RESUMEN
Las células T autoreactivas CD8+ se están empezando a reconocer como contribuidores importantes en distintos modelos de autoinmunidad; el papel que estas células juegan en enfermedades autoinmunes humanas tan sólo se está empezando a comprender. Estas células pueden actuar bien como ejecutoras de daño tisular, bien como reguladoras y, por lo tanto, ejercer un efecto anti-patogénico. Recientes avances en este campo incluyen una mejor comprensión de los mecanismos que controlan su activación, de sus mecanismos de acción, de su regulación negativa, y de sus especificidades antigénicas. Una contribución de especial importancia es el desarrollo de métodos analíticos que permiten la detección de estas especificidades antigénicas en pacientes humanos e individuos con riesgo genético a padecer enfermedades autoinmunes. Colectivamente, estos avances ofrecen esperanzas de cara al desarrollo de nuevas modalidades terapéuticas capaces de atacar selectivamente el compartimento celular CD8+ en los procesos autoinmunes.

PALABRAS CLAVE: Autoinmunidad / Linfocitos T CD8+ / Linfocitos T CD8+ supresores.

ABSTRACT
Autoreactive CD8+ T cells are emerging as important players in several animal models of autoimmunity; their roles in the human autoimmune diseases are only beginning to be understood. Autoreactive CD8+ T cells can act as pathogenic effector cells and mediate tissue damage, while other autoreactive CD8+ T cells may have regulatory properties and serve to protect self against autoimmune attacks. Recent advances made in the field include a better understanding of their activation, mechanism of action, negative regulation, and antigenic specificities. Importantly, advances have been made in the development of strategies that detect these antigenic specificities in human patients and at risk individuals. Together, these findings foster hope for the development of novel antigen-specific therapeutic strategies that target the CD8+ T cell compartment of autoimmune processes.

KEY WORDS: Autoimmunity / CD8+ T-lymphocytes / CD8+ suppressor T-lymphocytes.
INTRODUCTION

The design of the immune system incorporates a series of checkpoints, both centrally and in the periphery, that aim to preclude self-reactivity. In the thymus, positively selected thymocytes whose T cell receptors (TCRs) recognize self peptide/MHC complexes (MHCs) with high avidity are deleted. However, thymocytes expressing lower-affinity TCRs or TCRs whose cognate antigens are not presented in the thymus escape central tolerance and populate the peripheral lymphoid organs. There, these autoreactive T cells will have to overcome additional checkpoints, such as anergy, activation-induced cell death, and regulatory T cell (Treg)-mediated dominant inhibition, to be able to cause tissue damage. In addition, there are built-in mechanisms within the T cells themselves that negatively regulate T cell activation. These are achieved through receptor-ligand interactions between T cells and professional antigen presenting cells (APCs) or antigen-expressing non-hematopoietic cell types. In autoimmunity, these checkpoints are inadequate or defective.

In the case of T-cell mediated autoimmune disorders, such as Multiple Sclerosis (MS) and Type 1 Diabetes (T1D), CD4+ T cells were traditionally thought to be the key effectors of tissue damage. This was due, in part, to the fact that disease susceptibility and/or resistance are strongly associated with certain MHC class II alleles. More recently, it has become evident that cytotoxic CD8+ T cells also play major roles as effectors of autoimmunity. This is not surprising because, unlike most CD4+ T cell specificities, CD8+ T cells can directly recognize and kill antigen-expressing cell types. Activated CD8+ T cells can kill target cells via the Fas/Fas-ligand (FasL) pathway, or by releasing cytolytic granules at the effector/target cell junction. Activated cytotoxic T lymphocytes (CTLs) can also cause tissue damage by secreting high levels of pro-inflammatory cytokines, such as TNFα and IFNγ.

CD8+ T cells have been shown to contribute to the pathogenesis of several animal models of autoimmunity, notably type 1 diabetes (T1D) in the nonobese diabetic (NOD) mouse, and experimental autoimmune encephalomyelitis (EAE), a model of demyelinating central nervous system (CNS) diseases. Interestingly, and in addition to their role as pathogenic effectors, subsets of CD8+ T cells have also been identified as negative regulators of autoimmune responses in several models. Here, we discuss these recent findings on the roles of autoreactive CD8+ T cells in autoimmunity, with a focus on two types of organ-specific autoimmune disorders.

