Journal of Autoimmunity xxx (2013) 1–12

Contents lists available at SciVerse ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Review

Promotion and prevention of autoimmune disease by CD8+ T cells

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ARTICLE INFO

Article history:
Received 10 June 2013
Accepted 10 June 2013

Keywords:
Autoimmune disease
CD8+ T cell
Tolerance

ABSTRACT

Until recently, little was known about the importance of CD8+ T effectors in promoting and preventing autoimmune disease development. CD8+ T cells can oppose or promote autoimmune disease through activities as suppressor cells and as cytotoxic effectors. Studies in several distinct autoimmune models and data from patient samples are beginning to establish the importance of CD8+ T cells in these diseases and to define the mechanisms by which these cells influence autoimmunity. CD8+ effectors can promote disease via dysregulated secretion of inflammatory cytokines, skewed differentiation profiles and inappropriate apoptosis induction of target cells, and work to block disease by eliminating self-reactive cells and self-antigen sources, or as regulatory T cells. Defining the often major contribution of CD8+ T cells to autoimmune disease and identifying the mechanisms by which they alter the pathogenesis of disease is a rapidly expanding area of study and will add valuable information to our understanding of the kinetics, pathology and biology of autoimmune disease.

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1. Introduction

Significant effort has focused on understanding the process by which self-reactive lymphocytes escape tolerance and induce autoimmune disease. While it is well established that CD4+ helper T cells play an important part in the process of B cell activation during antibody-mediated autoimmunity and in cell-mediated disease, the role of CD8+ T cells is not as well established. It is recently becoming clear that CD8+ T cells, like their CD4+ counterparts, contribute to the induction, progression, pathogenesis and protection from many autoimmune diseases. Evidence primarily from studies in multiple sclerosis (MS) patients, the experimental autoimmune encephalomyelitis (EAE) mouse model and type 1 diabetes (T1D) demonstrates a critical role for CD8+ effector cells in the process of cell-mediated, tissue-specific autoimmune disease development. Fewer studies have evaluated CD8+ effector T cells in antibody-mediated autoimmune disease, and the field is confounded by the more recent re-identification of suppressor or regulatory CD8+ T cells.

Autoimmune disease susceptibility has strong links to certain molecules of major histocompatibility complex (MHC) class I or class II [1]. Disease susceptibility can be pinpointed to the MHC-I locus (as well as MHC-II) for T1D; in particular HLA-B*39 is strongly associated with T1D [2]. Likewise, using a genome-wide association study approach, it has been demonstrated that MS patients have altered disease susceptibility depending on their MHC I allele, with the HLA-A*0201 allele providing protection from disease [3]. As MHC-II has a strong association with general autoimmune disease susceptibility, it is possible that the influence of MHC-I is often hidden by that of MHC-II and other genes, and that many more diseases may be associated with particular MHC-I molecules.

CD8+ T cells have a well-documented role in the development of MS and diabetes. In early onset diabetes, CD8+ T cells are the most abundant pancreas-infiltrating cells during insulitis [4]. CD8+ autoreactive clones found in the peripheral blood are of the same antigen-specificity as the CD8+ T cells that infiltrate pancreas and cause disease [5]. Recent analysis of biopsy samples from early-stage MS patients identified CD8+ infiltrates in the cortex [6]. In agreement with a role for CD8+ T cells in disease initiation, depletion of CD4+ T cells in MS patients provided no benefit [7], while broader depletion of both CD4+ and CD8+ T cells led to fewer MS lesions and relapses [8]. Myelin basic protein (MBP)-specific CD8+ T cells can induce EAE [9], while myelin oligodendrocyte

Abbreviations: AIHA, autoimmune hemolytic anemia; ALPS, autoimmune lymphoproliferative syndrome; APC, antigen presenting cells; CTL, cytotoxic T lymphocytes; EAE, experimental autoimmune encephalomyelitis; HLA, human leukocyte antigen; LCMV, lymphocytic choriomeningitis virus; MBP, myelin basic protein; MOG, myelin oligodendrocyte glycoprotein; MPP, myelin proteolipid protein; MHC, major histocompatibility complex; MS, multiple sclerosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; T1D, type 1 diabetes; Tc, cytokine producing CD8+ effectors; TCR, T cell receptor; Treg, regulatory T cell; TRA, tissue restricted antigens.

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0896-8411/$ – see front matter Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.jaut.2013.06.004

glycoprotein (MOG)-reactive TCR transgenic CD8+ T cells alone can mediate optic neuritis and mild, late onset EAE, but MOG CD4+ T cells promote a more rapid disease [10]. Thus, there is evidence that CD8+ T effectors are present within tissue sites of disease and there appear to be differing effects by CD8+ T cells depending upon their antigen specificity.

Looking beyond MS and diabetes, the role of CD8+ T cells in other autoimmune diseases is beginning to be studied. Depletion of CD8+ T cells reduces the severity of disease in experimental autoimmune glomerulonephritis [11], experimental autoimmune myasthenia gravis [12] and several rheumatoid arthritis (RA) models [13,14]. In systemic lupus erythematosus (SLE) and anti-neutrophil cytoplasmic antibody associated vasculitis, an altered gene expression profile in CD8+ T cells correlates with an unfavorable disease outcome [15]. However, another study using a mouse model of SLE found no role for CD8+ T effector cells [16]. Perhaps these differences are related to the CD8+ regulatory T cells (CD8+ Tregs) that are now thought to be important in controlling SLE [17,18]. In patients with autoimmune hepatitis, antigen-specific CD8+ T cell clones have been identified [19], and a mouse model of disease confirms that antigen-specific CD8+ T cells are present in the liver, proliferate and produce cytokines, but are not alone sufficient for the establishment of severe disease [20]. In these autoimmune diseases, CD8+ T cells contribute to disease to varying degrees dependent upon the model of disease studied. But these studies begin to highlight CD8+ T cells as a critical modulator of disease that has been largely overlooked (Table 1).

In this review, we evaluate the striking, and sometimes conflicting, data on CD8+ effector T cell escape from tolerance and subsequent impact on development of autoimmune disease. We focus on the overall influence of CD8+ T cells in an attempt to define unifying modes of action by these cells, to ask questions and form a model for CD8+ effector T cell mechanisms leading to the breakdown of tolerance and induction of autoimmunity. A fundamental distinction should be made between autoimmune disease and inflammatory disease caused by CD8+ T cells. This review focuses on autoimmunity (ie. T cell mediated responses to self-antigens) where data are available.

Table 1
Evidence that CD8+ T effector cells play a role in autoimmune disease.

