Cell. Mol. Life Sci. (2012) 69:1615–1623
DOI 10.1007/s00018-012-0970-0

Cellular and Molecular Life Sciences

MULTI-AUTHOR REVIEW

Immune aging and autoimmunity

Jörg J. Goronzy · Cornelia M. Weyand

Received: 10 March 2012 / Revised: 13 March 2012 / Accepted: 13 March 2012 / Published online: 1 April 2012

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

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

J. J. Goronzy (✉) · C. M. Weyand
Division of Immunology and Rheumatology,
Department of Medicine, Stanford University School
of Medicine, CCSR Building Room 2215, Mail Code 5166,
269 Campus Drive West, Stanford, CA 94305-5166, USA
e-mail: jgoronzy@stanford.edu

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

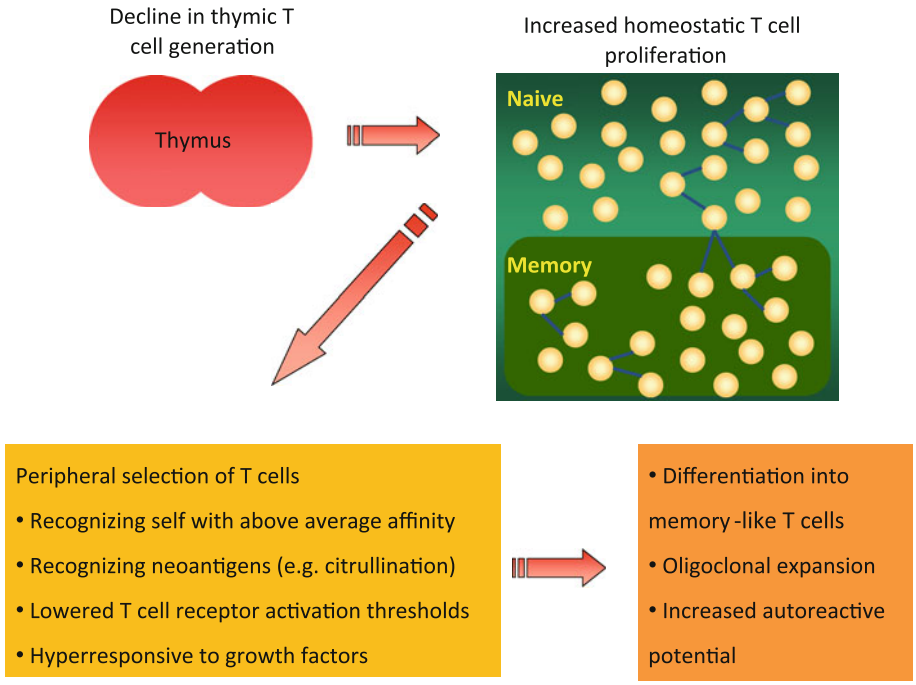

Fig. 1 Homeostatic proliferation as a risk factor for autoimmunity. Homeostatic proliferation is the major means of T cell replenishment in the adult when thymic production declines. Peripheral selection and T cell activation and differentiation induced by this turnover can generate a repertoire that is more difficult to control by peripheral tolerance mechanisms

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

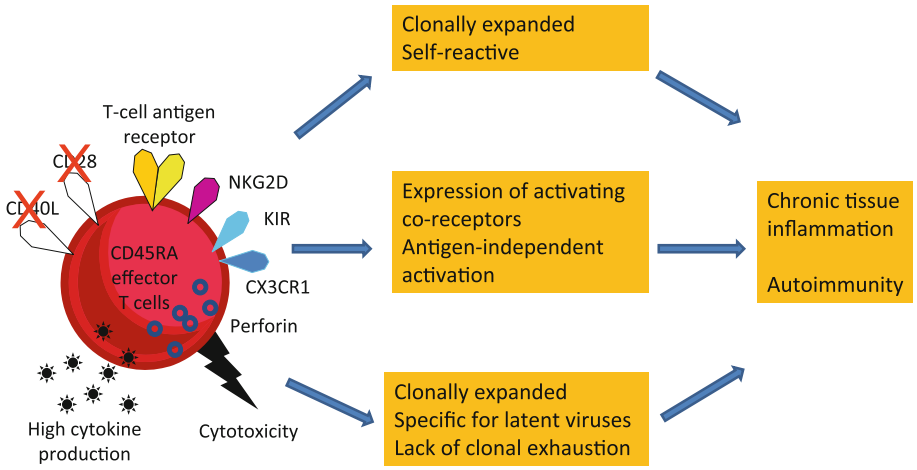

Fig. 2 End-differentiated $CD45RA^{+}CD28^{-}$ T effector memory cells in autoimmune inflammation. One of the most striking phenotypes of immune aging is the accumulation of terminally differentiated CD45RA effector memory T cells at the expense of naive and central memory T cells. Such cells contribute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

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.

