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Immune aging and autoimmunity

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Abstract

Age is an important risk for autoimmunity, and many autoimmune diseases preferentially occur in the second half of adulthood when immune competence has declined and thymic T cell generation has ceased. Many tolerance checkpoints have to fail for an autoimmune disease to develop, and several of those are susceptible to the immune aging process. Homeostatic T cell proliferation which is mainly responsible for T cell replenishment during adulthood can lead to the selection of T cells with increased affinity to self- or neoantigens and enhanced growth and survival properties. These cells can acquire a memory-like phenotype, in particular under lymphopenic conditions. Accumulation of end-differentiated effector T cells, either specific for self-antigen or for latent viruses, have a low activation threshold due to the expression of signaling and regulatory molecules and generate an inflammatory environment with their ability to be cytotoxic and to produce excessive amounts of cytokines and thereby inducing or amplifying autoimmune responses.

Keywords

Age; Autoimmunity; T cell memory; T cell homeostasis; CD45RA T effector cells

Introduction

In the current paradigm, autoimmune diseases develop when a memory T and B cell response to a self-antigen is established. Self-reactive naive T cells in the peripheral repertoire are generally of low affinity since the repertoire has been purged from T cell receptors that recognize self-peptides with high affinity. Induction of memory to such low affinity antigens is more difficult than a response to an exogenous antigen and requires a unique setting or coincidental co-occurrence of several cofactors. Models have been developed to explain how this barrier can be overcome, most notably the model of molecular mimicry [1]; an exogenous antigen activates T cells that cross-react on self-antigens; once primed, memory or effector T cells are able to entertain an autoreactive response and mediate an autoimmune disease based on their low T cell receptor activation thresholds and

the independence of costimulatory requirements. Other models have implied that suboptimal signal strength of autoreactive T cell responses can be overcome by environmental triggers that induce excessive costimulatory signals and activation of antigen-presenting cells [2, 3].

The general premise of these models is that an adaptive immune response to exogenous antigens is more easily induced than to endogenous antigen. Intuitively, one would therefore predict that the onset of autoimmune diseases declines with age; however, the opposite is correct; incidence of many autoimmune diseases increases although the ability to produce an adaptive immune response to new antigens declines and the ability to maintain memory T cell responses to control persisting infections decreases. Mortality and morbidity during the annual influenza epidemics increase in individuals older than 50 years, in particular in the very elderly population [4]. Influenza vaccinations are only marginally protective; in most studies, only 10–40 % of vaccinated individuals older than 60 years are able to yield a larger than fourfold increase in antibody titers, depending on age, vaccine strain, vaccine dose, and adjuvant [5, 6]. Similarly, the memory response to chronic infections vanishes with age; a classical example is the response to *Varicella zoster* virus that establishes latency during childhood with chickenpox infection. Reactivation is increasingly seen after the age of 50, manifesting as herpes zoster, and continues to occur more frequently with advancing age [7]. In spite of this general decline in immunocompetence, the propensity for autoreactivity increases with age [8]. Low-titered autoantibodies, including rheumatoid factor and antinuclear antibodies, have long been known to be a frequent finding in the elderly and are not necessarily associated with disease [9, 10]. More importantly, age is a risk factor for several autoimmune diseases in which adaptive immunity plays a central role. The classical example is giant cell arteritis which is a T cell-dependent granulomatous vasculitis of mid- and large-size vessels [11]. The vasculitis does not manifest before the age of 50 years; its annual incidence continues to increase up to the eighth decade in life. Several other autoimmune diseases also occur in the second half of life and/or peak in the elderly, e.g., rheumatoid arthritis [12]. Of interest, the immune system in these patients is not younger than their chronological age [13, 14]; on the contrary, it appears to be pre-aged by more than 20 years when biomarkers known to be associated with immune aging are examined.