- Antigen-specific CD8+ clones are present in the peripheral blood and/or within target tissues

  Addison's disease [130], autoimmune hepatitis [19,20], diabetes [4,5], MS [6], RA [131]
- Depletion of CD8+ T cells delays or prevents disease

  Glomerulonephritis [11], MS [8], myasthenia gravis [12], RA [13,14]
- MHC-I alleles associate with disease susceptibility

  Diabetes [2], MS [3]
- Adoptive transfer of CD8+ T cells induces disease in recipient mice

  Diabetes [27], MS [9,10]
- Elevated expression of lytic enzymes in CTLs correlates with disease severity

  Autoimmune hepatitis [28], diabetes [26], MS [22,25], Sjogren's syndrome polymyositis [23,24], SLE [21]
- Death receptor induced killing promotes disease

  Diabetes [32–36], EAE [37–39], Hashimoto's thyroiditis [30], lupus [29], RA [31]
- Down-regulation of CTL effector function exacerbates disease; defects in CTL function correlate with autoimmune susceptibility

  ALPS [42], lupus [40,132], Theiler's virus-induced CNS autoimmune disease [41]
- CD8+ T cells expressing effector cytokines are expanded during autoimmune disease

  Tc1: AIHA (unpublished observations), autoimmune hepatitis [20], diabetes [52]

  Tc17: diabetes [46], EAE [45], immune thrombocytopenia [47], MS [44]

2. Autoreactive effectors in autoimmune disease

2.1. Cytotoxic T cell responses – preventing and supporting autoimmunity

CD8+ effector T cells normally function in protection against viruses and in elimination of tumor cells. This is achieved through TCR/CD8 recognition of MHC class I:peptide complex presented by target cells resulting in the cytotoxic targeting of abnormal or infected cells. Upon recognition of antigen, naïve CD8+ T cells differentiate into cytokine producing effectors (Tc) or cytotoxic T lymphocytes (CTL) and undergo clonal expansion. Activated effector cells then migrate to peripheral tissues and upon re-recognition of antigen target that cell for destruction. Killing of target cells by CTLs is mediated through two major pathways, release of cytolytic granules containing granzyme B and perforin resulting in direct lysis of target cells, and induction of Fas signaling triggering apoptosis pathways. Granzyme B enters the target cell following the formation of pores. It is thought that perforin forms these pores on the target plasma membrane, helping granzymes transfer into the cytosol of target cells; however it is not clear that perforin is required for this task. Entrance of granzyme B into the target cell cleaves several substrates including caspase-3 resulting in activation of caspase-3 and activation of BID (a Bcl-2 family member) leading to the eventual mitochondrial release of cytochrome c. Alternatively, engagement of Fas death receptor on a target cell by Fas ligand on, or secreted by, the CTL activates caspase-dependent apoptosis.

CTL-mediated killing begins with the recognition of APC-presented MHC-I:peptide by TCR on naïve CD8+ T cells. This process results in activation, CTL differentiation and targeting of peripheral cells presenting the specific peptide. Each step in this process is a potential site of dysregulation leading to induction of autoimmune disease, and alterations or dysfunction of these processes have been documented in several autoimmune diseases. Perforin-deficient and Fas/FasL-deficient mice have allowed the direct assessment of the two major effector mechanisms of CTL killing in vivo and the impact on disease severity and kinetics. In SLE, MS patients at relapse, Sjogren's syndrome and polymyositis it has been observed that an increased number of CD8+ T cells express perforin and/or granzyme B, and in some studies this increase correlates with disease severity [21–25]. In the NOD model, perforin-deficient mice demonstrate decreased incidence of diabetes development, indicating that CTLs contribute to the progression of this disease [26]. In support of this conclusion, adoptive transfer studies in NOD mice demonstrate CD8+ T cell involvement in beta cell destruction and development of diabetes [27]. In patients with autoimmune hepatitis, FasL and granzyme B levels are elevated in the liver, suggesting a role for CTLs in hepatocyte apoptosis and liver damage [28].

In addition to alterations in lytic proteins, death receptors are often involved in disease. SLE patients have elevated effector-memory CD8+ populations that express the cytotoxic receptor 2B4 [29]. In Hashimoto's thyroiditis Fas-mediated killing of thyroid follicular cells by CD8+ CTLs is critical for disease development [30], and in RA Fas + CD8+ T cells are increased in number suggesting a potential role for CTLs in these autoimmune diseases [31]. In diabetes several studies have demonstrated a role for Fas-mediated apoptosis during disease. NOD.gld mice (Fas ligand mutation) and NOD.lpr mice (Fas receptor mutation) do not develop diabetes [32], and a beta cell-specific defect in Fas in NOD mice partially augments disease [33]. Supporting a direct targeting by CD8+ CTLs, inhibition of beta cell expression of Fas and MHC-I protects NOD mice from CD8-mediated destruction [34]. However, the almost absent development of diabetes in perforin-deficient

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NOD mice [26], and the conclusion that perforin-mediated killing is more important than Fas-mediated apoptosis to beta cell destruction and diabetes [35], has led to the suggestion that CTLs switch effector mechanisms during the progression of disease [36]. Fas-deficient and Fas ligand-deficient mice are also resistant to induced EAE [37]. However, as with diabetes, the importance of Fas ligand-mediated apoptosis appears to change over the course of EAE and MS disease [38,39]. Thus, in several autoimmune models, elevated CTL activity correlates with tissue destruction and disease.

In other cases, defects or down-regulation of CTL effector function appears to exacerbate disease, suggesting that CD8+ T cells are important in eliminating autoreactive cells or in some way reducing inflammation or the availability of autoantigen. In these diseases CTL activity seems to be necessary for protection or in delaying autoimmunity. In an induced murine model of lupus, expression of TRAIL exacerbated disease mostly through effects on CD4+ T cells, but also in part, by downregulating perforin-mediated CTL function likely reducing killing of autoreactive B cells [40]. In the absence of TRAIL, CD8+ T cells mediated enhanced killing of B cells resulting in less severe lupus-like disease [40]. Theiler's virus-induced central nervous system autoimmune disease occurs in the absence of perforin, likely due to a role for perforin in viral clearance. Thus in the case of epitope spread following viral infection, CTLs are thought to be critical for controlling or slowing the development of autoimmune disease [41]. Together these studies indicate that CTLs may also prevent autoimmune disease by eliminating self-reactive cells or preventing release of antigen by unhealthy cells.

Defects in Fas function correlate with susceptibility to several systemic autoimmune diseases, most notably autoimmune lymphoproliferative syndrome (ALPS). Defective Fas or Fas ligand results in the accumulation of lymphocytes, and likely to an increase in autoreactive lymphocytes. Susceptibility is primarily due to the absence of the immune response switch-off, a program partially mediated by Fas-induced apoptosis in which the majority of effector lymphocytes are eliminated following the eradication of infection. This controls homeostasis of lymphocyte numbers and likely reduces risk of self-reactive lymphocyte activation by molecular mimicry or cross-reactivity during infection. ALPS occurs due to genetic autosomal dominant mutations in Fas or Fas ligand resulting in a defect in apoptosis [42]. Clearly incomplete or defective clearance of apoptotic cells in an important source of self-antigens and the development of autoimmunity, potentially by leading to elevated risk for necrosis and inflammation [43]. Alternatively, the bystander killing of tissue near cells targeted by CTLs may release antigen, resulting in inflammation and further lymphocyte activation. Properly mediated apoptosis may prevent necrosis and inflammation, and sequester self-antigens. While systemic defects in Fas ligand alter the activation state of many lymphocyte populations, it is likely that alteration of CTL function plays some part in the susceptibility to autoimmune disease. Targeted mutations of this apoptosis pathway specifically in CTLs in individual disease models would directly address the component affect (proportion of effect) of CTLs on disease.

