



Origin of late-onset autoimmune disease

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Autoimmune disease occurs most often in young women. Incidences of systemic lupus erythematosus (SLE) and rheumatoid arthritis peak at approximately age 20, with a 3:1 (female-to-male) preference [1,2]. Incidences of type 1 autoimmune diabetes [3] and autoimmune skin diseases, such as vitiligo, peak at young age [4]. Two factors are responsible for the occurrence of autoimmune disease at midlife (age, 40–60): First, there is a detection bias. Some autoimmune diseases are not apparent at onset, because their progression is slow or their biochemical, physiologic, or visual detection is not obvious (Fig. 1). These diseases include thyroid disease, such as Hashimoto's thyroiditis, which has some symptoms that occur later in life [5]. Scleroderma is recognized relatively late compared with the detection of early-onset autoimmune disease [6]. Pulmonary fibrosis, such as the Hamman-Rich Syndrome or idiopathic pulmonary fibrosis, requires time for detection but is normally evident once symptoms occur in midlife [7]. The presence of Sjögren's syndrome becomes more apparent in older individuals, because destruction of the salivary gland is slow, and symptoms of dryness of the mouth or eyes are apparent only when most of the salivary glands or lachrymal glands are destroyed [8].

Second, aging alters many biologic functions and may alter the progression of autoimmune diseases. This article focuses on decreased apoptosis and increased oligoclonal activation of T cells as putative mechanisms that explain the occurrence of late-onset autoimmune diseases that is reported in humans and animal studies. The authors' have generated a model to show that there is initially

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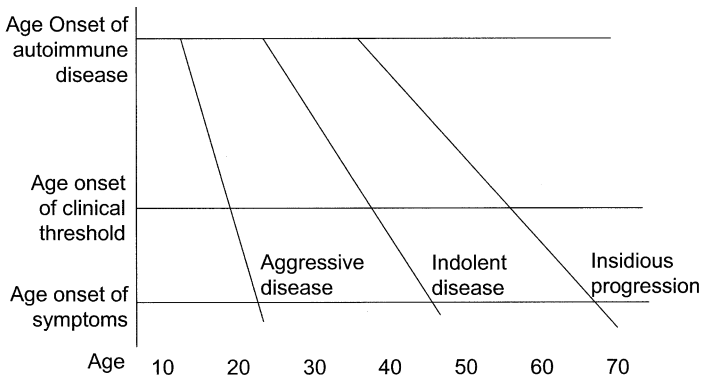


Fig. 1. Age of onset of autoimmune symptoms. The first factor leading to late-onset symptoms of autoimmune disease is first determined by the age of self-tolerance loss by T cells and B cells. This factor represents the initial aspect of autoimmune disease at the cellular level. In the case of aggressive disease, the immune response can be severe, and the organ damage can be readily detectable, leading to the earliest onset of symptoms. Juvenile-onset diabetes or aggressive lupus nephritis that occurs in young individuals are examples of this early-onset autoimmune disease. In contrast, if the self-tolerance loss at the cellular level occurs at a later age, and the disease progression is more indolent or insidious, the age of onset of symptoms may be delayed substantially. Certain autoimmune diseases, such as Sjögren's syndrome or idiopathic pulmonary fibrosis, can have a more focal T-cell inflammatory pattern that does not involve the entire organ. The T-cell inflammatory process could be milder, leading to a slower progression of disease. In cases in which the severity of the disease symptoms become severe only after most of the target tissue is destroyed, autoimmune disease presents at a late age.

a defect in activation-induced cell death (AICD) and that a more prominent defect in activation develops later. They hypothesize that late-onset autoimmune diseases occur between early (age 40) and late middle age (age 60), which is the time period between the onset of the AICD defect and a defect in activation.

T-cell senescence and autoimmune disease

Age-related oligoclonal expansion of T-cell populations

Many investigators noted that older humans and mice often develop extensive oligoclonal expansion clones of CD8⁺ T cells [9–14], but not CD4⁺ T cells [15]. This finding is correlated with an earlier onset of senescence in CD8⁺ T cells compared with the onset in CD4⁺ T cells. The oligoclonal expansion can be so extensive that in some individuals clones make up 80% of the total CD8⁺ T-cell pool. Marrack and colleagues reported that over 58% of mice older than 2 years and almost all humans older than 40 have CD8⁺ T cell clones, which are large enough to distort the otherwise predictable TCRV α and TCRV β repertoire of the CD8⁺ T cells of the host [11,16,17]. Spectrograph of this VDJ joining in humans and mice shows that the oligoclonal expansion seems to be random [14,18]. Different strains of genetically identical mice develop different oligoclonally

expanded populations. It has been difficult to demonstrate that this oligoclonal expansion is driven by the age-related accumulation of autoantigen-driven expansion of T cells or by other age-related factors that can induce loss of T-cell tolerance and skew TCR rearrangement. Posnett and co-workers showed that T cells from elderly subjects contained expanded subsets of T-cell receptor (TCR) V β populations [18,19]. These subsets were observed primarily among CD8 cells, but not CD4 cells, represented up to 37.5% of all CD8 cells, and were present in most elderly subjects. Two-color flow cytometry demonstrated that in three of five elderly subjects, similar expansions of TCR V β subsets were found specifically in the CD8⁺CD28⁻ subpopulation. This subset of cytotoxic T lymphocytes is known to exhibit a defect in proliferative responses to TCR stimuli and has been reported to exhibit characteristics of replicative senescent CD8 T cells [18]. It is possible that this oligoclonal expansion is driven by autoantigens that are present throughout the lifetime of the mouse or human.

