, which die by apoptosis once the primary adaptive immune response is over, a few of them become long-lived memory cells, which persist in a quiescent state in the absence of their cognate antigen. If these memory cells later encounter their cognate antigen, they become activated and mount a secondary immune response that is faster and stronger than the primary immune response from which they arose.

To mount effective adaptive immune responses without attacking the body's own cells and tissues, the immune system must be able to distinguish self from non-self. Multiple mechanisms are in place to ensure such self-tolerance. Central tolerance mechanisms in the thymus—the site of T-cell differentiation and maturation—eliminate newly generated T cells that are strongly autoreactive.[14] Only those precursor T cells whose TCRs interact weakly with the self-peptide–MHC complex survive and mature, a process known as positive selection. Conversely, precursor T cells whose TCRs interact strongly with self-peptide–MHC complex are eliminated, and this is known as negative selection. Thus, central tolerance results in mature T cells that are self-tolerant and self-MHC-restricted. Peripheral tolerance, which relies largely on the interaction between T cells and DCs, imposes another level of control. Early findings gave rise to the two-signal model of activation, which laid the foundation for the concept that combined triggering of the TCR and one or more co-stimulatory receptors is needed for the full activation of naïve T cells (Figures 1 and 2). Recent findings suggest that the two-signal model applies to the activation of memory T cells, too.[15] The TCR delivers Signal 1 when the TCR binds to the antigen or self-peptide–MHC complex; Signal 2 is a co-stimulatory signal elicited primarily by the CD28 receptor on the T-cell surface when it binds to the B7 molecule on the DC surface. In the absence of infection, DCs do not express B7. Therefore, a mature T cell that interacts strongly with self-peptide (rather than a pathogenic antigen) in the periphery will receive Signal 1 but not Signal 2. This kills the T cell or renders it refractory to activation, a state known as anergy (Figure 2), although weak interaction between the TCR and self-peptide–MHC complex in the periphery is required for the survival and homeostatic replication of mature T cells, as discussed below.

DELUDED PERPETRATORS OF RA

As outlined, intricate checkpoints exist to ensure that adaptive immune cells attack invading pathogens while sparing the body's own cells; but in certain individuals these checkpoints fail. The convergence of genetic predisposition and environmental triggers can result in an immune system that mistakenly recognizes some of the body's own molecules as foreign. As a result, the immune system trains its destructive efforts on the body's own tissues and organs, leading ultimately to the development of autoimmune disease.

Given the extensive interplay between the adaptive and innate immune responses, it comes as no surprise that both

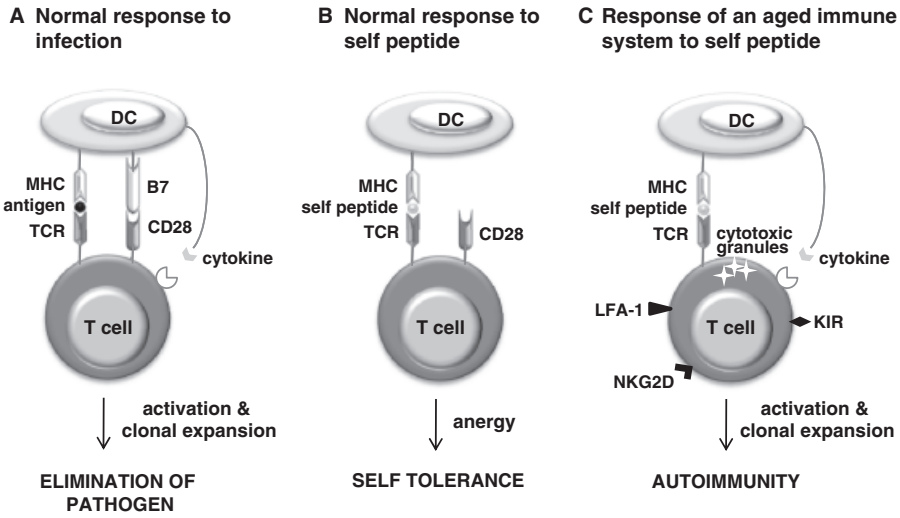

Figure 2. Breakdown of peripheral tolerance in aging. Normally, two signals are required for the full activation of T cells. (A) When a dendritic cell (DC) presents a pathogenic antigen to a T cell, the T-cell receptor (TCR) delivers Signal 1 when it binds to the antigen–major histocompatibility complex (MHC), whereas Signal 2 is delivered through the CD28 receptor on the T-cell surface when it binds to the B7 molecule on the DC surface. Secretion of cytokines from the DC provides further co-stimulatory signals. (B) In the absence of infection, DCs express no or very little B7. A T cell that interacts strongly with self-peptide (rather than with a pathogenic antigen) in the periphery will receive Signal 1 but not Signal 2. This kills the T cell or renders it refractory to activation, a state known as anergy. Although originally thought to be restricted to naïve T-cell activation, CD28 co-stimulation requirement has more recently been shown to extend to memory T-cell activation. (C) In the aged immune system, the T-cell repertoire is skewed toward recognition of self-peptide, probably as a result of multiple mechanisms acting on naïve and memory T cells. A predominance of memory cells also characterizes the aged T-cell repertoire. A subset of memory T cells have lost expression of CD28 and acquired expression of stimulatory killer immunoglobulin-like receptors (KIRs), NKG2D receptors, and lymphocyte function-associated antigen 1 (LFA1). De novo expression of these stimulatory receptors on memory $CD28^-$ T cells changes the way in which these T cells interact with their cellular environment, lowering the threshold for antigen-specific activation and even enabling activation independent of the appropriate antigen. Together with de novo expression of stimulatory receptors, development of cytotoxic granules endows $CD28^-$ T cells with certain natural killer cell functions, including cytotoxic killing. Furthermore, DCs secrete greater amounts of cytokines, and are able to induce T-cell proliferation, in response to self-peptides. These aberrations promote autoimmunity.