Together CTL functionality studies indicate that in some autoimmune diseases elevated CTL activity results in more severe and advanced disease, while in other diseases CTLs are needed for protection from disease, perhaps by removing excess antigen, minimizing inflammatory signals or eliminating autoreactive cells. Further, in diseases such as SLE, data suggest both a protective and a deleterious role for CD8+ CTL activity in disease development, perhaps indicating a changing role for CD8+ effectors during different stages of disease progression.

2.2. Effector subsets and cytokines

The importance of effector cytokines is well established in autoimmune disease. As many lymphocyte populations produce effector cytokines, the contribution of different effector lymphocytes to the production and effects of these cytokines is less clear. Adoptive transfer of lymphocyte subsets into cytokine-deficient hosts has established the relative contribution of a cytokine produced by a specific cell population to the development of disease pathology. Until recently CD4+ T cells have been targeted as the major lymphocyte population driving autoimmunity through overproduction or dysregulated production of effector cytokines. However, cytokines produced by natural killer cells and CD8+ T cells might also contribute to disease outcome.

In addition to direct targeting of infected cells, CD8+ T cells may contribute to the expansion of an immune response through secretion of effector cytokines. CD8+ effectors can drive adaptive immune responses through secretion of cytokines such as IFNγ, IL-4, IL-17 and TNFα. As has been found with CD4+ T cells, there are several CD8+ effector subtypes defined by the cytokines that they produce, including Tc1, Tc2 and the newly identified Tc17. Tc1 effectors produce IFNγ, induce many of the same effects as Th1 cells and are important in cellular immune responses. Tc2 cells like their Th2 counterpart are important in humoral immunity and in many autoimmune diseases probably have a protective role. Through their production of IL-4, IL-5 and IL-10, Tc2 cells can inhibit macrophage activation, among other functions. Tc17 cells, like Th17 CD4+ effectors, are thought to be primarily proinflammatory. These are non-cytotoxic CD8+ T cells that have low granule expression, and low granzyme B and perforin production. The numbers of Tc17 cells are expanded in several autoimmune diseases including MS [44], EAE [45], diabetes [46] and immune thrombocytopenia [47].

In the IL-2-deficient AIHA model, IFNγ is critical for early disease and as CD4+ T cells can transfer autoimmunity [48], it was logical to conclude that T helper cells producing IFNγ are the major driver behind initiation of this antibody-mediated disease [49]. However, CD8+ T cells in these mice also express elevated IFNγ and may contribute to disease progression (unpublished observations). This is likely true in the initiation of many cytokine-mediated autoimmune diseases. In a few cases it has been established that cytokines secreted specifically by CD8+ T cells can drive disease. In MS patients CD8+ T cell production of IL-17 in lesions is associated with active disease suggesting a role for IL-17 in pathogenesis of disease [44]. Furthermore, in the EAE model CD8+ T cells polarized to a Tc17 phenotype act to potentiate disease in conjunction with CD4+ T cells [45]. In this study, Tc17 cells expedited the induction of the disease in an IL-17A dependent manner, and patient data demonstrated Tc17 expansion in cerebrospinal fluid and a possible role for this population in MS [45]. Together these investigations support the role of IL-17 secretion by CD8+ T effectors as an important driver of autoimmune diseases and highlight the importance of CD8+ effector subsets in autoimmune disease pathogenesis.

By modulating the CD8+ effector subsets, we may influence the clinical manifestations of autoimmune disease as has been found with CD4+ T cell subsets. Many autoimmune diseases are driven by skewing of CD4+ T cell responses down one of the Th1, Th2, or Th17 effector pathways. As we further explore the role of CD8+ effector subsets and production of cytokines by these cells, we may begin to define a complementary or enhancing contribution by these cells, or perhaps a separate role for cytokines produced by CD8+ effectors. For example, in Th1-mediated autoimmunity is the contribution of IFNγ produced by NK cells and CD8+ T cells as important to disease outcome as that from CD4+ T cells? Do these different sources of cytokines affect distinct

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downstream signals or target cells? In EAE, Th2 CD4+ T cells protect against induction and progression of disease by down-regulating the Th1 response [50,51]; might Tc2 CD8+ T cells have a similar protective effect by altering the differentiation profile during disease? Autoimmune disease in the IL-2-deficient BALB/c model is Th1-mediated and transferable by activated CD4+ T cells [48]. However, with the additional elimination of CD28 mice do not develop the early, lethal autoimmune hemolytic anemia [48]. The CD4+ T cells from these mice do not produce elevated IFNγ, known to be required for the rapid autoimmunity in this model, but instead produce elevated IL-4 (unpublished data). Perhaps the absence of CD28 protects, in part, from early autoimmunity by skewing the activation to a Th2 effector population thereby preventing Th1 differentiation. Most autoimmune studies evaluating the balance of T effector subsets have examined CD4+ T cells exclusively. How might CD8+ T effector subsets alter or shift this balance and contribute to disease initiation, kinetics or severity? A few recent studies begin to address the contribution of CD8+ effector subsets.

HA-specific CD8+ T cell subsets adoptively transferred into rat insulin promoter (RIP)-HA transgenic recipient mice expressing HA in the pancreatic β cells allowed one group to evaluate the effectiveness of Tc subsets in promoting diabetes. In this model, Tc1 cells accumulate faster in the pancreas than Tc2 cells and result in enhanced diabetes kinetics at lower numbers of effector cells [52]. The differences in disease kinetics and severity were attributed to different profiles of chemokine receptor expression and subsequent ability of the CD8+ effector populations to migrate into specific target tissues, with Tc1 cells homing better to the pancreas. In autoimmune hepatitis type 2, IFNγ production by antigen-specific CD8+ T cells decreased with effective treatment of disease, suggesting that CD8+ T cells, particularly Tc1 effectors are important to the pathogenesis of this disease [19]. Tc2 cells have been primarily associated with protection from autoimmune disease and can downmodulate immune responses by downregulating MHC-II and expression of costimulatory molecules on dendritic cells in addition to secreting the anti-inflammatory cytokine IL-10 [53]. Tc2 effectors can likely also act in a pathogenic fashion in autoimmunity, just as Th2 cells, while considered to be mainly protective, can induce pathogenic effects in some diseases. Huber et al. came to a striking conclusion that Tc17 cells act directly via membrane-bound IL-17A to promote CD4+ T cell Th17 differentiation in the development of EAE. They further demonstrated that infiltration of CD4+ effectors into the CNS during early disease, when CD4 numbers are still fairly normal, requires CD8 “reverse” help [45]. These data demonstrate that different CD8+ effector populations can have distinct pathogenic outcomes.