Acknowledgments This work was supported by grants from the National Institutes of Health (AI 57266 and AI 90019).

References

1. Christen U, Hintermann E, Holdener M, von Herrath MG (2010) Viral triggers for autoimmunity: is the 'glass of molecular mimicry' half full or half empty? J Autoimmun 34:38–44
2. Green NM, Marshak-Rothstein A (2011) Toll-like receptor driven B cell activation in the induction of systemic autoimmunity. Semin Immunol 23(2):106–112
3. Shlomchik MJ (2009) Activating systemic autoimmunity: B's, T's, and tolls. Curr Opin Immunol 21:626–633
4. Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N et al (2003) Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 289:179–186
5. Rivetti D, Jefferson T, Thomas R, Rudin M, Rivetti A, et al (2006) Vaccines for preventing influenza in the elderly. Cochrane Database Syst Rev 3:CD004876
6. Goodwin K, Viboud C, Simonsen L (2006) Antibody response to influenza vaccination in the elderly: a quantitative review. Vaccine 24:1159–1169
7. Arvin AM (2008) Humoral and cellular immunity to varicella-zoster virus: an overview. J Infect Dis 197(Suppl 2):S58–S60
8. Goronzy JJ, Weyand CM (2003) Aging, autoimmunity and arthritis: T-cell senescence and contraction of T-cell repertoire diversity—catalysts of autoimmunity and chronic inflammation. Arthritis Res Ther 5:225–234
9. Ruffatti A, Rossi L, Calligaro A, Del Ross T, Lagni M et al (1990) Autoantibodies of systemic rheumatic diseases in the healthy elderly. Gerontology 36:104–111
10. Moulias R, Proust J, Wang A, Congy F, Marescot MR et al (1984) Age-related increase in autoantibodies. Lancet 1:1128–1129
11. Weyand CM, Goronzy JJ (2003) Medium- and large-vessel vasculitis. N Engl J Med 349:160–169
12. Doran MF, Pond GR, Crowson CS, O'Fallon WM, Gabriel SE (2002) Trends in incidence and mortality in rheumatoid arthritis in Rochester, Minnesota, over a forty-year period. Arthritis Rheum 46:625–631
13. Goronzy JJ, Weyand CM (2005) Rheumatoid arthritis. Immunol Rev 204:55–73
14. Goronzy JJ, Shao L, Weyand CM (2010) Immune aging and rheumatoid arthritis. Rheum Dis Clin North Am 36:297–310
15. Weng NP (2006) Aging of the immune system: how much can the adaptive immune system adapt? Immunity 24:495–499
16. Kong FK, Chen CL, Six A, Hockett RD, Cooper MD (1999) T cell receptor gene deletion circles identify recent thymic emigrants in the peripheral T cell pool. Proc Natl Acad Sci USA 96:1536–1540
17. Douek DC, McFarland RD, Keiser PH, Gage EA, Massey JM et al (1998) Changes in thymic function with age and during the treatment of HIV infection. Nature 396:690–695
18. Hazenberg MD, Borghans JA, de Boer RJ, Miedema F (2003) Thymic output: a bad TREC record. Nat Immunol 4:97–99
19. Naylor K, Li G, Vallejo AN, Lee WW, Koetz K et al (2005) The influence of age on T cell generation and TCR diversity. J Immunol 174:7446–7452
20. Goronzy JJ, Weyand CM (2005) T cell development and receptor diversity during aging. Curr Opin Immunol 17:468–475
21. Hakim FT, Memon SA, Cepeda R, Jones EC, Chow CK et al (2005) Age-dependent incidence, time course, and consequences of thymic renewal in adults. J Clin Invest 115:930–939
22. Koetz K, Bryl E, Spickschen K, O'Fallon WM, Goronzy JJ et al (2000) T cell homeostasis in patients with rheumatoid arthritis. Proc Natl Acad Sci USA 97:9203–9208
23. Surh CD, Sprent J (2008) Homeostasis of naive and memory T cells. Immunity 29:848–862
24. Wallace DL, Zhang Y, Ghattas H, Worth A, Irvine A et al (2004) Direct measurement of T cell subset kinetics in vivo in elderly men and women. J Immunol 173:1787–1794
25. Cicin-Sain L, Messaoudi I, Park B, Currier N, Planer S et al (2007) Dramatic increase in naive T cell turnover is linked to loss of naive T cells from old primates. Proc Natl Acad Sci USA 104:19960–19965
26. Labrecque N, Whitfield LS, Obst R, Waltzinger C, Benoist C et al (2001) How much TCR does a T cell need? Immunity 15:71–82
27. Polic B, Kunkel D, Scheffold A, Rajewsky K (2001) How alpha beta T cells deal with induced TCR alpha ablation. Proc Natl Acad Sci USA 98:8744–8749
28. Seddon B, Zamoyska R (2002) TCR and IL-7 receptor signals can operate independently or synergize to promote lymphopenia-induced expansion of naive T cells. J Immunol 169:3752–3759
29. Kassiotis G, Zamoyska R, Stockinger B (2003) Involvement of avidity for major histocompatibility complex in homeostasis of naive and memory T cells. J Exp Med 197:1007–1016
30. Kieper WC, Burghardt JT, Surh CD (2004) A role for TCR affinity in regulating naive T cell homeostasis. J Immunol 172:40–44
31. Goronzy JJ, Weyand CM (2001) T cell homeostasis and autoreactivity in rheumatoid arthritis. Curr Dir Autoimmun 3:112–132