arms of the immune system play important roles in the initiation and perpetuation of RA. Several lines of evidence indicate the role of T cells in RA pathogenesis; RA is associated with genes encoding molecules involved in T-cell activity (e.g., *HLA-DR4, CTLA4, PTPN22*),[16] T-cell numbers are abnormally high in rheumatoid joints,[17] and T cells drive the development of arthritis in animal models of RA.[18] Evidence of B-cell involvement has come from the presence of B cells in rheumatoid joints,[19] the detection of autoantibodies that are specific to RA,[20] the ability of autoantibodies to exacerbate or induce arthritis in mice,[21,22] and the therapeutic efficacy of B-cell-depleting agents in patients with RA.[23] Innate immune cells, including DCs and macrophages, may contribute to the breach of self-tolerance in RA, by presenting arthritogenic antigens to autoreactive T cells, and to the destruction of joint cartilage, by producing proinflammatory and degradative mediators.[24–26]

Although characterized by inflammation, as well as cartilage and bone erosion, in the synovial joints, RA is unequivocally a systemic disorder and can affect multiple organs in addition to the joints. The mechanisms by which self-tolerance is initially breached in RA remain undefined but probably involve dysregulation of the immune system at a systemic level, followed eventually by immune targeting of the joints and hence the clinical manifestation of RA. The predilection of this systemically engendered autoimmunity for synovial joints has been attributed to the synovial microarchitecture, which facilitates immune responses, rather than to targeting of joint-specific antigens.[27] RA is a heterogeneous disorder, and disease etiology probably differs between distinct RA subsets. Smoking is the only accepted environmental risk factor for RA and is thought to trigger RA by inducing protein citrullination (a posttranslational modification in which arginine residues are converted to citrulline residues) in the lungs. Citrullination of proteins results in the formation of new epitopes, and thus, in certain individuals, the immune system may not recognize citrullinated proteins as self. In individuals whose genetic make-up is conducive to a strong immune response to citrullinated proteins, antibodies against citrullinated proteins develop; these are specific to RA and appear before the onset of disease.[28] Protein citrullination is known to occur in synovial joints as a result of inflammation, and systemic anticitrulline immunity elicited in the lungs may therefore go on to target citrullinated proteins in the joints, precipitating the joint pathology characteristic of RA.[28] Although less substantiated, a link between periodontitis and the development of RA has also been proposed. As with smoking, it has been postulated that periodontitis triggers RA by inducing an immune response against citrullinated proteins, because certain periodontal pathogens can citrullinate proteins found in periodontal tissue.[29]

AGING T CELLS

Age-Related Decrease in Generation of New T Cells

Like RA, aging is associated with dysregulation of the immune system. One of the most widely studied phenomena in the immunobiology of aging is the decline in generation of new T cells. Because the thymus is the site of T-cell differentiation and maturation, any changes in thymic function would be expected to affect the output of T cells. Indeed, thymic involution has long been considered instrumental in the age-related decline in T-cell generation.[30] Beginning approximately at puberty, progressive atrophy of the thymus involves profound changes in the structure and cytokine milieu of the thymus and results in a dwindling of T-cell production. Although thymic involution is a physiological process that starts early in life, the progressive decline in T-cell production eventually takes its toll on the immune system late in life (Figure 3).

An alternative explanation for the decline in T-cell generation may lie in a drop in the supply of T-cell progenitors to the thymus. Because progenitor cells derived from hematopoietic stem cells (HSCs) in the bone marrow must continually replenish immature T cells in the thymus, demise of HSCs could conceivably account for the decline in T-cell generation. Much of the investigation into this possibility has exploited the ability of telomeres—structures at the end of chromosomes that protect against chromosomal instability—to serve as markers of cellular division and ultimately cellular senescence. Telomere length is referred to as a "mitotic clock,"[31] because telomeres in dividing cells progressively erode until a limiting degree of shortening is attained and the cells permanently withdraw from the cell cycle. Demand for new immune cells, and hence for division of HSCs, is high. For this reason, HSCs express telomerase, an enzyme that attenuates telomere attrition; nevertheless, shortening does occur in HSCs as a function of age.[31] Furthermore, in HSC-transfer experiments in mice, HSCs derived from older donors repopulated the depleted lymphoid compartment of the host less effectively than did HSCs from young donors,[32] suggesting that HSC replication in old age is defective.