The timing of cytokine expression during different stages of disease can alter the outcome of some autoimmune diseases. For example, in diabetes using the RIP-CD80 model, blockade of TNFα after postnatal day 30 results in rapid CD8-dependent diabetes, while blockade at day 25 delays disease development and at day 21 eliminates disease [54]. In another study it was found that the role for CD8+ T cells is in the initiation of disease and CD4+ T cells are more relevant in the progression of disease [55]. This finding fits well with Huber et al. demonstrating that EAE is more rapidly initiated when CD8+ T cells are present, but CD4+ T cells are necessary to drive disease [45]. Imbalance in CD4+ Th cell populations is a factor in many autoimmune diseases, it is thus not surprising that Tc dysregulation, as with CD4+ effector T cells, would also influence disease outcome. Ongoing study is needed to define the contribution of different effector populations and their role during different phases of autoimmunity. However, there is growing evidence that CD8+ T effectors are a critical player in the development of autoimmune disease (Table 1).

3. CD8+ regulatory T cells in autoimmunity

In addition to an effector or pathogenic role, CD8+ T cells can also provide a regulatory influence (or participate in a regulatory capacity). A role for CD8+ Tregs has been demonstrated for Grave’s disease [56], Myasthenia gravis [57], SLE [18] as well as others [58]. Adoptive transfer of CD8+ Tregs can control AIHA in the anti-murine RBC rat model [59]. It has been suggested that CD8+ Tregs normally control AIHA in this model but become defective leading to, or as disease develops. In support of this idea, CD8+ Treg numbers are decreased and produce less IL-10 in AIHA patients [60]. Newer combinations of surface markers have allowed for a more accurate analysis of CD8+ Tregs relative to effectors, but the increased number of described regulatory populations has also made comparison between studies sometimes challenging. For this review we focus primarily on the pathogenic role of CD8+ T cells, however, many studies have highlighted the importance that loss or dysregulation of the CD8+ regulatory cell population has on autoimmune disease and we will highlight a few of these.

Although CD8+ Tregs were first discovered over 30 years ago, much of what we know about regulatory T cells we have learned from CD4+ Tregs. CD4+ and CD8+ Tregs are characterized by expression of the transcription factor forkhead box protein 3 (Foxp3). They are generated in the thymus in response to self-antigen, or in the periphery in response to foreign or self-antigen. CD4+ Tregs express high levels of CD25 (IL-2Rα), while in comparison, one population of CD8+ Tregs is distinguished by CD122 expression (IL-2Rβ) and another by CD25 expression [61]. From CD4+ Treg studies it is known that IL-2 is required for the homeostasis, survival and functionality of these cells [62–64]. In the absence of IL-2, there is a drastic reduction in the percentage of peripherally-derived CD4+ Tregs and a defect in their functionality [63,65]. It is not clear if IL-2 is similarly required for CD8+ Treg generation, survival and functional activity, but it has been suggested in part based on their high expression of the IL-2R. Shameli et al. have recently demonstrated that increased IL-2 production promotes the regulatory function of CD8+CD122+ Tregs [66]. Thus, IL-2 has at least some overlapping functions in CD4+ and CD8+ Tregs.

Garnering further information from CD4+ Treg studies, populations of both CD4+ and CD8+ Tregs have been shown to suppress immune responses via secretion of IL-10 [67–69], and through direct interactions via expression of CTLA-4 [61,70]. One major difference between CD4+ and CD8+ Tregs appears to be in the CD8+CD28^{low} Treg population [71]. CD28-B7 interactions are necessary in CD4+ Tregs for their thymic development and peripheral maintenance [72]. This requirement for CD28 is only partially due to reduced production of IL-2 [48,73,74]. This CD8+CD28^{low} population that expresses similar markers as CD4+CD25+ Tregs (such as Foxp3 and CTLA-4) has been found to suppress several autoimmune diseases [57,75]. Thus both similarities and differences have been found between CD4+ and CD8+ Tregs, and this is an area of ongoing study by many groups.

Recently, it has been suggested that CD4+ Tregs constitute an unstable T cell subset that can reprogram into effector T cells producing effector cytokines and driving pathogenesis. Zhou et al. found that CD4+ T cells once expressing FoxP3 can downregulate its expression, lose their suppressive capacity and develop an activated-memory phenotype [76]. These ‘ex-Tregs’ produce pro-inflammatory cytokines, can be found in diabetic mice and transfer diabetes [76]. Could CD8+ Tregs also be unstable and contribute to autoimmune disease development as ‘ex-Treg’ effectors? This question has not yet been addressed in CD8+ Tregs. While there are many similarities between the development, functional mechanisms and requirements for homeostasis, some differences exist

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that require additional characterization and experimentation. It is also not clear how each population may work together or independently to protect from autoimmunity. Are both populations of Tregs always dysregulated or dysfunctional during development of disease, or is the loss of suppressive capacity by one enough to tip the balance toward disease?

4. Mechanisms of CD8+ T cell tolerance and why they fail

4.1. Central tolerance

In broad terms central tolerance is dominated by deletion of self-reactive lymphocytes during thymic maturation in an event termed negative selection. This process can be viewed as the first line of defense against autoreactivity. T cells with very low avidity for MHC:peptide complex die by neglect due to the absence of TCR signals required for induction of pro-survival proteins. T cells whose TCR reacts with strong avidity undergo apoptosis-induced deletion or differentiate into Tregs through a largely undefined mechanism. This leaves about 2–5% of thymic T cells with the optimal low to intermediate affinity for MHC bound to self-peptide that survive positive and negative selection and exit the thymus as mature CD4+ or CD8+ T cells. Thymic epithelial cells (TECs) make up the principal population of cells with which developing thymocytes interact and provide a source for self-antigen presented via MHC-I and MHC-II molecules for developing thymocytes to sample. Both ubiquitously expressed self-antigens, as well as highly specialized tissue restricted antigens (TRAs) are presented by medullary TECs (mTECs) [77]. The critical importance of negative selection of TRA-specific thymocytes is underscored by data from humans and mice with deficiencies in Aire, a transcription factor critical for TRA expression by mTECs that has been extensively reviewed [78]. Aire deficiency in humans causes autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) and a similar disease in mouse models. APECED patients develop severe multi-organ autoimmune disease due to the lack of TRA expression by mTECs.