Replicative senescence limits oligoclonal expansion

An immunologic force that opposes oligoclonal expansion is replicative senescence. Thus, chronically activated CD8⁺ or CD4⁺ T cells in humans normally do not expand infinitely (referred to as replicative senescence). This phenomenon has been documented in vitro culture systems [9,10]. This system allowed investigators to count the number of doublings of T cells that were isolated from different age groups of individuals after repeated stimulation. McCarron et al examined the longevity of T-cell clones and found that clones that were derived from neonates averaged 52 population doublings (PD), those from young adults (age, 20–30) managed 40 PD, and those from the elderly (age, 70–90) only had 32 PD [20]. Adibzadeh and colleagues [21,22] combined the in vitro and in vivo observations made by McLean and Michie [23] to estimate that the average and maximum lifespan of a human memory cell is 15 and 35 years, respectively. If such repeated in vitro stimulation mimics high stimulation and cell cycle of certain T cells in vivo, the finding would suggest that despite a constant stimulation and accumulation of newly generated self-antigens throughout life, the activated T cells eventually would become senescent, and the autoreactive T-cell response would subside as the individual ages. One hypothesis is that replicative senescence is one way for cytotoxic CD8 T cells to prevent unwanted expansion and maintain homeostasis [24,25]. Because the theory of replicative senescence opposes the finding of increased oligoclonal expansion of CD8 T cells that occurs with age, abnormal oligoclonal expansion of CD8 T cells must occur before the onset of T-cell replicative senescence and may occur stochastically in certain replicative-competent CD8⁺ T cells (Fig. 2).

Decreased apoptosis proceeds T-cell senescence

Although replicative senescence may be one mechanism that maintains T-cell homeostasis, at least in young individuals, it more widely is known that AICD is

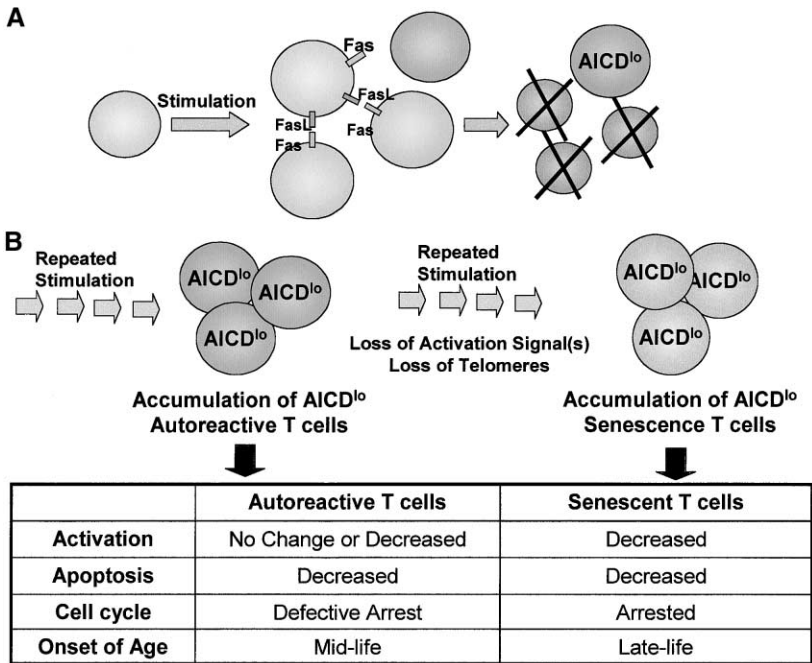


Fig. 2. Late-onset autoimmune disease is initiated between the age of decreased AICD and the older age of decreased activation of T cells. (A) In younger individuals, stimulation of T cells leads to up-regulation of Fas, FasL, and Fas–FasL engagement-induced apoptosis signaling. This AICD process eliminates most of the T cells that are activated in response to a stimulus to prevent the accumulation of autoreactive T cells. (B) In older individuals, decrease in AICD occurs in a stochastic fashion and in different T-cell populations within an individual. This occurs at a stage of pre- or early senescence in T cells and is similar to that observed in other cells, such as presenescent fibroblasts. This model would predict that at mid-life there would be an accumulation of AICD^{low} autoreactive T cells, and these cells still can be activated, albeit at a lower level. Apoptosis is decreased, and cell-cycle entry is delayed or arrested. With age, presenescent T cells progress to fully senescent cells. This change is promoted by repeated stimulation and is associated with loss of activation signals and further shortening of telomeres, especially in humans. Fully senescent T cells develop that have decreased activation, AICD, and complete cell-cycle arrest.