Nevertheless, total numbers of HSCs do not appear to differ between young and older people; rather, a shift in HSC subpopulations characterizes aging.[32] HSCs can be classified according to their fixed differentiation potential; lymphoid-biased HSCs give rise predominantly to lymphoid cells (e.g., T cells and B cells), myeloid-biased HSCs to myeloid cells (e.g., DCs and macrophages), and "balanced" HSCs to approximately 90% lymphoid and 10% myeloid cells. The different HSC subpopulations have distinct self-renewal capacities, such that lymphoid-biased HSCs have a shorter lifespan than do myeloid-biased HSCs.[32] Studies in mice have shown that the aged HSC compartment is depleted of lymphoid-biased HSCs and enriched in myeloid-biased HSCs.[33] The depletion of lymphoid-biased HSCs could translate to an insufficiency in the supply of precursor T cells and thus account for the age-related decline in T-cell generation.

Although evidence of an age-related defect in HSC replication is increasing, thymic involution is probably the primary cause of the age-related decline in T-cell output, because naïve T-cell repopulation after bone marrow transplantation is much more severely compromised in breast cancer patients aged 50 and older than in younger patients.[34]

Loss of T-Cell Diversity and Co-Stimulation Control: A Cause of Autoimmunity?

The decline in T-cell generation, invoked as central to immunosenescence, results in a reduction in T-cell diversity.[30] The T-cell system is under homeostatic control; generation of new T cells by the thymus, elimination of T cells by apoptosis, and self-replication of existing T cells in the periphery are interlinked processes that are finely counterpoised to maintain the total size of the T-cell system. Thus, a decline in generation of new T cells elicits a compensatory increase in proliferation of naïve and memory T cells in the periphery, a process that is accentuated in older people (Figure 3).[30] Such homeostatic proliferation of peripheral T cells is dependent on interaction between the TCR and the self-peptide–MHC complex that the specific TCR recognized during positive selection of the T cell in the thymus.[35,36] Animal studies have shown that naïve T cells adoptively transferred to T-cell-depleted mice undergo homeostatic, self-peptide-driven proliferation to fill the deficient lymphoid compartment of the host.[35] Not all T cells, however, are able to proliferate in this manner—a selectivity ascribed to differences in TCR affinity for the self-peptides inducing proliferation[35]—and it has thus been suggested that homeostatic proliferation involves competitive exclusion of TCRs.[37] It has been proposed that the increase in homeostatic T-cell proliferation synergizes with the decline in T-cell generation to reduce T-cell diversity and bias the immune system toward recognition of self (autoimmunity).[37]

Another way in which age-dependent changes in the T-cell compartment may promote an autoimmune diathesis is through changes in the receptors expressed by T cells. With the progressive decline in T-cell generation and the increase in antigenic load comes a shift toward predominance of memory T cells, many of which undergo changes in receptor expression and thereby in function. Most striking is the emergence in older people of a subset of memory T cells characterized by a contracted TCR repertoire and the loss of CD28 expression. The age-related loss of CD28 expression occurs in $CD4^+$ and $CD8^+$ T cells but is more common in $CD8^+$ T cells; $CD8^+$ and $CD4^+$ T cells apparently undergo the same phenotypic changes with aging, but $CD8^+$ T cells do so more rapidly.[30,38–40]

Despite CD28's role in ensuring appropriate activation of T cells,[15] $CD4^+CD28^-$ T cells retain their ability to produce lymphokines and appear to be autoreactive,[12,40] a phenomenon attributable to de novo receptor expression.[13] In addition to losing expression of a pivotal co-stimulatory receptor, $CD4^+CD28^-$ T cells acquire expression of other stimulatory receptors, such as killer immunoglobulin-like receptors (KIRs), NKG2D, and lymphocyte function-associated antigen 1 (LFA-1), that are not normally expressed on $CD4^+$ T cells. De novo expression of these receptors on $CD4^+CD28^-$ T cells changes the way in which these T cells interact with their cellular environment, lowering the threshold for antigen-specific activation and even enabling activation independent of the appropriate