Basic principles of T cell memory aging

T cell homeostasis

The concept of autoimmune disease as a consequence of immune aging is certainly counterintuitive. What are the basic changes in the peripheral T cell repertoire that could account for an increased susceptibility for autoimmune disease with aging? One of the most striking findings in immune aging is the decline in regenerative thymic capacity [15]. Thymic activity starts to decline after puberty. In humans, frequencies of T cell receptor excision circle (TREC)-positive cells are the major means to estimate thymic activity [16, 17]. How long TRECs can persist in nondividing individual cells is unknown, and TREC frequencies therefore tend to overestimate thymic activity [18]. TREC frequencies exponentially decline to minute levels in the sixth decade of age, suggesting that thymic activity is at best minimal [19]. Studies determining the ability to respond to T cell depletion with increases in TREC frequencies are more informative and have shown that only few

individuals after the age of 40–50 years are able to rebuild T cell repertoires through thymic generation of new T cells [20, 21]. There is no evidence that this is different in patients with autoimmune diseases of elderly onset. On the contrary, the frequency of TREC-positive T cells is age-disproportionately reduced in patients with rheumatoid arthritis [22], suggesting that disease is not caused by the generation of autoreactive T cells that escape thymic selection in the elderly thymus.

Homeostatic proliferation is the major means to generate new T cells during adult life [23]. Frequencies of proliferating naive and memory T cells are relatively stable throughout adulthood up to older age suggesting that even in the young adult most of the replenishment is done through homeostatic proliferation rather than thymic production. Our own studies of the frequencies of Ki67-positive cells [19] as well as turnover studies after metabolic deuterium labeling [24] have failed to document an increase in constitutive proliferative rates. Only after the age of 70–75, proliferative rates start to increase likely due to increased T cell loss rather than decreased thymic production. Studies in nonhuman primates have confirmed these general concepts [25].

Homeostatic proliferation is sufficient to compensate for T cell loss, and at least based on peripheral blood counts no frank lymphopenia is observed, with the exception of the very elderly. However, it is undetermined whether homeostatic proliferation over many years biases the repertoire towards higher affinity recognition of self-antigens. Naive T cell homeostasis is dependent on T cell receptor signaling; in genetically manipulated mouse models of modified T cell receptor or proximal signaling molecules expression or deletion of corresponding MHC ligands, T cell survivals were shortened [26–28]. At least in murine models of lymphopenia-induced proliferation, T cells with higher affinity T cell receptors to self-peptide MHC ligands undergo faster proliferation than do lower affinity T cells [29, 30]. Peripheral selection over the many years that humans survive thymic demise could, therefore, explain increased receptor self-reactivity with age [31, 32]. In addition to T cell receptor signaling, increased sensitivity to growth factor signals, such as IL-7 could bias the peripheral repertoire. In computer simulation of homeostatic proliferation over several generations, even small differences in growth factor sensitivity resulted in clonal dominance (data not shown). Ultimately, both mechanisms would be predicted to lead to a contraction in repertoire diversity. In humans, clonal sizes of individual naive T cells seeded in the young are likely too large to permit generating frank holes in the repertoire with age; with about 10^{11} naive CD4 T cells and 10^6 different T cell receptor β chains and about 100 different $\alpha\beta$ chain combinations for each β chain, clonal size of each naive T cell can be estimated at about 1,000 [33]. However, homeostatic proliferation over time may result in increasing diversity of clonal sizes even within the naive T cell population with hyperresponsive autoreactive T cells present in frequencies that are high and reach the frequencies of memory T cells. Estimates in repertoire diversity studies in patients with rheumatoid arthritis suggest that this may in fact be the case in patients with rheumatoid arthritis [34]. The advent of massive parallel T cell receptor sequencing will allow testing this prediction in general for the elderly [35, 36].