the predominant mechanism for preventing the expansion of unwanted T cells [26–30]. One hypothesis of age-related accumulation of autoreactive T cells suggests that this abnormal regulation of T cells can result from the development of an abnormal apoptosis signaling pathway that occurs with age [31]. The authors’ evidence showed that after in vitro stimulation with anti-CD3 T cells from middle-aged (12- to 16-month-old) B6 mice, there is an increase in the AICD-resistant population of CD8 T cells [32]. Transfer of these CD8 T cells from middle-aged B6 mice into younger mice showed that there was defective induction of Fas, Fas ligand (FasL), and apoptosis of these T cells in vivo and that this defective deletion of autoreactive T cells was associated with chronic systemic infiltration of these T cells into different tissues [33]. These results

suggest that this age-related apoptosis defect can occur in CD8 T cells that have not been challenged with any known antigens and is associated with an intrinsic defect in apoptosis.

In many mouse models of autoimmune disease that are caused by genetic defects of T-cell apoptosis, an age-related onset and progression of the autoimmune features is obvious. This finding is most evident in Fas-deficient *lpr* (lymphoproliferative) and FasL-deficient *gld* (generalized lymphoproliferative disease) mice. At a young age, the *lpr* and the *gld* mice did not show symptoms of autoimmune disease. Significant enlargement of the lymph nodes was apparent at 12 weeks of age in *gld* mice. By 20 weeks, lymph nodes were 50-fold larger in *gld* mice than in isogenic C3H/HeJ-+/+ mice [34,35]. Some *lpr* mice lived to an older age (>20 weeks), and the lymphoproliferative disease seemed to regress. This event occurs in about 20% of mice and is not determined genetically (J.D. Mountz, unpublished data, 1985). It may be caused by stochastic variation that affects the severity of the lymphoproliferative disease and by longevity selection for mice with less severe disease. The cellular basis for the stochastic variation may reside in the thymus. The authors [36] extended the observation of Steinberg's group [37] that the thymus is required for lymphoproliferative disease to occur, and neonatal thymectomy eliminates the disease. The authors analyzed T-cell output from the thymus by bromodeoxyuridine staining and showed that thymus output of the precursors to the abnormal CD4⁻CD8⁻B220⁺ and CD4⁺B220⁺ T cells continues until 3 to 4 months of age. Shortly after the decrease in thymic T-cell output, lymph-node size regressed. These results indicate that thymus output is required to sustain the autoimmune-lymphoproliferative disease in *lpr* mice.

Severe impairment of the T-cell proliferative response that is accompanied with a defective IL-2 response is a key feature in autoimmune strains that have a T-cell apoptosis defect [38–40]. Addition of exogenous IL-2 during the primary activation of T cells from adult *lpr* mice was reported to overcome the defect in CD25 expression and the defective AICD response after anti-CD3 stimulation [40,41]. These results suggest that up-regulation of the Fas- and FasL-mediated apoptosis pathway is coupled with up-regulation of the T-cell proliferative response, which is maintained by the IL-2 signaling pathway in mice. The common γ -chain, represented in the receptors for IL-2, IL-4, IL-7 and IL-15, has been proposed to be defective in these receptors in aged T cells [42]. Defective apoptosis of T cells may predispose *lpr* and *gld* mice to early onset of T-cell proliferative senescence. Such a control mechanism of T-cell senescence may be different between mice and humans. Because mice have longer telomeres, there may be alternative mechanisms that have evolved in mice to allow use of apoptosis or replicative senescence to regulate T-cell homeostasis.

At the molecular level, decreased apoptosis is a common theme in both autoimmune disease and T-cell senescence. Another possible theme involves the dysregulation of T-cell activation and cell-cycle control. T-cell senescence is associated with the up-regulation of genes, such as p21, that are associated with

cell-cycle arrest, whereas p21 deficiency significantly enhances T-cell activation and homeostatic proliferation and can induce a mild lupus-like autoimmune disease in mice [43]. Similarly, mice lacking the gene for the p53-associated cell-cycle arrest effector (gene, *Gadd45a*) also exhibit a lower threshold of T-cell activation and develop an autoimmune disease that is similar to systemic lupus erythematosus (SLE) in humans [44]. These observations suggest that cellular senescence may be an important internal clock that can be used to prevent the expansion of abnormal T cells in aged individuals. A comparison of senescent T cells and autoreactive T cells is shown (see Fig. 2).

Age-related apoptosis defects in human T cells

Many investigators have reported alterations of apoptosis in T cells from aged individuals. Some studies showed that aging is associated with the accumulation of T cells that are more susceptible to apoptosis [45–49], whereas other studies found that aging is associated with the accumulation of T cells that are less susceptible to apoptosis [19,50–53]. The apparent discrepancies between these observations may be caused by differences in the stimuli, phenotypes of cells, experimental conditions, and different models used in these studies.