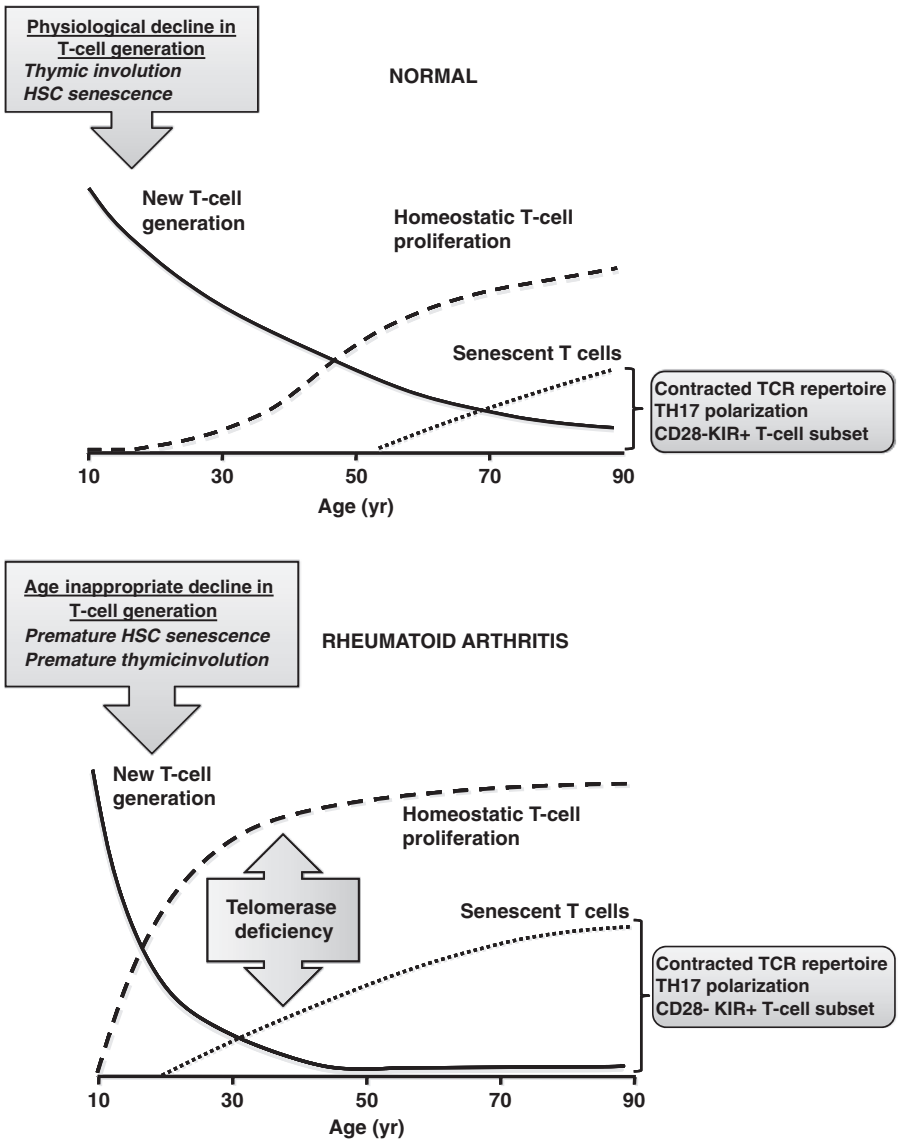

Figure 3. Accelerated decline in T-cell generation leads to premature emergence of senescent T cells in rheumatoid arthritis (RA). In healthy individuals, the generation of new T cells progressively declines. The homeostatic proliferation of mature T cells in the periphery compensates for this decline. With age, progressively fewer new T cells enter the T-cell compartment, and mature T cells must increasingly proliferate to fill the void. Eventually, the continually replicating mature T cells become exhausted and take on a senescent phenotype characterized by blunted replicative potential, contracted T-cell repertoire, T_H17 polarization, loss of CD28 expression, and de novo expression of stimulatory receptors such as killer-like immunoglobulin receptors (KIRs). In patients with RA, T-cell generation is age-inappropriately low, matching that of healthy individuals 20 to 30 years older; consequently, homeostatic T-cell proliferation is greater, resulting in premature senescence of T cells. In (normal) aging, the progressive decline in T-cell generation hinges on involution of the thymus but may also involve senescence of hematopoietic stem cells (HSCs). In RA, the age-inappropriate decline in T-cell generation, and hence T-cell senescence, has been ascribed to premature thymic involution or premature HSC senescence. Premature T-cell senescence has also been attributed to deficiency in telomerase activity in mature T cells. The line graphs are adapted from Figure 1 in Weyand and Goronzy 2002.[49]

antigen.[13] T cells that are prone to react with self-antigen and are no longer restricted by a co-stimulation requirement—the central tenet of peripheral tolerance—would skew the immune system toward an autoimmune propensity. Deficiency in co-stimulation may amplify this propensity by rendering $CD28^-$ T cells resistant to apoptosis.[41,42]

The role of $CD8^+CD28^-$ T cells in inflammation and autoimmunity is more complex. Loss of CD28 renders $CD8^+$ T cells unable to produce lymphokines and endows a certain subset of $CD8^+$ T cells with the ability to suppress the antigen-presenting function of DCs,[12] but de novo expression of NKG2D receptor expression enables a subset of $CD8^+$ T cells to kill cells in an antigen-independent fashion.[43,44]

How these $CD28^-$ T-cell populations arise is a matter of debate. One argument is that culpability lies in the compensatory proliferation of peripheral T cells that occurs with aging, because the homeostatic cytokine interleukin (IL)-15 is able to drive the generation and proliferation of $CD28^-$ T cells,[45] but mounting evidence suggests that

repeated antigenic stimulation of T cells may be responsible. In vitro, repeated exposure of T cells to the same antigen suppresses CD28 expression and telomerase activity;[11,12] in vivo, $CD28^-$ T cells have shorter telomeres than their $CD28^+$ counterparts.[13,46] The total antigenic load and the duration of exposure to specific antigens both increase with age. In particular, chronic viral infections are thought to put increasing pressure on the immune system by imposing a need for constant immune surveillance and thus clonal expansion of immune cells. Cytomegalovirus (CMV) is a virus that establishes chronic infection and is found in as much as 50% of the adult population and 90% of elderly individuals.[47] The presence of antibodies against CMV is associated with an increase in numbers of $CD28^-$ T cells—although whether this is simply a reflection of the increase in CMV infection with age, which is itself associated with the emergence of $CD28^-$ T cells, is unclear.[47] Nonetheless, a longitudinal study of CMV-seronegative patients who experienced a primary CMV infection after receiving a CMV-seropositive kidney graft showed that CMV-specific $CD4^+CD28^-$ T cells develop after recovery from CMV infection, independent of patient age.[48] Thus, it has been postulated that chronic CMV infection is a major contributor to immunosenescence.[47]

T-Cell Aging in RA: Cause or Consequence?