While CD8+ T cells escape thymic negative selection in Aire-deficient mice, their relative importance to the autoimmune pathology in these mice may be more limited than CD4+ T cells. Adoptive transfer of CD4-depleted or CD8-depleted lymphocytes from Aire-deficient mice into immunodeficient hosts revealed that CD4+ T cells were necessary for immune infiltration of target tissues, while CD8+ T cells did not appear to be sufficient to cause the characteristic autoimmune infiltrates [79]. However, subsequent studies in Aire-deficient mice have demonstrated that CD8+ T cells do contribute to particular disease manifestations. Aire deficiency, when combined with CBL-B deficiency, an ubiquitin ligase critical for anergy induction of peripheral T cells, results in severe autoimmune exocrine pancreatitis [80]. This disease required CD8+ T cells to develop. Thus, autoreactive CD8+ T cells escaping Aire-dependent central tolerance may be well controlled by anergy induction. However, when anergy mechanisms are compromised, autoreactive CD8+ T cells that escape central tolerance become highly pathogenic. Aire-deficiency also leads to a defect in the $CD8^{+}CD28^{low}$ Treg population. This population normally controls inflammation in a CD4-transfer experimental colitis model. However, $CD8^{+}CD28^{low}$ Tregs from Aire-deficient mice are incapable of preventing colitis, possibly due to an altered TCR repertoire of this population [81]. Evidence from APECED patients suggests that a loss of Aire function results in CD8+ T cells with dysregulated IL-7 signaling and altered CD8+ T cell homeostasis, which likely plays a role in the disease pathogenesis [82]. Combined, these observations suggest that defects in the CD8+ T cell population result from a lack of Aire and can contribute to autoimmune disease, especially when other mechanisms of peripheral tolerance are compromised.

Beyond AIRE-expressing mTECs, there are several alternative mechanisms of TRA presentation and clonal deletion of developing CD8+ T cells in the thymus. Deletion of MBP reactive cells in TCR transgenic mice has provided a model to define the relative contributions of cellular players and sources of antigen in this process. Using bone marrow chimeras in which MBP expression was restricted to defined bone marrow-derived or non-bone marrow-derived populations, the relative contribution of each cell type was determined. Interestingly, MBP was found to be synthesized and directly presented by bone marrow-derived cells, which was sufficient to mediate MHC-I restricted central tolerance [83]. mTECs also were shown to cross-present MBP that they acquired from an exogenous source. These data suggest that TRA presentation to developing CD8+ cells in the thymus is not entirely mediated by autonomous activity of mTECs and may partially explain the relatively mild contribution of CD8+ T cells in the autoimmune phenotype of Aire-deficient mice. In a humanized EAE mouse model an alternative mode of negative selection has been described for myelin proteolipid protein (PLP)-specific CD8+ T cells. A transgenic, pathogenic TCR specific for PLP45-53 presented on the HLA-A3 allele strongly recognizes a non-myelin peptide presented by HLA-A2 [55]. This degenerate recognition leads to negative selection in the thymus in mice expressing both HLA-A3 and HLA-A2, while CD8+ T cells do not undergo efficient negative selection, are present in the periphery, and cause disease in mice where only HLA-A3 is expressed. These findings demonstrate a protective function of certain MHC alleles via their ability to induce negative selection of pathogenic CD8+ T cell clones and may explain the protective effects attributed to the HLA-A2 allele in MS patients [84].

4.2. Peripheral tolerance mechanisms

Central tolerance is often incomplete allowing potentially harmful self-reactive T cells to escape into the periphery. Some antigens are not expressed in the thymus or are expressed at low levels that do not induce deletion of self-reactive cells. Once in the periphery, self-reactive T cells are normally controlled by one of three primary mechanisms: anergy, deletion or suppression by Tregs. Anergy is a state of unresponsiveness actively maintained by the presence of antigen. While CD4+ T cells stimulated in the absence of costimulation become anergic, evidence indicates that CD8+ T cell stimulation may require costimulatory signals for induction of anergy. Anergy may occur via several mechanisms, including downregulation of TCR and CD8 expression [85,86], or impairments in signaling [87]. Normal homeostatic control, such as limiting availability of cytokines, growth and survival factors may also help to maintain anergy.

In addition to MHC:peptide recognition by the TCR, T cells must receive a second costimulatory signal to become activated and differentiate into an effector cell. When CD4+ T cells do not receive this costimulatory signal, or receive instead an inhibitory signal, such as CD28:CTLA-4 or PD-1:PD-L1, they become anergic. In many autoimmune diseases these inhibitory signals are dysfunctional in CD4+ and CD8+ T cells [88,89]. Unlike in CD4+ T cells, CTLA-4 is not necessary for CD8+ T cell anergy [90], while PD-1 signaling is a critical component of CD8 anergy induction [88]. CD8+ T cells appear to require strong signals for full activation. The presence of inflammatory cytokines or the state of dendritic cell maturation influences the outcome of T cell activation. Low MHC-I and costimulatory molecule expression by dendritic cells results in tolerance, while an inflammatory condition with mature dendritic cell cross-presentation of antigen allows CD8+ T cell activation. The presence of CD4+ T cell help can provide an additional “third” signal important for CD8+ T cell activation. Together, a myriad of

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studies indicate that the fate of T cell activation or anergy induction is based on the combined outcome of costimulatory and inhibitory signals during antigen recognition. Tregs recognizing self-antigens can further influence the fate of a CD8+ T cells by down-modulating immune responses of self-reactive lymphocytes.

Although not as well characterized as CD4+ Tregs, CD8+ Tregs play a well-established role in peripheral tolerance and under normal conditions act to prevent activation, expansion and differentiation of self-reactive lymphocytes. Tregs act to limit immune responses and are one major mechanism of peripheral tolerance and control of autoimmunity. In some autoimmune diseases CD8+ Tregs do keep autoimmunity somewhat in check. This is evident by the increase in disease that occurs in some models when CD8+ Tregs are depleted. However, in many autoimmune diseases either CD8+ Tregs cannot keep up with the rapid expansion of effector cells or these cells become defective contributing to the onset of disease. Depending upon the autoimmune disease, depletion of bulk CD8+ T cells has resulted in amelioration of disease, or more severe and rapid disease. Elimination of CD8+ T cells resulting in more advanced autoimmune is most likely due to the removal of CD8+ Tregs and their suppressive capacity, allowing uncontrolled effector pathogenic responses.

Self-reactive CD8+ T cells can escape central tolerance either because their cognate antigen is not expressed in the thymus or because the antigen is expressed at low concentrations and does not sufficiently activate these CD8+ T cells. Under normal healthy conditions, these CD8+ T cells may never encounter their antigen in the periphery and persist in a naïve state called clonal ignorance. This is often achieved through antigen restriction to immune privileged sites. However, if these sites become accessible by the T cells or if antigen is released, then these self-reactive cells must be contained by other tolerance mechanisms or activation may occur. Antigen release during infection and subsequent inflammation and tissue damage can break ignorance and drive autoimmunity. Voehringer et al. demonstrated using a transgenic mouse system that infection with lymphocytic choriomeningitis virus (LCMV) could break CD8+ T cell ignorance and induce autoimmune hepatitis [91]. The role of bystander activation and molecular mimicry in driving autoimmunity following infection will be further described below.