Despite these discrepancies, the studies suggest that alterations in the apoptosis of T cells may be an important mechanism of immune deficiency and autoimmune disease in aged individuals. The authors previously examined activation-induced defects of apoptosis in human peripheral T cells from younger individuals (mean age, 31 ± 3) and from older individuals (mean age, 67 ± 8) [54]. After *in vitro* activation of T cells with phytohemagglutinin (PHA) and IL-2, apoptosis was measured in T-cell subsets using 7-amino actinomycin D staining and three-color flow cytometry. There was no significant difference in apoptosis of the total CD3⁺ T-cell population at early and late time points. Increased apoptosis in the CD3⁺CD45RO⁻ T-cell population of older subjects was observed by culture day 6. Although the total numbers of CD3⁺CD45RO⁻ cells were not different between the younger (age, <33) and older (age, >65) subjects, 32% of these cells did not undergo apoptosis in younger subjects, whereas 90% of these cells in older subjects did. These results suggest that accumulation of CD45RO⁺ T cells may occur in aged subjects partly because of the preferential elimination of CD45RO⁻ cells with activation. As new or continued immune response requires differentiation of CD45RO⁻ T cells to CD45RO⁺ T cells after activation, increased apoptosis, instead of survival, could lead to observed T-cell immune deficiency in aged individuals.

Role of late-age thymic output in alteration of T-cell apoptosis and autoimmune disease

In human and animal models, thymus output is high at a young age, when most severe autoimmune diseases occur. Use of T-cell receptor excision circles (TRECs) assay revealed that daily thymic output decreases exponentially by two

orders of magnitude by age 80, and thymic output decreases faster after age 30 [55]. This study indicates that thymus output that continues into middle or old age is maybe a beneficial process that leads to rejuvenation of immune responses and the reestablishment of new immune responses to new environmental challenges or endogenous tumor antigens. The authors' made a similar observation in their analysis of thymic involution using the C57BL/6 X DBA/2 (BXD) recombinant inbred strains of mice (H.-C. Hsu, unpublished data, 2002). They found that strains that exhibit a relatively slow thymus involution and continuous output of T cells to the periphery yield the best CD8 cytotoxic T-cell response and respond best to challenge with virus or tumor antigens at late age [56]. It seems likely that, in some cases, excessive output of naïve T cells, or improper deletion of potentially autoreactive T cells before export from the thymus or after seeding the peripheral lymphoid population, may lead to a chronic inflammatory response or development of autoreactive T cells. However, a large thymus is not always associated with autoimmune disease and acceleration of thymic involution can occur in humans and mice with autoimmune disease, possibly because of an enforcement or a development of a negative-feedback mechanism to prohibit excessive thymic output (Fig. 3) [57]. Dysregulation of this process may lead to production or accumulation of autoreactive T cells.

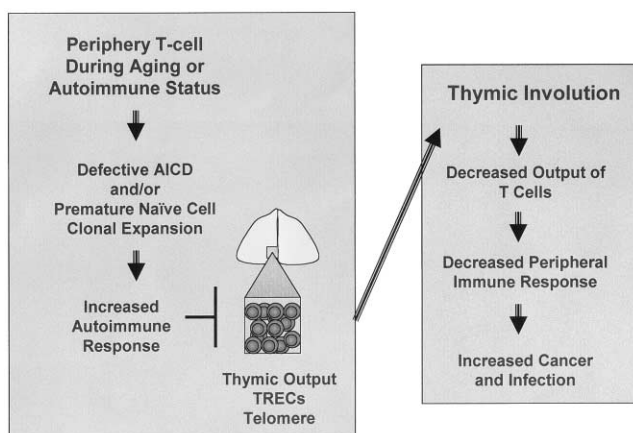


Fig. 3. Age-related interaction between the export of T cells by the thymus and the peripheral T-cell immune response. At an early age, most T cells mature in the thymus and are exported to the periphery as naïve T cells. During middle age, the size of the peripheral T-cell pool is maximized with a combination of memory T cells and T cells with defective AICD or T cells that have undergone oligoclonal expansion. These potentially autoreactive T cells may be associated with the suppression of thymic output, which can be measured as an age-related decrease in TRECs and in telomere shortening. Thymic involution and a decrease in exported T cells from the thymus, then occurs. In older age, this change could lead to a decreased peripheral immune response and increased susceptibility to cancer and infection. Age-related autoimmune disease most likely occurs when there is oligoclonal expansion and the emerging of an AICD-resistant T-cell population that has not undergone full senescence.