32. Goronzy JJ, Weyand CM (2001) Thymic function and peripheral T-cell homeostasis in rheumatoid arthritis. Trends Immunol 22:251–255
33. Arstila TP, Casrouge A, Baron V, Even J, Kanellopoulos J et al (2000) Diversity of human alpha beta T cell receptors. Science 288:1135
34. Wagner UG, Koetz K, Weyand CM, Goronzy JJ (1998) Perturbation of the T cell repertoire in rheumatoid arthritis. Proc Natl Acad Sci USA 95:14447–14452
35. Warren RL, Freeman JD, Zeng T, Choe G, Munro S et al (2011) Exhaustive T-cell repertoire sequencing of human peripheral blood samples reveals signatures of antigen selection and a directly measured repertoire size of at least 1 million clonotypes. Genome Res 21(5):790–797
36. Robins HS, Srivastava SK, Campregher PV, Turtle CJ, Andriesen J, et al (2010) Overlap and effective size of the human CD8+ T cell receptor repertoire. Sci Transl Med 2:47ra64
37. Cho BK, Rao VP, Ge Q, Eisen HN, Chen J (2000) Homeostasis-stimulated proliferation drives naive T cells to differentiate directly into memory T cells. J Exp Med 192:549–556
38. Goldrath AW, Bogatzki LY, Bevan MJ (2000) Naive T cells transiently acquire a memory-like phenotype during homeostasis-driven proliferation. J Exp Med 192:557–564
39. Goldrath AW, Luckey CJ, Park R, Benoist C, Mathis D (2004) The molecular program induced in T cells undergoing homeostatic proliferation. Proc Natl Acad Sci USA 101:16885–16890
40. Williams KM, Hakim FT, Gress RE (2007) T cell immune reconstitution following lymphodepletion. Semin Immunol 19:318–330
41. Jendro MC, Ganten T, Matteson EL, Weyand CM, Goronzy JJ (1995) Emergence of oligoclonal T cell populations following therapeutic T cell depletion in rheumatoid arthritis. Arthritis Rheum 38:1242–1251
42. Akbar AN, Fletcher JM (2005) Memory T cell homeostasis and senescence during aging. Curr Opin Immunol 17:480–485
43. Nikolich-Zugich J (2008) Ageing and life-long maintenance of T-cell subsets in the face of latent persistent infections. Nat Rev Immunol 8:512–522
44. Czesnikiewicz-Guzik M, Lee WW, Cui D, Hiruma Y, Lamar DL et al (2008) T cell subset-specific susceptibility to aging. Clin Immunol 127:107–118
45. Effros RB, Dagarag M, Spaulding C, Man J (2005) The role of CD8+ T-cell replicative senescence in human aging. Immunol Rev 205:147–157
46. Weng NP, Akbar AN, Goronzy J (2009) CD28(−) T cells: their role in the age-associated decline of immune function. Trends Immunol 30:306–312
47. Moss P (2010) The emerging role of cytomegalovirus in driving immune senescence: a novel therapeutic opportunity for improving health in the elderly. Curr Opin Immunol 22:529–534
48. Schmidt D, Goronzy JJ, Weyand CM (1996) CD4+ CD7− CD28− T cells are expanded in rheumatoid arthritis and are characterized by autoreactivity. J Clin Invest 97:2027–2037
49. Zal B, Kaski JC, Arno G, Akiyu JP, Xu Q et al (2004) Heat-shock protein 60-reactive CD4+ CD28 null T cells in patients with acute coronary syndromes. Circulation 109:1230–1235
50. Messaoudi I, Warner J, Nikolich-Zugich D, Fischer M, Nikolich-Zugich J (2006) Molecular, cellular, and antigen requirements for development of age-associated T cell clonal expansions in vivo. J Immunol 176:301–308
51. Zhang R, Shah MV, Loughran TP Jr (2010) The root of many evils: indolent large granular lymphocyte leukaemia and associated disorders. Hematol Oncol 28:105–117
52. Shah MV, Zhang R, Loughran TP Jr (2009) Never say die: survival signaling in large granular lymphocyte leukemia. Clin Lymphoma Myeloma 9(Suppl 3):S244–S253