The occurrence of ignorance versus other mechanisms of tolerance, such as deletion or anergy, depends on antigen dose and duration of exposure. Low dose OVA expression in the pancreas failed to elicit a CD8+ T cell response in RIP-OVA mice, while high dose OVA resulted in T cell deletion [92]. These data in combination with other studies indicate that low dose antigen allows a state of T cell ignorance, while high dose leads to clonal deletion. As is true for CD4+ T cells [93], the duration of antigen exposure contributes to the fate of CD8+ T cell activation. Systemic prolonged exposure to antigen, such as in chronic viral infection, allows initial CD8+ T cell activation followed by anergy induction [94], and cells can regain responsiveness if exposure to antigen is removed [95].

In addition to negative selection occurring in the thymus, there is increasing support for peripheral mechanisms to delete TRA-specific T cells in the lymph nodes [96–98]. As naïve T cells migrate readily through lymph nodes this would be an effective site for TRA expression to mediate clonal deletion. A subset of lymph node stromal cells expresses Aire [97,98]. These cells have been referred to as extra-thymic Aire-expressing cells (eTACs) [97]. Aire expression in these cells is necessary for their presentation of many TRAs. There is evidence that eTACs may provide more than functional redundancy to mTECs as the TRAs expressed in eTACs and mTECs have little overlap [97]. Thus, eTACs may constitute a population that serves a unique role in peripheral tolerance induction.

The role of eTACs in the clonal deletion of CD8+ T cells has been demonstrated in a transgenic mouse model that expresses islet-specific glucose-6-phosphate (IGRP) under the control of the Aire locus [97]. IGRP is not expressed in the thymus or lymphoid organs in wild-type mice. Transfer of IGRP-specific CD8+ T cells resulted in their deletion due to IGRP presentation by eTACs. These results indicate that eTACs can function in a similar capacity to Aire expressing mTECs to delete autoreactive CD8+ T cells in the periphery.

Similar to Aire-deficient mTECs that express TRAs, other Aire-deficient stromal subsets in the lymph nodes have been shown to express TRAs [98,99]. In an OVA transgenic model where truncated OVA expression is driven by the intestinal fatty acid promoter, expression of truncated OVA is observed in lymph node stromal cells independent of Aire [98]. OVA-specific CD8+ T cells transferred into these mice are peripherally deleted. These findings have been extended beyond transgenically driven antigens; peripheral deletion of autoreactive CD8+ T cells has been demonstrated in a non-transgenic model where physiological levels of the self-antigen tyrosinase are expressed by lymph node stroma [100]. These findings provide evidence that peripheral tolerance of CD8+ T cells can be mediated by both eTACs and other lymph node stromal cells and is not an artifact of transgenic over-expression systems.

4.3. TCR avidity to self-antigen and disease

The failure to negatively select CD8+ T cells that will go on to initiate autoimmune disease can stem from multiple causes. Insufficient amounts of antigen may be presented by mTECS or bone marrow-derived APCs to facilitate clonal deletion. This can be the result of poor expression of the antigen by thymic APCs or poor binding of the antigen to the MHC complex. Clinical data from T1D patients suggests that many targeted peptides exhibit poor MHC-I binding [101,102]. Also, the avidity of autoreactive TCRs can be sufficiently low so that effective clonal deletion does not occur. Thus, not all self-reactive T cells undergo negative selection either because their antigen is not expressed in mTECs or due to weak avidity for their antigen allowing escape.

TRA-specific relatively low avidity CD8+ T cells that escape negative selection due to their sub-threshold signaling have been demonstrated to exist in the periphery and are capable of causing autoimmunity, even in the presence of Tregs [103]. Recently, low avidity CD8+ T cell transgenic lines have been generated allowing detailed study of selection and disease-causing ability in a clonal manner. One model generated utilizes RIP-mOVA mice that express membrane-bound OVA in mTECs. Crossing these mice with OT-1 TCR transgenic mice, which possess a high avidity OVA-specific TCR, results in efficient negative selection in the thymus. Enouz et al. generated a related TCR specific to OVA, requiring 50 times the peptide concentration in vitro to induce a similar IFNγ response [104]. This TCR, termed OT-3, possessed OVA avidity just below the negative selection threshold, escaped negative selection, and survived in the periphery. Infection of OT-3/RIP-mOVA mice with *Listeria monocytogenes* expressing OVA peptide resulted in effective activation of OT-3 cells and induction of diabetes.

Another model demonstrating the importance of CD8+ TCR avidity is the RIP-LCMV model. RIP-LCMV mice express the LCMV glycoprotein (LCMV-GP) on the C57BL/6 background and the LCMV nucleoprotein (LCMV-NP) on the BALB/c background [105]. Upon LCMV infection, both mice develop CD8 dependent T1D, but at vastly different rates [106]. This result was attributed to differences in TCR avidity. RIP-LCMV-GP mice with rapid onset do not express GP in the thymus, while RIP-LCMV-NP mice express NP in the thymus, and delete TCRs with high avidity to NP. This led to a 10-fold lower TCR avidity for NP relative to the TCR avidity for GP. In addition to delayed disease kinetics, the CD8+ T cells also required

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help from CD4+ T cells to induce disease in LCMV-NP mice, while the high avidity CD8+ T cells in RIP-LCMV-GP mice caused disease independent of CD4 help [106,107].

In summary, mouse models for T1D suggest that while CD8+ T cells of high avidity cause rapid, dramatic disease [108,109], these high avidity clones are limited in their disease causation due to central and peripheral tolerance mechanisms. Strategies to delete high and intermediate reactivity TCR clones specific to IGRP have been utilized, leaving only very low avidity clones incapable of causing T1D [110]. While the contributions of relatively low avidity interactions between autoreactive CD8+ T cells and peptide presenting APCs in other autoimmune disorders need to be further evaluated, there is evidence from the EAE model that this may be a generalizable phenomenon [111].

4.4. Pathogen-induced CD8 activation and disease

For many years, there has been a clear connection between infection, chronic inflammation, lymphoproliferation and development of autoimmune diseases. Infection can lead to activation of a CD8 immune response and tissue damage through several mechanisms. 1) Infected cells can be targeted by pathogen-specific CD8+ cells leading to tissue damage. While this is a major cause of disease, it is not autoimmune in nature and will not be discussed; 2) Infection can result in cross-reactivity of pathogen-specific CD8+ T cells to self-antigens with structural similarity (molecular mimicry); 3) Infection can cause normally non-disease-causing CD8+ T cells with avidity for self-antigens to become activated and acquire effector functions due to the inflammatory milieu (bystander activation); 4) CD8 T cells expressing two functional TCRs can become activated by a pathogen through one TCR and attack self-antigen via reactivity of the second TCR. These mechanisms are likely to occur across the spectrum of autoimmune disorders, but many of the examples below will focus on the diabetes model, which has been extensively studied.