Chronic inflammation, autoimmune disease, and hypersensitivity

Effects of genetics and environment on onset of autoimmune disease

Failure to clear an infectious agent or failure to down-regulate the immune response after clearance of the infectious agent may promote autoimmune disease or chronic inflammation in the elderly. The cytotoxic T-cell response to influenza virus infection in aged humans and mice peaks at a later time point and persists longer than in younger counterparts [58]. Although certain responses, such as a febrile response to infectious agents, are reduced with age, other responses, such as pulmonary infiltration and coughing, bronchitis, and pneumonitis, tend to be increased after an episode of influenza. This increase may be caused by the late-onset immune response and the persistence of influenza-specific CD8⁺ and CD4⁺ T cells [59]. The chronic inflammation may result from defective AICD of the inflammatory cells that eliminate the infectious agents. In some cases, persistence chronic T-cell inflammatory response prevents the detection of the inciting agents.

Chronic inflammation after an environmental trigger in apoptosis-defective mice

To investigate chronic inflammation after an environmental trigger, the authors used two models of postinfectious arthritis and autoimmunity in mice. Arthritis was investigated using a *Mycoplasma pulmonis* model that was injected into normal mice, Fas-deficient *lpr* mice, and FasL-deficient *gld* mice [60]. In the *lpr* and *gld* mice, normal clearance of the mycoplasma occurred when the infectious agent was given at intermediate doses. Mycoplasma was not detectable 4 weeks after administration in any of the mice. The normal B6-+/+ mice exhibited a mild swelling of the feet during the presence of the infectious agent, which disappeared once the infectious agent had cleared. In contrast, the *lpr* and *gld* mice exhibited an almost identical early-stage swelling of the feet, and this swelling progressed to a chronic, highly erosive arthritis and synovitis, despite clearance of the organism (Fig. 4). The organism could not be detected by genetic or culture methods from the joint in early- or late-stage arthritis. The arthritis was caused by chronic inflammation that mainly involved T cells, because the arthritis was abrogated by systemic administration of antigen-presenting cell (APC) gene therapy, in which FasL expression was induced by adenovirus transfection [61,62]. This therapy resulted in the homing of the APC to the lymph nodes and joint and in the release of FasL near T cells in the synovium. This study presents a model of infectious arthritis, which is caused by the combination of a genetic defect and an environmental trigger. The authors propose that the AICD defect that occurs with age may cause a chronic T-cell-mediated inflammatory response to an infectious agent.

A second postinfection model that the authors have used is the mouse cytomegalovirus (MCMV) model [63]. MCMV exhibits high tropism to the mouse lung, kidney, liver, and salivary gland. In normal mice, high MCMV titers cleared

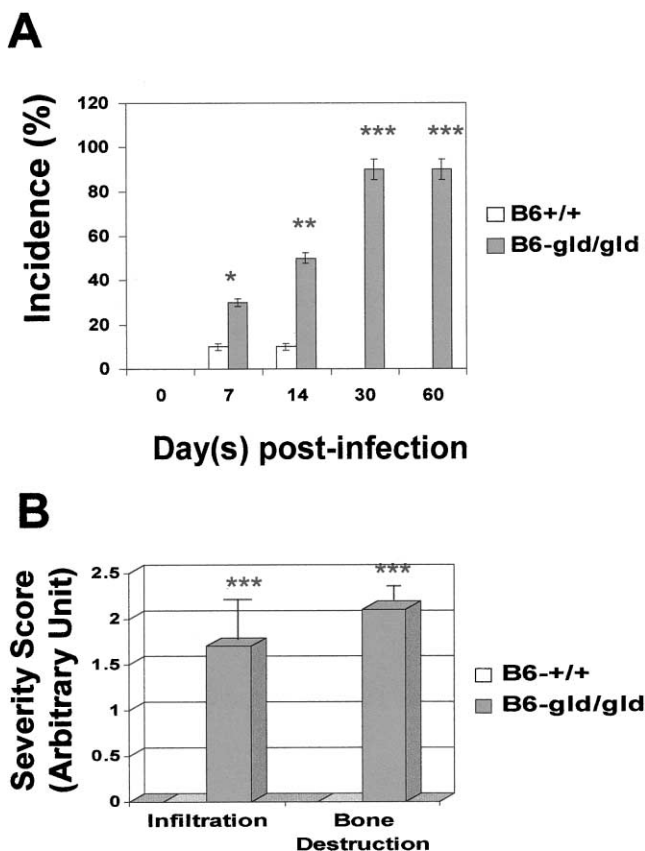


Fig. 4. Increased severity and incidence of *M. pulmonis*-induced arthritis. Mice were infected with 5×10^7 colony-forming units (CFU) of *M. pulmonis*. (A) Infected mice were evaluated blindly at the indicated time points for the incidence of acute and chronic arthritis. Mice were sacrificed 4 weeks after the infection. (B) The pathologic changes of acute and chronic arthritis were evaluated. Results are representative of two independent experiments. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.005$ (values compare the two groups of mice at the same time point). (Adapted from Hsu HC, Zhang HG, Song GG, et al. Defective Fas ligand-mediated apoptosis predisposes to development of a chronic erosive arthritis subsequent to *Mycoplasma pulmonis* infection. *Arthritis Rheum* 2001;44:2146–59; with permission.)