As a functional consequence of lymphopenia-induced homeostatic proliferation, naive T cells in murine models differentiate into a memory-like state [37–39]. Cells change their

expression of homing receptors, their requirement for CD28 costimulation is diminished and they acquire effector functions such as rapid cytokine production upon restimulation. In contrast to normal T cell activation, they do not express activation markers such as CD69 and CD25. Whether the lymphopenia-induced transition into memory-like T cells also occurs with compensatory homeostatic proliferation in elderly adults who do not have sufficient thymic activity is unclear. Frequencies of memory T cells increase with age, however, this may reflect cumulative antigen-specific stimulation over lifetime rather than a consequence of homeostatic proliferation-associated differentiation. Such a differentiation may require multiple divisions, such as seen in lymphopenic situations in contrast to the few divisions that are needed to replenish steady-state loss. However, episodic lymphopenia is not uncommon in normal life, not only after medical immunosuppressive or chemotherapeutic interventions but also as a side-effect of certain viral infections [40]. If homeostatic proliferation plays a significant role in memory cell generation with age, one would expect age-associated sharing of T cell receptor sequences in the naive and memory cell compartments in conjunction with increasing and not decreasing diversity of the memory compartment. We have observed increased T cell receptor sequence sharing in the very elderly, however, in the context of declining diversity suggesting that the sharing was a consequence of memory T cells reacquiring naïve phenotypes rather than naive T cells differentiating into memory-like cells [41]. Again, the advent of deep sequencing should allow addressing this question.

Accumulation of end-differentiated effector T cells

In addition to thymic demise and the associated change in mechanisms that govern T cell generation and homeostasis, shifts in functional T cell subset distributions are a consistent age-associated finding [42, 43]. Diminution of naive T cells is interpreted as cumulative antigenic stimulation in the absence of de novo generation but may also include homeostatic proliferation-induced phenotypic transitions. Reduction in naive T cell numbers is more prominent for CD8 and CD4 cells [44]; in fact, many elderly individuals maintain a sizable naive CD4 compartment. Within the memory population, the accumulation of end-differentiated effector T cells is most striking, again much more so for the CD8 than the CD4 compartment. T cells lose the expression of CD28 and CD27 and regain the expression of CD45RA [45]. Such end-differentiated CD45RA effector T cells are expanded at the expense of central memory and normal effector cells and comprise more than 50 % of the CD8 compartment in the majority of elderly individuals. Individuals with expansion of CD4⁺CD28⁻CD45RA⁺ cells can also be found, however, such a finding is more selective and not a general feature of the elderly population, suggesting that factors other than age are essential for the expansion of end-differentiated CD4 effector T cells and that these factors are infrequent in a general population [46]. The accumulation of end-differentiated CD28⁻ effector cells is usually oligoclonal and several dominant clonotypes can be identified. The oligoclonality is indicative of chronic antigenic stimulation underlying this expansion, and, indeed, the size of the CD28⁻ T cell compartment is higher in individuals with chronic cytomegalovirus (CMV) infections than in uninfected individuals [47]. Furthermore, CMV-specific T cells in many adults have at least, in part, the phenotype of end-differentiated CD8 T cells [42]. CMV, more than other herpes viruses, has a unique position in directing the expansion of this subset, the reasons for which are unknown. However, the T cell subset

includes T cell receptors specific for other viral antigens, T cell responses to autoantigens have also been described [48, 49].

In addition to chronic antigen-specific stimulation, changes in growth behavior may contribute to the expansion of these oligoclonal populations. In murine models, a considerable fraction of age-associated oligoclonal T cell population does not appear to derive from antigen-specific stimulation by exogenous antigens [50]. In humans, the expansion of the subset of end-differentiated effector cells can present as large granular lymphocytosis or even leukemia [51]. Phenotypically and functionally, these large granular lymphocytes are not different from other end-differentiated effectors cells; the diagnosis essentially relies on the dominance of a single T cell receptor clonotype. These T cells may have an increased responsiveness to certain growth factors such as IL-15 [52]. Defects in apoptosis may also be important for large granular lymphocyte survival and accumulation and have also been described for normal oligoclonal CD28⁻ populations [53]. Of interest to note, large granular lymphocyte leukemia is frequently associated with autoimmune manifestations and treatment is that of immunosuppression by methotrexate and cyclosporine and not chemotherapy.