4.4.1. Molecular mimicry

Molecular mimicry is the situation where foreign antigen structurally resembles self-antigen. If the foreign antigen is sufficiently similar to host antigen, a strong immune response to that foreign antigen may cause immune cross reactivity against the host and drive autoimmune disease. This is unlikely to be due to identical overlap in antigen structure as effective central tolerance should delete autoreactive T cells of strong self-avidity. Thus, it is likely that a similar protein structure leads to activation of moderate avidity TCRs able to escape central tolerance mechanisms. Molecular mimicry has been shown to exist between pathogens and self-antigens that are targeted by both humoral and cell-mediated immune responses in patients with various autoimmune diseases [112,113]. There is strong evidence that infection with *Campylobacter jejuni*, which has homology to the GM-1 ganglioside, precedes disease in Guillain–Barre syndrome and this can be replicated in animal models [114].

Animal models have confirmed a causative role for mimicry in autoimmune responses by CD8+ T cells and have allowed for mechanistic studies. The RIP-LCMV model has provided much information pertaining to molecular mimicry in T1D initiation. In RIP-LCMV mice, LCMV NP or GP is expressed by pancreatic islet cells as a self-antigen. Subsequent infection with LCMV results in diabetes due to molecular mimicry [105,115]. Additional studies show that exact self and foreign antigen overlap is not required if the CD8 TCR is of sufficiently high avidity to the mimicked self-peptide. Also using the RIP-LCMV model, Gronski et al. demonstrated that self-peptide mimics expressed by LCMV cause disease if the self-TCR avidity to them is sufficiently strong [108]. The authors found that an altered LCMV peptide with 5-fold less TCR avidity than the self-antigen was still able to cause T1D. However, LCMV expressing an altered peptide with 20-fold less TCR avidity was unable to elicit disease. Despite the lack of diabetes, even these lower avidity interactions cause CTL induction and insulitis. In diabetes, reports have indicated there are potentially many viruses that can lead to cross-reactivity with islet self-antigens [116–118]. This breadth of viral mimics may help explain the lack of direct correlation between any single virus and a large portion of T1D cases and may support findings that only a subset of T1D cases can be attributed to any particular virus. In addition to T1D, many other infection models have shown a role for molecular mimicry, including multiple sclerosis, autoimmune stromal keratitis, and treatment resistant Lyme arthritis [119–121].

4.4.2. Bystander activation

During the course of a normal immune response to viruses and bacteria, the inflammation that occurs may induce bystander activation, a situation where CD8+ T cells become activated independent of cross-reactivity to pathogenic epitopes. In the case of chronic viral infection, ongoing inflammation can drive proliferation, differentiation and ultimately effector responses of self-reactive CD8+ T cells normally controlled by Tregs or through anergy. Chronic inflammation provides costimulatory (second) signals to anergic self-reactive T cells via APCs and a “third signal” via inflammatory cytokines. Inflammation can activate APCs that then produce cytokines to induce T cell effector differentiation. The threshold of TCR signaling required for activation of low-avidity cells is decreased by inflammation. In Behcet’s disease, an inflammatory disorder characterized by uveitis and epithelial ulcers, MIC-A-specific CD8+ T cells become activated by a stress inducible antigen expressed by the epithelium [122]. Thus, inflammation in these patients results in the development of autoimmunity to an antigen normally not expressed. This CD8 mediated attack can exacerbate and prolong disease at inflamed sites. During the course of an autoimmune disease, inflammation is often progressively elevated due to increased antigen release during tissue destruction, ongoing activation of lymphocytes and infiltration of lymphocytes and monocytes into tissues. This progressively expanding inflammatory setting provides a positive feedback loop that amplifies the autoimmune response, thus bystander activation and subsequent inflammation can be a hugely detrimental problem in the development of autoimmunity.

4.4.3. Dual antigen-receptor expression

The possibility that T cells can express dual TCR has provided a novel mechanism by which tolerance can be broken. It is estimated that 1–8% of peripheral T cells in mice and humans express dual TCR on their cell surface due to incomplete allelic exclusion at the TCRα locus [123,124]. These TCRs can both be functional and contribute to immune responses and disease [125,126]. In a graft-versus-host disease model, dual TCR expressing T cells are strongly increased in the alloreactive population of both CD4+ and CD8+ T cells [127]. Evidence is beginning to accumulate linking dual TCRs to the development of autoimmune disease (Table 2).

Table 2
Dual TCR expression in autoimmune disease.

Disease model implicated	Dual TCR population	References
Alopecia areata	CD8+	[133]
Autoimmune arthritis	CD4+	[134]
Diabetes	T cell, CD4+	[135–137]
Experimental autoimmune encephalomyelitis	CD8+	[128,138]
Multiple sclerosis	CD8+	[129]
Psoriasis vulgaris	CD8+	[129]

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In the context of autoimmunity, the situation might arise in which one TCR has low avidity to self-antigen, while the second TCR has high avidity to foreign antigen. In this situation the self-antigen specific TCR must be of relatively low avidity to survive negative selection. However, unlike the self-antigen specific single-TCR T cells, a dual TCR can provide a mechanism by which effective, strong T cell activation can occur, resulting in massive clonal expansion and effector functionality. This has been demonstrated as a mechanism to break tolerance in an EAE model. In this model transgenic CD8+ cells specific for MBP become activated upon infection with vaccinia virus expressing MBP [128]. Rather than due to viral mimicry, the authors found that wild-type vaccinia virus could also initiate the activation of MBP transgenic T cells independent of the vaccinia expression of MBP and also independent of bystander activation. They discovered EAE onset was due instead to dual TCR expression for viral antigen and MBP. The relevance of dual TCR expression to human disease is still largely unknown. However, a recent report analyzing TCRα and β chains from autoimmune lesions of patients with psoriasis vulgaris and multiple sclerosis has identified the presence of dual TCRα chains in several isolated CD8+ clones [129]. Further characterization will be required to establish if these dual TCR-expressing clones are indeed contributing to the breakdown of tolerance.

In conclusion, there are multiple mechanisms by which tissue-specific autoreactive CD8+ T cells can become activated. These mechanisms are unlikely to occur in a mutually exclusive manner. For example, tissue-specific CD8+ T cells activated due to molecular mimicry or viral infection of the targeted tissue may lead to tissue-specific cell destruction, which may release self-antigens that are presented by activated APCs and lead to autoantigen targeting and epitope spreading via bystander activation.