from the lung, liver, and kidney 4 weeks after administration of the infectious agent (Fig. 5A) and cleared from the salivary gland after about 6 months [63]. A similar clearance rate was observed in AICD-deficient *lpr* and *gld* mice (see Fig. 5A). The clearance was confirmed by biochemical and culture techniques. As in the *M. pulmonis* model, parenchymal inflammation persisted in the lung, liver, and kidney of *lpr* and *gld* mice after clearance of MCMV. In normal mice, inflammatory response and T-cell infiltration in these organs were observed only during the course of MCMV infection (Fig. 5B). Administration of the APC-Fas ligand gene therapy used in the *M. pulmonis* model resulted in down-modulation and abrogation of this chronic inflammatory response in the *gld* mice [64,65]. In the

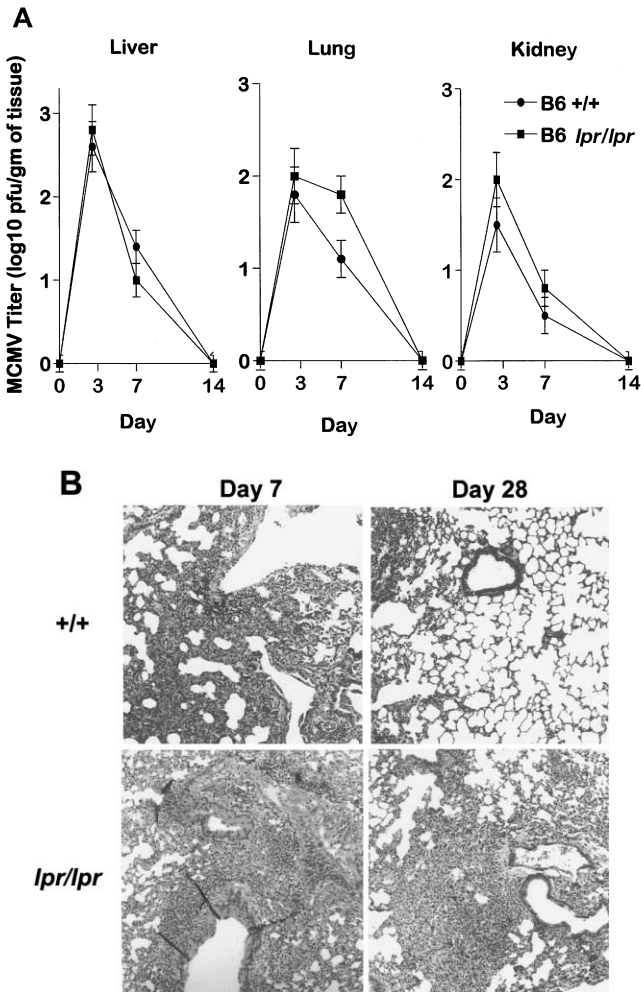


Fig. 5. (A) Defective clearance and chronic inflammation in AICD-deficient *lpr* mice after infection with MCMV. MCMV was injected intravenously into normal C57BL/6 (B6-+/+) or B6-*lpr/lpr* mice. The *lpr* mice have a mutation of Fas and have defective AICD. In these mice, higher titers of virus occurred at an early stage after infection, especially in the lung and kidney. In the liver, lung, and kidney, MCMV was eliminated after 4 weeks in the B6-+/+ and B6-*lpr/lpr* mice. (B) In B6-+/+ mice, clearance of the virus from the lung was associated with resolution of the inflammatory process. In AICD-deficient B6-*lpr/lpr* mice, clearance of the virus from the lung was not associated with clearance of inflammation. The authors suggest that an AICD defect that occurs in middle-aged humans and mice, combined with an environmental exposure, such as a viral infection, triggers a chronic inflammatory or autoimmune disease that does not resolve. (See also Color Plate 1.) (Adapted from Fleck M, Kern ER, Zhou T, Podlech J, Wintersberger W, Edwards CK 3rd, Mountz JD. Apoptosis mediated by Fas but not tumor necrosis factor receptor 1 prevents chronic disease in mice infected with murine cytomegalovirus. *J Clin Invest* 1998;102:1431–43; with permission.)

salivary gland, a similar effect was seen in the normal mice and *lpr* mice. Clearance of MCMV took several months, but the rates of clearance were similar between the two strains of mice. Normal mice cleared signs of inflammation, whereas *gld* and *lpr* mice exhibited a chronic, destructive sialadenitis that was similar to that in Sjögren's syndrome. At the time of this chronic sialadenitis, no MCMV was detected in the salivary glands of *lpr* and *gld* mice. This sialadenitis was caused by chronic immune-cell infiltration and could be abrogated by direct administration of the gene therapy into the salivary gland [64].

These results suggest that environmental triggers may not lead to chronic inflammation or autoimmune disease in individuals with normal AICD function; however, these triggers may predispose individuals with apoptosis or AICD defect to chronic inflammation and autoimmune disease. Older individuals who exhibit age-related T-cell AICD defects may be susceptible to certain environment-induced autoimmune disease.