That T-cell aging is accelerated in RA has long been recognized. Still unclear is the extent to which such premature immunosenescence increases susceptibility to RA or is a result of RA, contributing to the pathology only once the disease is already established.

In patients with RA, thymic output of T cells is age-inappropriately low, matching that of healthy individuals 20 to 30 years older (Figure 3), and the TCR repertoire in naïve and memory T-cell populations is smaller.[7–10,37,49] The perturbation in T-cell homeostasis is detected early in RA and is not influenced by the duration of disease,[8,50] suggesting that a premature decline in T-cell diversity may predispose to the development of RA. It has been proposed that *HLA-DR4* alleles that are known genetic risk factors for RA confer susceptibility to RA in part by inducing premature immunosenescence,[51,52] and an increase in homeostatic proliferation of naïve T cells has been shown to predate the onset of RA.[27] Children with the autoimmune disease juvenile idiopathic arthritis (JIA) also exhibit abnormalities in T-cell homeostasis that are evident early in the disease and do not progress over the course of the disease (although the mechanisms by which such T-cell perturbations arise may differ between JIA and RA).[53,54] Because children are relatively antigen-inexperienced, the detection of T-cell perturbations in JIA suggests that immunosenescence can develop because of a primary defect that is independent of long-standing exposure to viral or other environmental antigens and lead to autoimmune disease.

Although the delay in reconstitution of naïve T cells after T-cell ablation and autologous HSC transplantation in patients with treatment-refractory RA provides some evidence that premature thymic involution occurs in RA,[55] the notion of HSC senescence as an alternative or additional explanation for the RA-associated reduction in T-cell generation is gaining momentum. Levels of circulating bone marrow–derived progenitor cells have been shown to be normally low in patients with RA, and the remaining progenitor cells had markedly shortened telomeres and defective proliferative responses.[7]

Premature telomere shortening in RA is seen in lymphocytes, too.[8,51] Although accelerated telomere shortening in T cells could reflect premature senescence of progenitor HSCs or greater homeostatic proliferation of T cells, another explanation has recently been advanced: that upregulation of the telomerase enzyme is faulty in RA. Naïve $CD4^+$ T cells from patients with RA were shown to be defective in inducing telomerase after priming with antigen and to be more susceptible to apoptosis, a defect that was reversed when telomerase activity was artificially restored to the cells.[50] Surprisingly, the survival-enhancing effects of telomerase were independent of telomere length; the recent identification of telomerase as a modulator of Wnt signaling[56]—a pathway important in promoting cell proliferation and survival—may help explain this observation. Regardless of the means, a reduction in the survival of naïve $CD4^+$ T cells in the periphery might place further demands on homeostatic proliferation and lead to greater remodeling of the T-cell repertoire. The deficiency in telomerase activity was found to be independent of the duration or severity of RA, suggesting that it may contribute to the development of RA.[50]

Although a decrease in thymic output and in naïve $CD4^+$ T-cell survival may confer susceptibility to RA, it is less clear how other features of immunosenescence—such as the emergence of memory $CD28^-$ T cells—affect RA. As in aging, clonally expanded $CD28^-$ T cells accumulate in RA. The focus in RA has been on $CD4^+CD28^-$ T cells, whose frequency in RA is high.[9] $CD4^+CD28^-$ T cells isolated from patients with RA secrete lymphokines without the need for co-stimulatory signals and appear to be autoreactive.[9,57]

So, how do these $CD28^-$ T cells arise in RA, and what role do they play? It could be that they arise because of the accelerated homeostatic proliferation and, through autoreactivity, contribute to the breach of tolerance that leads to the development of RA. Although recent findings suggest that the emergence of $CD4^+CD28^-$ T cells in RA does not correlate with the decline in thymic output,[52] it remains possible that the greater susceptibility of naïve RA $CD4^+$ T cells to apoptosis promotes the emergence of memory $CD4^+CD28^-$ T cells through homeostatic remodeling of the T-cell compartment.[50] The alternative argument is that the emergence of $CD28^-$ T cells is secondary to the development of RA. In this scenario, the generation of $CD28^-$ T cells stems from the chronic immune stimulation associated with RA in a manner analogous to the exhaustion of the immune system in older adults by CMV-mediated chronic stimulation of the immune system. Loss of CD27 (another T-cell co-stimulatory molecule), gain of cytotoxic potential, and evidence of antigen-driven clonal expansion are features of $CD4^+CD28^-$ T cells seen in RA and after primary CMV infection.[46,48] $CD4^+CD28^-$ T cells isolated from patients with RA react to CMV, and reactivation of latent CMV by RA-associated inflammation has been proposed as yet another explanation for the generation of $CD28^-$ T cells.[46,48] It could be that CMV-induced $CD28^-$ T cells promote

inflammatory disease by continuing to respond to persistent CMV antigens or by cross-reacting with autoantigens.