Even although end-differentiated CD28⁻ T cells may result from chronic viral stimulation, they do not show any evidence of clonal exhaustion. T cells have all the attributes of activated effector cells including chemokine receptor profiles reminiscent of effector cells, cytotoxic ability through the expression of perforin and granzyme B, high production of cytokines and low threshold to respond to activating stimuli [54, 55]. Cytotoxic ability is not limited to CD8 cells, but is also found in CD4 cells. Negative regulatory receptors characteristic of clonal exhaustion, such as PD-1 and BTLA, are not expressed [56]. Instead, MHC class I-recognizing regulatory receptors that are usually expressed on NK cells are frequently found, including different killer immunoglobulin-like receptors (KIR), the immunoglobulin-like transcript CD85j, and NKG2D [57–60]. The pattern of KIR expression is consistent with a clonal progeny of a T cell that is diversified in KIR expression with clonal expansion [61]. NKG2D as well as stimulatory KIRs have been implicated in the clonal expansion of end-differentiated T cells as well as LGL leukemia cells [62]. These receptors may also circumvent the need for antigen recognition and lead to the activation of these cells even in the absence of a stimulating antigen.

T cell aging and autoimmunity

Homeostatic proliferation as a risk factor for autoimmunity

While homeostatic proliferation is essential to maintain a functional T cell system for many years after the regenerative power of the thymus has ceased, it may also be hazardous for the host (Fig. 1) [63]. Lymphopenia has been shown to be a risk factor for autoimmunity in several animal models; this risk could be attributed to the activity of homeostatic cytokines. Lymphopenia is important for the pathogenesis of autoimmune diabetes mellitus in the NOD mouse, as well as the biofeeding rat [64, 65]. Disease development in the NOD mouse is dependent on IL-21-mediated homeostatic expansion of islet-specific T cells. Calzascia et al. [66] demonstrated that β -islet cell self-reactive CD4 T cells were not sufficient and IL-7-mediated homeostatic proliferation was necessary to induce overt diabetes mellitus.

Adoptive transfer of autoreactive T cells only transferred disease with the provision of endogenous or exogenous IL-7. In our own studies, lymphopenia also appeared to contribute to arthritis development in the SKG mice. SKG mice are lymphopenic and have increased homeostatic proliferation, possible to compensate for defective thymic generation. The arthritis development in this model is dependent on IL-6 production, which has generally been interpreted as evidence for the role of Th17-producing cells in disease pathogenesis [67]. Alternatively, the function of IL-6 as a homeostatic cytokine, in particular for naive CD4 T cells can also play an important role for disease pathogenesis in the SKG mice.

The model of lymphopenia-associated autoimmunity appears to be relevant for human disease. The classical example is the immune reconstitution inflammatory syndrome (IRIS) where the reconstitution of a functional T cell compartment upon institution of highly active antiretroviral therapy (HAART) in HIV-infected patients is associated with a systemic inflammatory disease [68]. The inflammation is transient; however, in the long-term, many patients with HIV infection, even if successfully treated, develop premature age-associated multi-organ diseases that are attributed to an accelerated aging of the immune system. Evidence for the relevance of this model has also been provided for several autoimmune diseases, in particular rheumatoid arthritis (RA), and may be one of the mechanisms how age is a risk factor for autoimmune disease [14, 69]. In epidemiological studies of rheumatoid arthritis, age is an important risk factor for both disease onset as well as disease severity [12, 70]. Even more significantly, accelerated immune aging by more than 20 years is one of the major immunological phenotypes of the adaptive immune system in RA patients. Several findings have provided indirect evidence that the accelerated aging is secondary to an increased replicative history to compensate for lymphopenia. In T lymphocytes from RA patients, telomeres are shortened [22]. Telomeric erosion is seen in naive T cells as well as in memory T cells, suggesting that telomeric erosion does not reflect the expansion of the few effector cells that are involved in the disease process, but is a global phenomenon in the lymphoid system in RA patients. Moreover, frequency of TRECs is decreased in RA T cells, which either indicates accelerated degeneration of thymic activity with age or a history of increased T cell turnover that has led to the dilution of existing TREC-expressing T cells [22]. Finally, T cell receptor diversity is decreased in RA patients, again consistent with the model that patients with RA have undergone a period of increased homeostatic proliferation, which caused a peripheral selection of a contracted repertoire [34].