5. Conclusion: future directions and unifying themes

As highlighted in this review and others, there are many tolerance mechanisms in place that act to prevent self-reactivity and autoimmune disease. We set out in this review to determine whether prior investigations into the mechanisms of effector CD8+ T cell contribution to disease could be used in defining differences in CD8 responses between cell-mediated versus antibody-mediated disease or tissue-specific versus systemic disease. Instead the data across multiple autoimmune diseases suggests that any normal function of CD8+ effectors can be circumvented during the process of self-reactive lymphocyte activation and resultant autoimmune disease development (Fig. 1). One challenge to this goal is that many studies evaluating CD8+ T cell function have been performed in diabetes, MS/EAE and lupus, but there are relatively few in depth studies across other autoimmune diseases. Perhaps as we begin to expand our understanding of CD8+ effectors in multiple autoimmune disease settings, and as CD8+ T cell functionality studies in these diseases become more mechanistically detailed, we can begin to identify emerging themes and dysregulated pathways utilized by CD8+ T cells in these distinct autoimmune diseases.

Simply looking at one population of effector cells, the CD8+ T cells, demonstrates the complexity and multiplicity of functions, and potential for dysfunction that may contribute to the development of autoimmune disease (Table 3). Add to this the involvement of different immune cells, mechanisms of action, antigen-specificities and target tissues, and it becomes truly challenging to discern the critical dysregulated mechanisms leading to autoimmunity. Different autoimmune diseases may develop dependent upon the antigen being targeted and the influence of these various immune cells, some acting to drive disease and others working to induce tolerance and block autoimmunity. Studying CD8+ T cells and their effector fate decisions may prove useful in the treatment of some autoimmune diseases. Learning how to optimally exploit the balance of effector responses or their functional diversity for clinical application will require a greater understanding of how these cells are regulated at developmental and functional stages. This would allow more specific manipulation of CD8+ T cell responses in disease without altering other immune populations and functions.

Autoimmunity is a complex problem resulting from dysregulation of cytokines, chemokines, signaling pathways and the contribution of many cell types. Unveiling the step-by-step process leading to autoimmune disease and ultimately the ability to effectively treat disease will require and in-depth understanding of each of these cells and their mechanisms. Future studies will require the ability to understand the role of each individual contributor to disease and the inter-relationship of these factors. We are left with many questions about the dominant effector cell populations during different stages of disease and which of the many potential effector mechanisms might be driving the process of autoimmunity in various diseases.

This paper and this issue are dedicated to the contributions of Dr. Abul Abbas in teaching, research and public service. It is part of the journal's attempt to thank and acknowledge truly outstanding

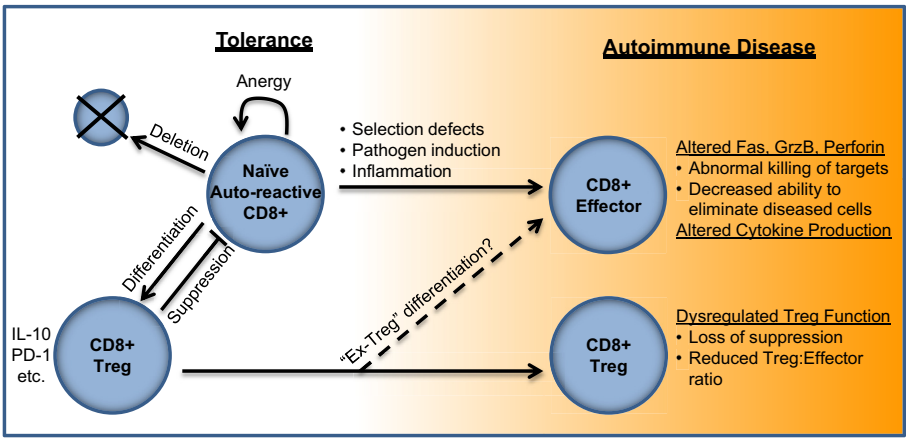

Fig. 1. Potential influence of CD8+ T cells on autoimmune disease. Self-reactive CD8+ T cells are normally controlled by mechanisms of central and peripheral tolerance, but when these controls are dysregulated CD8+ T cells can promote the development of autoimmune disease. Changes in cytolytic or death receptor signals, skewed differentiation of effectors or loss of regulatory function in the CD8+ T cell population may promote autoimmune pathogenesis.

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Table 3
Mechanisms of CD8+ T cell dysregulation in autoimmune disease.

CD8+ T cell mechanisms	Diseases implicated
CTL effectors	
Tissue infiltration	Autoimmune hepatitis [19,20], diabetes [4,5], MS [6], RA [131]
Elevated lytic proteins	Autoimmune hepatitis [28], diabetes [26], MS [22,25], Sjogren's syndrome polymyositis [23,24], SLE [21]
Altered death receptors (Fas, etc.)	Autoimmune hepatitis [28], diabetes [32–34,36], lupus [29], Hashimoto's thyroiditis [30], MS/EAE [37–39], RA [31]
Cytokine producing effectors	
Elevated Tc1 (IFNγ)	AIHA (unpublished observations), autoimmune hepatitis [19], diabetes [52]
Elevated Tc17 (IL-17)	Diabetes [46], EAE [45], immune thrombocytopenia [47], MS [44]
Genetic susceptibility	
Aire deficiency	APECED
Fas defects	ALPS
MHC-I association	Diabetes [2], MS [3], ulcerative colitis [139]
Treg dysregulation	
Altered function &/or reduced numbers	AIHA [60], diabetes [140], EAE [141], MS [142], RA [143], SLE [18,144], ulcerative colitis [145]
Tolerance dysregulation	
Selection defects	Autoimmune hepatitis [91], T1D [101,102]
Molecular mimicry	Autoimmune hepatitis [146,147], autoimmune stromal keratitis [120], Guillain–Barre syndrome [114], Lyme arthritis [121], MS [119], T1D [105,116–118,148]
Dual antigen receptor expression	Alopecia areata [121], EAE [114,120], MS [115], psoriasis vulgaris [115]

individuals whose work has implications for patients who suffer from autoimmunity. Our previous honorees have included Ian Mackay, Harry Moutsopoulos, Noel Rose, Chella David, and Pierre Youinou [149–151]. Over the course of his career, Dr. Abul Abbas has contributed vast information to our current understanding of how some of these factors and cell populations interact during homeostasis and escape tolerance during autoimmune development. He has trained and mentored many others who now also ask critical questions about the mechanisms of tolerance and the breakdown of these mechanisms during autoimmune disease. It was a privilege to train with Dr. Abbas (K.K.H.) and an honor to contribute to this issue highlighting his contributions to the field. We congratulate him for his recognition as a distinguished immunologist in this special issue of the *Journal of Autoimmunity*.

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Please cite this article in press as: Gravano DM, Hoyer KK, Promotion and prevention of autoimmune disease by CD8+ T cells, Journal of Autoimmunity (2013), http://dx.doi.org/10.1016/j.jaut.2013.06.004

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