Manifestation of age-related autoimmune symptoms

Based on the authors' studies of autoimmune mice and aged mice, the authors hypothesize that age-related T-cell alteration primarily may be associated with AICD defects, which may lead to acceleration of activation defects and T-cell senescence. The course of this alteration, however, manifests the clinical symptoms and the susceptibility to inciting triggers that may predispose individuals to autoimmune diseases. Age-related differences in T-cell activation and AICD may lead to different clinical features of early- and late-onset forms of arthritis.

Osteoarthritis

The primary arthritis seen with aging is degenerative joint disease or osteoarthritis (OA), which can be inflammatory or noninflammatory. The inflammatory type can consist of synovium that is infiltrated with T cells and B cells. There does not seem to be an age-related autoimmune component to this type of arthritis, but the increased inflammation, the dysfunction of the innate immune response, or decreased AICD may aggravate this type of arthritis.

Rheumatoid arthritis

Rheumatoid arthritis (RA) normally is seen in young women aged of 20 to 30 (male-to-female ratio, approximately 3:1) [66]. In middle-aged individuals and the elderly, the female preference is decreased, and clinical features change [66]. RA in younger individuals usually is associated with systemic manifestations, including Sjögren's syndrome, rheumatoid nodules, pulmonary interstitial inflammation, fibrosis, and vasculitis. In late-onset RA, the levels of rheumatoid factor and the vasculitis features may be less predominant [66].

Yudoh and colleagues examined age-related changes in cellular activity, replicative capacity, and expression of senescent cells in osteoblasts from

periarticular bone samples obtained from 15 patients with RA and 15 age-matched patients with OA [67]. They found that in both groups, the rate of cell proliferation, the levels of osteoblastic markers, mean telomere length, and replicative lifespan in osteoblastic cells gradually decreased with age. The percentage of senescent osteoblastic cells in the periarticular bone increased with age in both groups, and the rate of expression of senescent cells was higher in patients with RA than in age-matched patients with OA. The age-related decreases in the osteoblastic activity and replicative capacity of osteoblastic cells from periarticular bone were greater in patients with RA than in patients with OA. These results suggest that increased proliferation, which may lead to replicative senescence, is not restricted to T cells in patients with RA.

Koetz and co-workers studied the ability of patients with RA to produce T cells and to maintain T-cell homeostasis [57]. They reported an increased self-replication of T cells in patients with RA, which was indicated by shortening of telomeres in circulating T cells in patients aged 20 to 30. The degree of telomere loss was not related to disease duration or to the use of disease-modifying medication and was most pronounced in $CD4^+ CD45RO^-$ (naïve) T cells. These data are consistent with the concept that the sizes of naïve and memory compartments are controlled independently and suggest that the reduction in TREC-positive T cells and telomere shortening does not reflect an expansion of the memory compartment [68]. The loss of TREC-positive T cells could be a consequence of a primary defect in peripheral T-cell homeostasis. Alternatively, patients with RA may have impaired thymic function, in which the increased turnover of peripheral T cells is a secondary compensatory event.

Spondyloarthropathy

The types of spondyloarthropathy consist of the HLA-B27-related arthropathy, including ankylosing spondylitis, psoriatic arthritis (PsA), and gastroenteritis-associated arthritis. Some of these conditions, such as psoriatic arthritis, may be associated with psoriasis skin disease. Enteritis-associated arthritis can be related to underlying ulcerative colitis or Crohn's disease. For psoriatic arthritis, the arthritis can occur before, during, or after the appearance of the skin disease [69,70]. PsA has a more severe onset and a more destructive outcome in elderly subjects (age at onset, >60) than in younger subjects. This behavior may be influenced by age-related immune changes associated, as suggested by the higher concentrations of IL-1 β and IL-6 found in the synovial fluid of patients with early-onset PsA than in those with late-onset PsA [71]. In both of these cases, there tends to be an increase in the arthritis component with age. This increase may be caused by the usual onset of these diseases as colitis or skin disease and their development into arthritis. In cases in which the symptoms of arthritis first are associated with the primary disease, advancing age may allow the disease to progress and the arthritis symptoms to be more obvious. It is not clear if late-onset psoriatic arthritis occurs by chance or is caused by a collective accumulation of symptoms.

Caplanne et al compared 8 patients with late-onset spondylarthropathy with 32 patients with early-onset spondylarthropathy and reported that the onset of spondylarthropathy is uncommon after age 55 [72]. Inflammatory bowel syndrome was diagnosed in three patients with early-onset disease, but not in patients with late-onset disease. Although more studies are needed to confirm these findings, this study suggests that patients with early-onset spondylarthropathy have a higher incidence of proinflammatory response than do patients with late-onset spondylarthropathy.