Several mechanisms appear to work in concert, or, alternatively, different mechanisms may be functioning in different patients, but generate the same end result of accelerated immune aging in RA. Hematopoietic stem cells in patients with RA have shortened telomeres, suggesting that immune aging is already evident prior to differentiation into lineages [71, 72]. Possibly, such a stem defect contributes to defective generation of T cells already at an earlier age, which could explain the reduced TREC frequency and also the repertoire contraction seen in RA patients. Hematopoietic stem cells are known to switch commitment from lymphoid lineages to myeloid lineages with age [73]. This switch appears to be cell inherent; accelerated hematopoietic stem aging may therefore compromise lymphoid generation. At the level of T cells, naive T cells from RA patients have an increased propensity to undergo apoptosis. Fujii et al. [74] identified defective induction of telomerase

activity due to reduced hTERT transcription in RA patients as the underlying cause. Reduced telomeric activity was not only associated with telomeric erosion but also increased the susceptibility to undergo apoptosis during proliferation independent of telomere lengths. Increased cell death, possibly in conjunction with defective de novo generation, will induce increased homeostatic proliferation to compensate for or to prevent lymphopenia. The same outcome can also result from defective DNA repair mechanisms other than telomerase. T lymphocytes from RA patients have reduced expression of members of the MRN complex and the kinase, ataxia telangiectasia mutated (ATM), which function in concert to repair DNA double-strand breaks [75]. Reduced expression of this repair complex has functional consequences. T cells from RA patients have significantly more DNA damage as determined by the DNA electrophoresis at the single-cell level compared to healthy age-matched controls. The increased DNA damage is associated with increased apoptosis rates. The primary defect appears to be a decreased expression of ATM; ATM transfection of RA T cells restored the expression of MRN, as well as rendered T cells more resistant to apoptosis.

The functional consequences of these defects all converge in lymphopenia compensated by increased homeostatic proliferation which, then again, accelerates immune aging. Increased homeostatic proliferation could favor the selection of autoreactive T cells and the differentiation into memory-like cells and thereby provide a foundation for overcoming peripheral tolerance mechanisms and inducing an autoimmune disease.

End-differentiated effector T cells as a key player in autoimmune inflammation

Based on clinical correlations, the accumulation of end-differentiated effector cell populations that normally occur with aging and is in part due to chronic viral stimulation appears to contribute to autoimmune injury. Increased frequencies of end-differentiated CD28⁻ T cells were first described in patients with RA who had severe disease and often extraarticular manifestations [76]. The finding was consistent with the clinical observations that patients with the large granular lymphocyte syndrome, in addition to the classical autoimmune manifestation of neutropenia, frequently express a rheumatoid factor and had inflammatory synovitis, sometimes even classical rheumatoid arthritis. Conversely, a subset of patients with rheumatoid arthritis who develop neutropenia do not have classical Felty syndrome, but large granular lymphocytes underlying the neutropenia. These studies suggested that the large granular lymphocyte syndrome may only be the tip of the iceberg of effector T cell-induced autoimmunity and that, in a broader context, accumulated end-differentiated effector cells are contributors to inflammatory tissue injury. In early RA, frequencies of CD28⁻ cells are prognostic predictors for the likelihood to develop erosive disease, supporting the notion that these cells are actively involved in the RA disease process [70]. Expansion of end-differentiated CD28⁻ cells in the peripheral blood is also characteristic of patients with ANCA-associated vasculitides [77]. In active vasculitis, peripheral blood frequency of these cells decline, which has been interpreted as the cells homing to the inflamed tissue. A gene-expression signature of CD8 effector memory T cells predicts outcome in several autoimmune diseases including ANCA-associated vasculitides and systemic lupus erythematosus [78].

Obviously, such end-differentiated cells have a chemokine and homing receptor profile that allows them to infiltrate inflamed tissue. Indeed, in several studies, such cells are the dominant T cell population in target tissues, such as the synovitis in patients with RA, the unstable plaque in patients with atherosclerotic disease and the vasculitic lesion in patients with Wegener's granulomatosis [79–81]. They appear to be a major contributor to effector functions and account for the cytokine production in the tissue, as well as they are able to exert cytotoxic activity towards epithelial cells and vascular smooth muscle cells [82–84].