53. Schirmer M, Vallejo AN, Weyand CM, Goronzy JJ (1998) Resistance to apoptosis and elevated expression of Bcl-2 in clonally expanded CD4+ CD28− T cells from rheumatoid arthritis patients. J Immunol 161:1018–1025
54. Park W, Weyand CM, Schmidt D, Goronzy JJ (1997) Co-stimulatory pathways controlling activation and peripheral tolerance of human CD4 + CD28− T cells. Eur J Immunol 27:1082–1090
55. Weyand CM, Brandes JC, Schmidt D, Fulbright JW, Goronzy JJ (1998) Functional properties of CD4 + CD28− T cells in the aging immune system. Mech Ageing Dev 102:131–147
56. Serriari NE, Gondois-Rey F, Guillaume Y, Remmerswaal EB, Pastor S et al (2010) B and T lymphocyte attenuator is highly expressed on CMV-specific T cells during infection and regulates their function. J Immunol 185:3140–3148
57. Fann M, Chiu WK, Wood WH 3rd, Levine BL, Becker KG et al (2005) Gene expression characteristics of CD28 null memory phenotype CD8+ T cells and its implication in T-cell aging. Immunol Rev 205:190–206
58. Warrington KJ, Takemura S, Goronzy JJ, Weyand CM (2001) CD4+, CD28− T cells in rheumatoid arthritis patients combine features of the innate and adaptive immune systems. Arthritis Rheum 44:13–20
59. Namekawa T, Snyder MR, Yen JH, Goehring BE, Leibson PJ et al (2000) Killer cell activating receptors function as costimulatory molecules on CD4+ CD28 null T cells clonally expanded in rheumatoid arthritis. J Immunol 165:1138–1145
60. Bigouret V, Hoffmann T, Arlettaz L, Villard J, Colonna M et al (2003) Monoclonal T-cell expansions in asymptomatic individuals and in patients with large granular leukemia consist of cytotoxic effector T cells expressing the activating CD94:NKG2C/E and NKD2D killer cell receptors. Blood 101:3198–3204
61. Snyder MR, Muegge LO, Offord C, O'Fallon WM, Bajzer Z et al (2002) Formation of the killer Ig-like receptor repertoire on CD4+ CD28 null T cells. J Immunol 168:3839–3846
62. Chen X, Bai F, Sokol L, Zhou J, Ren A et al (2009) A critical role for DAP10 and DAP12 in CD8+ T cell-mediated tissue damage in large granular lymphocyte leukemia. Blood 113:3226–3234
63. Hickman SP, Turka LA (2005) Homeostatic T cell proliferation as a barrier to T cell tolerance. Philos Trans R Soc Lond B Biol Sci 360:1713–1721
64. Ramanathan S, Poussier P (2001) BB rat lyp mutation and Type 1 diabetes. Immunol Rev 184:161–171
65. King C, Ilic A, Koelsch K, Sarvetnick N (2004) Homeostatic expansion of T cells during immune insufficiency generates autoimmunity. Cell 117:265–277
66. Calzascia T, Pellegrini M, Lin A, Garza KM, Elford AR et al (2008) CD4 T cells, lymphopenia, and IL-7 in a multistep pathway to autoimmunity. Proc Natl Acad Sci USA 105:2999–3004
67. Hirota K, Hashimoto M, Yoshitomi H, Tanaka S, Nomura T et al (2007) T cell self-reactivity forms a cytokine milieu for spontaneous development of IL-17 + Th cells that cause autoimmune arthritis. J Exp Med 204:41–47
68. Muller M, Wandel S, Colebunders R, Attia S, Furrer H et al (2010) Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. Lancet Infect Dis 10:251–261
69. Thewissen M, Somers V, Venken K, Linsen L, van Paassen P et al (2007) Analyses of immunosenescent markers in patients with autoimmune disease. Clin Immunol 123:209–218
70. Goronzy JJ, Matteson EL, Fulbright JW, Warrington KJ, Chang-Miller A et al (2004) Prognostic markers of radiographic progression in early rheumatoid arthritis. Arthritis Rheum 50:43–54
71. Schönland SO, Lopez C, Widmann T, Zimmer J, Bryl E, Goronzy JJ, Weyand CM (2003) Premature telomeric loss in rheumatoid arthritis is genetically determined and involves lymphoid and myeloid cell lineages. Proc Natl Acad Sci USA 100:13471–13476