A further clue to the contribution of $CD28^-$ T cells in RA comes from the nature of their autoreactivity; $CD28^-$ T cells appear to react not to autoantigens known to trigger RA in animal models but to more-ubiquitous autoantigens, an observation suggested to indicate that, rather than contribute to the initial breach of tolerance, these cells promote more-severe and systemic disease.[9,13,46] In support of this concept, accumulation of $CD4^+CD28^-$ T cells is especially marked in patients with RA who have extraarticular inflammatory complications,[58] and $CD4^+CD28^-$ T cells are also independently associated with atherosclerotic disease.[59] $CD28^-$ T cells exhibit greater expression of the chemokine receptor CX3CR1, which could enhance their ability to infiltrate tissues.[13] In addition to reacting to tissue components by producing inflammatory cytokines, $CD4^+CD28^-$ T cells can directly damage tissue; by acquiring KIR and NKG2D receptors and cytolytic granules (e.g., perforin and granzyme B), $CD4^+CD28^-$ T cells take on cytotoxic effector functions typical of NK cells.[13] $CD28^-$ T cells may perpetuate and amplify intraarticular inflammation and tissue damage in RA, because expansion of the $CD28^-$ T-cell subset is detected not only in the blood, but also in the synovial tissue of patients with RA.[52]

How similar, then, are the changes in the T-cell compartment in aging and in RA, and what are the implications? The age-related decline in T-cell generation and diversity appears to hinge on involution of the thymus, possibly with some involvement of HSC senescence; a decline is also seen in RA, and there is evidence that it may stem from premature HSC senescence or thymic involution—but it may also involve apoptotic hypersensitivity of naïve $CD4^+$ T cells. Because it occurs early in the course of RA and is not associated with disease duration, it has been proposed that the decline in T-cell generation and diversity contribute to the development of RA. Emergence of $CD28^-$ T cells is also common to aging and RA, but whether this is a cause or a consequence of RA remains to be determined. Nevertheless, findings suggest that $CD4^+CD28^-$ T cells may contribute to the pathogenesis of RA by promoting inflammation and autoimmunity. The role of $CD8^+CD28^-$ T cells in RA is less clear, with different subtypes of $CD8^+CD28^-$ T cells shown to have opposing effects on inflammation and tissue destruction.[12,60]

THE CHANGING FACE OF NAÏVE $CD4^+$ T CELLS

Aging is also associated with a shift in the predominance of different activated naïve $CD4^+$ T-cell subsets. Antigen-activated naïve $CD4^+$ T cells can be divided into distinct T-cell populations based on the cytokines they produce. For many years, such subdivision was thought to be limited to T-helper (T_H)1 $CD4^+$ T cells and T_H2 $CD4^+$ T cells, with a high T_H1 to T_H2 ratio favoring T-cell-mediated inflammation and a low one favoring antibody-mediated responses. An expanded cast of T_H cells has since been revealed, and the spotlight is currently on T_H17 cells. Although it has long been felt that T_H1 cells (producers of interferon gamma) play a part in T-cell-mediated autoimmunity, recent findings suggest that T_H17 cells (producers of IL-17) are of prime importance in certain autoimmune diseases. RA is one such autoimmune disease; overexpression of IL-17 in the knee joint induces RA-like features in mice, IL-17-positive cells are detected in synovial biopsies from patients with RA, and neutralizing antibodies against IL-17 ameliorated disease in mouse models of RA and in patients with RA in Phase I clinical trials.[61] Studies in mice showed that aging was associated with a defect in differentiation of $CD4^+$ T cells into T_H1 and T_H2 cells, whereas differentiation into T_H17 cells remained unaffected.[62] Not only were T_H17 cells more prevalent, but also the amount of IL-17 that each T_H17 cell produced was greater in aged mice. It could be that this skewing of the $CD4^+$ T-cell response toward a T_H17 bias promotes RA-associated inflammation and joint pathology in older adults, but still unclear is the extent to which these findings can be extrapolated to aging in humans, as well as the relative importance of different T_H subsets in RA.

OVERREACTING MEMORY B CELLS

As in the T-cell compartment, homeostasis in the B-cell compartment appears to be actively maintained. Although numbers of mature peripheral B cells do not decrease with age,[63] studies in mice suggest that the generation of new mature B cells decreases with age but that this is associated with an increase in B-cell longevity, such that total B-cell numbers remain stable.[64] Nevertheless, B-cell function is markedly altered in aging. B-cell responses to primary antigenic challenge decrease with age.[65,66] This reduction in overall antibody levels is probably a corollary of the decrease in B-cell generation; the decline in T-cell helper activity also plays an important role, because the $CD4^+CD28^-$ T cells that prevail in aging no longer express CD40,[40] a ligand required for the production of antibodies by naïve B cells.