In the most straightforward model, the pool of end-differentiated effector cells in autoimmune diseases may be the consequence of memory transition of autoreactive T cells during homeostatic proliferation and, therefore, be specific for relevant autoantigens (Fig. 2). Indeed, initial studies showed that CD28⁺CD4⁺ T cells from RA patients proliferate in autologous mixed lymphocyte reaction [48]. Also, such cells were specific for a heat shock protein in patients with acute coronary syndrome [49]. In other reports, however, CD28⁺ end-differentiated effector T cells in peripheral blood of patients with autoimmune disease are specific to viral antigens and in particular CMV, as they are in healthy elderly [69]. A possible interpretation of these findings is that the antigen specificity of these cells is less important for the autoimmune manifestations than their sheer frequency. Obviously, this would imply that these cells recognize their original, frequently viral antigen, in the inflamed tissue and thereby amplify the immune response underlying the autoimmune disease. Products from infectious organisms in inflamed tissue from patients with autoimmune diseases have been identified in numerous studies. Although none of these organisms has been convincingly demonstrated to be an initiator of the autoimmune disease, they may represent an important amplification loop by activating cells from the preexisting effector cell pool and, in particular, the end-differentiated effector cells.

Alternatively, the CD28⁺ effector cell populations may have, at least in part, escaped a need for antigen-specific stimulation. In contrast to normal effector cell populations in chronic viral infections, they do not express negative regulatory receptors that have been associated with clonal exhaustion [56]. In contrast, they express receptors of several families that also include stimulatory variants. In the context of certain tissues and environmental cues, the stimulatory receptors may be sufficient to convey an activation signal [85]. This concept is of particular interest for NKG2D that recognizes MICA and other ligands that are expressed in various tissues upon a stress response [86, 87]. Alternatively, such costimulatory receptors may lower the threshold that is required for antigen-specific activation substantially and therefore render an antigen-specific effector cells that has been selected for one particular viral peptide broadly cross-reactive [59, 88, 89]. Obviously, this model represents a generalization of the classical molecular mimicry model.

Conclusions

The clinical observation that the incidence of autoimmune diseases increases with age and that some of the autoimmune diseases are even confined to the elderly appears first to be paradoxical considering that immune competence to a novel infectious organism declines with age and the aging immune memory cell is less able of recall responses and to control chronic viral infections. However, on second thought, the finding is not so perplexing.

Autoimmune diseases have a long latent phase, and numerous tolerance checkpoints have to be overcome to develop overt disease [90]. Checkpoint failures largely appear to resemble a stochastic process that could just accumulate over lifetime, but also be specifically induced by the aging process. Immune aging is more than a functional degeneration at a single-cell level resulting in defunct subpopulations. It is a system-wide process that can lead to the selection of a more self-reactive repertoire and transition of self-reactive naive T cells into memory-like cells. The accumulation of effector memory cells that is typically seen with age appears to be a facilitator of chronic inflammation in the elderly.

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Abbreviations

ATM	Ataxia telangiectasia mutated
CMV	Cytomegalovirus
HAART	Highly active antiretroviral therapy
IRIS	Immune reconstitution inflammatory syndrome
KIR	Killer immunoglobulin-like receptors
TREC	T cell receptor excision circle

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Fig. 1.

Homeostatic proliferation as a risk factor for autoimmunity. Homeostatic proliferation is the major means of T cell replenishment in the adult when thymic production declines.

Peripheral selection and T cell activation and differentiation induced by this turnover can generate a repertoire that is more difficult to control by peripheral tolerance mechanisms

Fig. 2. End-differentiated CD45RA⁺CD28⁻ T effector memory cells in autoimmune inflammation. One of the most striking phenotypes of immune aging is the accumulation of terminally differentiated CD45RA effector memory T cells at the expense of naive and central memory T cells. Such cells contribute to tissue inflammation through antigen-specific as well as antigen-independent mechanisms