The clinical features that distinguish early-onset from late-onset autoimmune diseases, such as systemic lupus erythematosus, RA, and psoriatic arthritis, are compared (Table 1). Although it commonly is believed that aging generally

Table 1
Comparison of early- and late-onset autoimmune symptoms in several autoimmune diseases

Disease	Clinical features	Early onset	Late onset	Reference
Systemic lupus erythematosus SLE	SLE disease activity index	More severe	Milder	[81]
	Hypocomplementemia	Higher frequency	Lower frequency	[82]
	Anti-DNA antibody	Higher frequency	Lower frequency	
	Gender bias	Female (13.3:1)	Female (3.2:1)	
	Prevalence of lupus nephritis	High	Low	
	Organs involved	High	Low	[83]
	Major relapses	High	Low	[84]
	Incidence of cutaneous lesions	High	Low	
	Serositis	Lower occurrence	Higher occurrence	
	Complaints of fever, alopecia, arthritis, and malar rash	More frequent	Less frequent	
Rheumatoid arthritis	Gender bias	Female (4:1)	Similar (1.6:1)	[66]
	Rheumatoid factors	Positive (60%)	Positive (36%)	[85]
	Involvement of shoulder joint	Lower (28%)	Higher (48%)	
	Inflammatory activity (ESR, CRP)	Lower	Higher	
	Extra-articular symptoms	Less severe	More severe	
Psoriatic arthritis	Gender bias	Similar	Male (9:3)	[86]
	Family history	Higher	Lower (paternal)	[71]
	Spondyloarthritis	Higher (43%)	Lower (17%)	
	Polyarthritis	Lower (34.5%)	Higher (50%)	
	Dactylitis	50%	25%	
	Sacroiliitis	41.5%	Asymmetric (17%)	
	HLA-B27	Positive (7.7%)	None	
	Foot-bone erosions	Less severe	More severe	
	CRP level	Lower	Higher	
Synovial-fluid levels of IL-1 β and IL-6	Lower	Higher		

Abbreviations: CPR, C-reactive protein; ESR, erythrocyte sedimentation rate.

accelerates or worsens the symptoms of autoimmune diseases, studies found less severe symptoms and a lower frequency of occurrence in older patients. A lesser degree gender bias was associated with the late-onset form of the autoimmune disease, suggesting that a dramatic decrease in the hormonal influences on late-onset autoimmune disease. Increased secretion of proinflammatory cytokines and increased inflammatory activity were associated with late-onset disease. Because no clear evidence was provided to follow the course of the autoimmune symptoms in patients with late-onset disease, these observations are not sufficient enough to explain the effect of the T-cell transitional defect that occurs during the senescent process on the development of late-onset autoimmune disease. These observations, however, do provide suggestive evidence that the onset of T-cell immune senescence, including T-cell AICD defects, activation defects, and replicative senescence, may be important in the manifestation of the autoimmune symptoms in middle-aged and elderly populations.

Prospects for therapy of age-related autoimmune disease

Immunosuppressive therapy

Autoimmune disease normally is treated with immunosuppressive therapy, such as prednisone, methotrexate, or cyclophosphamide. Late-onset autoimmune disease can be caused by decreased apoptosis, chronic inflammation, and oligoclonal expansion and is treated with these immunosuppressants. Caution is required, however, because autoimmune disease in the elderly can result in immune defects and autoimmunity.

Cytokines that might be associated with homeostatic proliferation

Homeostatic adjustments of T-cell numbers are important after an immune response, which is a time when most of the specific effector cells die by apoptosis. This change occurs after the onset of lymphopenia that is induced by different insults, including viral infection, toxic agents, radiation, and cytotoxic drugs. The role of thymic involution in homeostatic proliferation is unclear. In humans, it has been reported that peripheral mechanisms are generally sufficient to maintain normal T-cell number, function, and adequate TCR diversity in healthy hosts [73]. This finding suggests that the age-related homeostatic defects of T cells can be corrected by manipulating the peripheral microenvironment.

The peripheral factors that regulate T-cell homeostatic proliferation in a nonlymphopenic state were addressed in experiments that involved the injection of large numbers of bystander T cells and a small number of syngeneic naïve T cells, which could be distinguished with intracellular dyes. It was observed that naïve T cells could act as bystander inhibitors, whereas the activated and memory T cells were not efficient inhibitors [74]. Bystander naïve T cells did not require

signaling through the TCR and did not undergo homeostatic proliferation to inhibit homeostatic proliferation of the syngeneic naïve T cells. The regulation is mediated by non-MHC factors, such as stromal cell-derived cytokines, or by direct intracellular contact.

Cytokines that regulate homeostatic proliferation include IL-7, IL-12, and IL-15 [75–77]. IL-7 is associated with the survival of memory of T cells [78]. IL-2 suppresses and IL-15 promotes the survival of CD8 memory T cells [79]. Knockout mice that lack the IL-15 α receptor are lymphopenic and are devoid of CD8⁺ peripheral T cells [80]. It is not known if naïve T cells in the elderly have similar survival rates compared with the rates of younger individuals or if the aged versus younger microenvironments differ in supporting naïve T-cell survival. These questions are the subject of ongoing research.

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