In contrast to total antibody levels, autoantibody levels increase with advancing age—and memory B cells formed before the onset of immunosenescence are thought to be the culprit. Two scenarios have been proposed that might explain the late appearance of autoantibodies.[67] One possibility is that autoantibodies are present in young, healthy individuals but that tolerance mechanisms keep their levels low; impairment of tolerance with age (as discussed above) would allow autoreactivity to develop. Alternatively, the initial B-cell response may have targeted a foreign, pathogenic antigen, and late-onset autoreactivity may then arise owing to cross-recognition of a self-antigen that is newly exposed (because of tissue damage that accumulates over time) or newly formed (neo-antigens, because of inflammation-mediated modification of a self-peptide). Exposure of normally sequestered self-antigens, owing to tissue damage or cartilage destruction, is important in the pathogenesis of RA.[68–70] In addition, generation of neo-antigens through inflammation-mediated citrullination of self-peptides and ensuing autoantibody targeting of the citrulline-modified peptides are increasingly recognized as key events in the pathogenesis of RA.[20,70,71]

DCS: WHEN THE REGULATORS FAIL TO REGULATE

The aberrations that typify immunosenescence do not involve changes solely in the adaptive arm of the immune system. Innate immune cells, including DCs, macrophages, neutrophils, and NK cells, also become dysregulated with

age.[72] Of primary interest in the context of this review are DCs, owing to their dual role as presenters of antigen and inducers of self-tolerance.

The finding that DC-depleted mice spontaneously develop autoimmunity underscores the importance of DCs in maintaining self-tolerance,[73] although the recent discovery of functionally distinct DC subsets—plasmacytoid (pDC) and myeloid (mDC)—has hinted at greater complexity within the DC network. Evidence suggests that these two DC subsets exert different effects on the immune response and autoimmunity. pDCs can induce the differentiation of B cells into plasma cells and could therefore promote autoantibody production, but they appear also to play a role in the induction of tolerance.[24] Consistent with a tolerance-inducing role for pDCs in inflammatory arthritis, selective pDC depletion in mice exacerbated articular pathology and enhanced the T- and B-cell autoimmune responses against the self-antigen type II collagen.[74] mDCs are primarily proinflammatory,[24] and exogenously activated and antigen-pulsed mDCs have been shown to induce inflammatory arthritis in mice through the priming of autoreactive T cells and the production of proinflammatory cytokines.[25]

As discussed, clonally expanded $CD28^-$ T cells in older individuals lose their requirement for CD28 co-stimulation.[40] Presentation of arthritogenic self-antigens by DCs to autoreactive $CD4^+CD28^-$ T cells could therefore contribute to the development of RA in older adults. In addition, changes in the levels and activity of DCs themselves could skew the immune response in older individuals. Although a decrease in tolerogenic pDCs or an increase in proinflammatory mDCs could favor the development of RA, such putative shifts in DC subpopulation with age have not yet been definitively demonstrated.[75] In contrast, evidence of functional impairment of DCs in aging and its possible contribution to autoimmunity is substantive. DCs from older individuals seem to react more strongly than DCs from young individuals to apoptotic cells and to an intracellular self-antigen: human deoxyribonucleic acid (DNA).[76] Moreover, the DNA-activated DCs from older individuals induced T cells to proliferate, whereas the less-activated DCs from young individuals were unable to do so. DC function is not restricted to antigen presentation and cytokine secretion; it also involves the clearance of cell debris and apoptotic cells through phagocytosis. Efficient clearance of apoptotic cells is important in limiting inflammation and preventing autoimmunity; if left in the tissue, apoptotic cells undergo secondary necrosis, resulting in release of proinflammatory mediators and intracellular self-antigens. DCs derived from older individuals were shown to have impaired phagocytic capacity, a defect that could result in the accumulation of apoptotic cells.[77] Thus, aberrations in DC function with age may result not only in greater reactivity to self-antigens, but also in greater exposure to self-antigens.

CYTOKINES: STOKING THE SYNOVIAL INFLAMMATION

Aging and RA are both considered states of chronic inflammation. Serum levels of the proinflammatory cytokines tumor necrosis factor (TNF) and IL-6, important players in the pathogenesis of RA, are high in older adults.[78] The chronic, systemic upregulation of a cluster of proinflammatory cytokines, including TNF and IL-6, in older adults is known as "inflamm-aging"[78] and is thought to form part of the so-called immune-risk phenotype, a collection of immune-related parameters that are predictive of morbidity and mortality in older adults.[79]

TNF and IL-6 have pleiotropic functions in the immune system; accordingly, they are involved in the autoimmune responses and the tissue destruction that underpin RA. TNF induces matrix metalloproteinase release from leukocytes, driving tissue destruction; adhesion-molecule expression on endothelial cells, promoting infiltration of inflammatory cells into the synovium; angiogenesis and synovial-fibroblast hyperplasia, which support pannus formation; and T-cell activation, resulting in perpetuation of autoimmune responses.[26] IL-6 modulates autoimmunity by promoting T-cell activation and antibody production. It also drives tissue destruction by activating macrophages and osteoclasts, which mediate cell-matrix degradation and bone resorption, respectively.[26,80] The therapeutic efficacy of biologic agents targeting TNF and IL-6 has borne out the importance of these cytokines in inflammatory arthritis. Blockade of TNF is now the standard treatment for RA, and an antibody targeting the IL-6 receptor provides some therapeutic benefit.[80,81]

The increase in TNF and IL-6 levels with advancing age would thus be expected to promote multiple processes involved in the pathogenesis of RA. In addition to enhancing the recruitment and activation of immune cells, the increase in circulating TNF in older adults may reduce the expression of CD28 and the activity of telomerase in T cells.[82] Thus, inflamm-aging could potentially augment the synovitis and the systemic autoimmunity associated with RA.