72. Colmegna I, Diaz-Borjon A, Fujii H, Schaefer L, Goronzy JJ et al (2008) Defective proliferative capacity and accelerated telomeric loss of hematopoietic progenitor cells in rheumatoid arthritis. Arthritis Rheum 58:990–1000
73. Beerman I, Maloney WJ, Weissmann IL, Rossi DJ (2010) Stem cells and the aging hematopoietic system. Curr Opin Immunol 22:500–506
74. Fujii H, Shao L, Colmegna I, Goronzy JJ, Weyand CM (2009) Telomerase insufficiency in rheumatoid arthritis. Proc Natl Acad Sci USA 106:4360–4365
75. Shao L, Fujii H, Colmegna I, Oishi H, Goronzy JJ et al (2009) Deficiency of the DNA repair enzyme ATM in rheumatoid arthritis. J Exp Med 206:1435–1449
76. Martens PB, Goronzy JJ, Schaid D, Weyand CM (1997) Expansion of unusual CD4+ T cells in severe rheumatoid arthritis. Arthritis Rheum 40:1106–1114
77. Komocsi A, Lamprecht P, Csernok E, Mueller A, Holl-Ulrich K et al (2002) Peripheral blood and granuloma CD4(+)CD28(−) T cells are a major source of interferon-gamma and tumor necrosis factor-alpha in Wegener's granulomatosis. Am J Pathol 160:1717–1724
78. McKinney EF, Lyons PA, Carr EJ, Hollis JL, Jayne DR, et al. (2010) A CD8+ T cell transcription signature predicts prognosis in autoimmune disease. Nat Med 16:581, 586–591
79. Wilde B, Thewissen M, Damoiseaux J, van Paassen P, Witzke O et al (2010) T cells in ANCA-associated vasculitis: what can we learn from lesional versus circulating T cells? Arthritis Res Ther 12:204
80. Berden AE, Kallenberg CG, Savage CO, Yard BA, Abdulahad WH et al (2009) Cellular immunity in Wegener's granulomatosis: characterizing T lymphocytes. Arthritis Rheum 60:1578–1587
81. Liuzzo G, Goronzy JJ, Yang H, Kopecky SL, Holmes DR et al (2000) Monoclonal T-cell proliferation and plaque instability in acute coronary syndromes. Circulation 101:2883–2888
82. Nakajima T, Schulte S, Warrington KJ, Kopecky SL, Frye RL et al (2002) T-cell-mediated lysis of endothelial cells in acute coronary syndromes. Circulation 105:570–575
83. Sato K, Niessner A, Kopecky SL, Frye RL, Goronzy JJ et al (2006) TRAIL-expressing T cells induce apoptosis of vascular smooth muscle cells in the atherosclerotic plaque. J Exp Med 203:239–250
84. Pryshchep S, Sato K, Goronzy JJ, Weyand CM (2006) T cell recognition and killing of vascular smooth muscle cells in acute coronary syndrome. Circ Res 98:1168–1176
85. Snyder MR, Weyand CM, Goronzy JJ (2004) The double life of NK receptors: stimulation or co-stimulation? Trends Immunol 25:25–32
86. Eagle RA, Trowsdale J (2007) Promiscuity and the single receptor: NKG2D. Nat Rev Immunol 7:737–744
87. Van Belle TL, von Herrath MG (2009) The role of the activating receptor NKG2D in autoimmunity. Mol Immunol 47:8–11
88. Snyder MR, Lucas M, Vivier E, Weyand CM, Goronzy JJ (2003) Selective activation of the c-Jun NH2-terminal protein kinase signaling pathway by stimulatory KIR in the absence of KARAP/DAP12 in CD4+ T cells. J Exp Med 197:437–449
89. Sawai H, Park YW, Roberson J, Imai T, Goronzy JJ et al (2005) T cell costimulation by fractalkine-expressing synoviocytes in rheumatoid arthritis. Arthritis Rheum 52:1392–1401
90. Goodnow CC (2007) Multistep pathogenesis of autoimmune disease. Cell 130:25–35