But what is the source of these high levels of cytokines in older adults? Although macrophages, innate effector cells central to the synovitis in RA, are generally thought to be the primary producers of these cytokines,[26,78] aging is associated with a decrease in macrophage production of proinflammatory cytokines.[83,84] In contrast, senescence of fibroblast and epithelial cells is associated with a change in the secretory profile of these cells, involving an increase in secretion of multiple growth factors, adhesion molecules, and proinflammatory cytokines, including IL-6.[85] In addition, aging is associated with low-grade inflammation in adipose tissue, and TNF and IL-6 expression has been shown to be greater in adipocytes from aged mice than from young mice.[86]

CONCLUSIONS

Longer life expectancy means that research into the immunobiology of aging is of increasing importance. Aging has a profound effect on the immune system, and older adults are more susceptible to infections and cancer, as well as to certain autoimmune diseases, such as RA. Pathological features typical of immune dysfunction in older adults, including loss of T-cell diversity and dysregulation of T-cell reactivity, high levels of autoantibodies and proinflammatory cytokines, and perturbation of DC activation, characterize RA (Figure 4). The greater autoimmunity associated with aging of the immune system could underpin the systemic breach of tolerance that leads to RA, a notion in

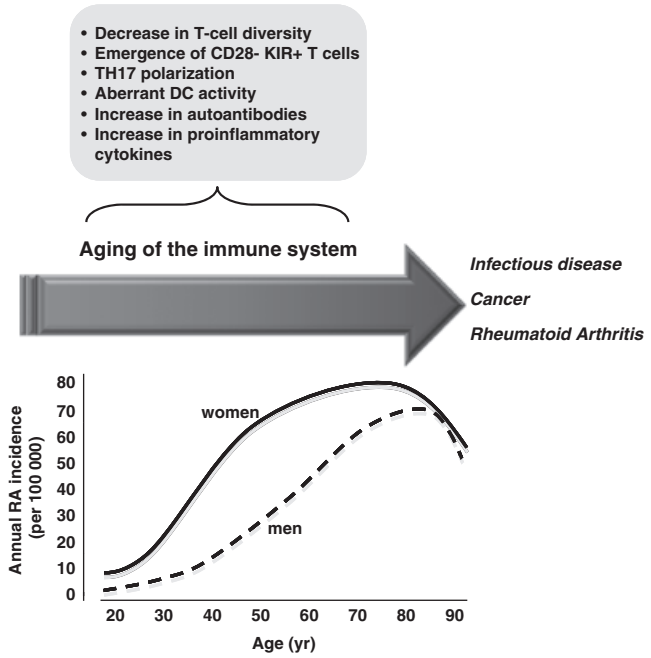

Figure 4. Aging of the immune system increases susceptibility to disease. The arrow indicates the progressive decline in integrity of the immune system with age. Such aging of the immune system, or immunosenescence, involves a decrease in T-cell generation and diversity and an increase in levels of proinflammatory cytokines and autoantibodies. Loss of peripheral T-cell tolerance, owing to dysregulation of dendritic cells (DCs) and T cells, may also be involved. An increase in incidence of several diseases, including infectious disease, cancer, and rheumatoid arthritis (RA) parallels the decline in immune function. The line graph of RA incidence is a schematic approximation of the general trend in incidence with age. That RA incidence is generally higher in women, increases progressively with age, and decreases in the oldest age groups is a finding consistent across multiple studies; the late decrease is observed earlier in women than in men.[1–4]

keeping with the documented increase in incidence of RA in older adults; a defect that results in premature aging of the immune system might also predispose to the development of RA in young adults. Alternatively, certain features of immunosenescence might be the result, rather than the cause, of RA. Even so, immunosenescence arising secondary to the development of RA might perpetuate and amplify the disease, by augmenting systemic autoreactivity or synovial joint inflammation, although not all aspects of immunosenescence favor the development of RA,[60,84] and differences in clinical features between early-onset and late-onset RA have been documented.[87] A clear picture of the relationship between immunosenescence and RA is still being sought.

Like RA, aging can be considered a heterogeneous, polygenic disorder. Further insight into the links between immunosenescence and RA might enable the identification of older individuals who are at risk of developing RA. Subpopulations of elderly individuals with specific immunosenescent parameters could potentially be screened for predictors of RA; although reliable predictors of the development of RA remain to be attained, anti-CCP antibodies[88] appear promising, and other prognostic biomarkers are being developed. In addition, unraveling the mechanisms underlying immunosenescence should shed light on the pathogenesis, and inform strategies for the treatment, of RA in young adults. Several strategies aimed at reversing T-cell senescence are close to or in clinical trials[89] and could potentially present a novel approach to the treatment of RA.

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