PATHOGENIC ROLE OF AUTOACTIVE CD8+ T CELLS

CD8+ T cells in T1D. T1D is a prototypic T cell-dependent autoimmune disease characterized by a CD4+ and CD8+ T cell-dependent autoimmune process that specifically targets the pancreatic beta cell. Epidemiological studies have shown that inheritance of certain human MHC class I alleles, such as HLA-A*0201, increases the genetic susceptibility for T1D when expressed in the context of certain MHC class II alleles. Importantly, significant CD8+ T cell infiltration was observed within the pancreas of recently-diagnosed diabetic patients, as well as in diabetic patients transplanted with pancreatic grafts from healthy monozygotic twins or HLA-identical siblings. There is also extensive evidence from studies using murine models of T1D that CD8+ T cells play crucial roles in the pathogenesis of T1D. NOD mice lacking the β2-microglobulin or the CD8α genes are T1D-resistant. Furthermore, transfer of diabetes from young female NOD mice into NOD.scid recipients using splenic lymphocyte subsets is most efficient when CD4+ and CD8+ T cells are transferred together. Studies of beta cell-specific TCR-transgenic mice have demonstrated that autoreactive CD8+ T cells have pathogenic activity.

In NOD mice, CD8+ T cells are found in the earliest lymphocyte infiltrates of pancreatic islets. Wong et al. reported the presence of a population of CD8+ T cells recognizing an insulin-derived epitope in the islets of 3-4-week-old NOD mice. These cells wane with age and are progressively replaced by another population of CD8+ T cells that recognize an epitope consisting of residues 206-214 of the beta cell antigen islet-associated glucose-6-phosphatase catalytic subunit-related protein (IGRP206-214). IGRP206-214-reactive CD8+ T cells are highly diabetogenic, are prevalent in the islets and circulation of pre-diabetic NOD mice and undergo cyclic expansion and contraction prior to the onset of overt diabetes. Another unique feature of the IGRP206-214-reactive CD8+ T cell subset is that it undergoes a process of avidity maturation during disease progression, whereby low-avidity clonotypes are progressively replaced by their higher-avidity, more pathogenic counterparts. This process is developmentally controlled, such that during early stages of the disease, the high-avidity clonotypes (unlike their lower avidity counterparts) are kept in check by both central and peripheral tolerance. At the level of the target organ, on the other hand, pancreatic islet inflammation shelters these clonotypes from peripheral tolerance and fuels their local expansion, allowing them to undertake the diabetogenic process.

Our recent data suggest that low-avidity autoreactive CD8+ T cells are not pathogenic, and that they may actually possess immune regulatory properties. We have shown that...
selective deletion of high-avidity IGRP206-214-reactive CD8+ T cells through systemic administration of IGRP206-214 mimotopes frees up a “niche” within pancreatic islets that fosters the recruitment, expansion and local retention of protective (anti-diabeticogenic) low-avidity CD8+ T cells(33). Notably, deletion of both high and low-avidity IGRP206-214-reactive clonotypes enhanced the recruitment of subdominant IGRP epitope specificities to islets and did not hinder diabetes development. The hypothetical anti-diabeticogenic properties of these low-avidity CD8+ T cells have been documented in a strain of NOD mice that expresses a transgenic low-affinity IGRP206-214-reactive TCR (also referred to as 17.6-NOD mice). These mice, which do not develop diabetes, export a population of non-pathogenic, low-avidity autoreactive CD8+ T cells (expressing low levels of the low affinity transgenic TCR along with endogenous TCR chains) that suppresses the pathogenic activity of CD8+ T cells expressing high levels of the transgenic TCR (lacking expression of endogenous TCR chains). The latter engage target peptide-MHC complexes with high avidity and possess pathogenic activity. In fact, selective removal of the low-avidity, non-pathogenic CD8+ T cells of these mice by introduction of a Rag2 gene deficiency (which does not impair the development of the pathogenic high-avidity subset) resulted in the loss of protection from diabetes (our unpublished observations).

Antigenic epitopes recognized by diabeticogenic CD8+ T cells. Identification of auto-reactive T cell clones present in the peripheral blood of diabetic patients provides important information that may aid in the monitoring of disease progression or clinical assessment of the efficacy of therapeutic interventions aimed at curbing autoimmunity. Recent years have seen advances in this area. Using an ELISPOT approach, peripheral blood mononuclear cells (PBMCs) are isolated and tested for reactivity against a panel of peptides. Candidate peptides can be selected based on their predicted or characterized binding to specific HLA class I molecules(32,33) or from products of natural antigen processing via proteasome digestion(34). Using this approach, researchers have identified several diabetes-associated antigenic epitopes, including peptides derived from prepro-islet amyloid polypeptide (ppIAPP), IGRP and glial fibrillary acidic protein (GFAP)(32), as well as several epitopes in the pro-insulin polypeptide(35-37).

A number of recent reports described the identification of HLA-A*0201-restricted CD8+ T cell epitopes for T1D using “humanized” HLA-transgenic mice. These mice, designated NOD.β2mnull.HHD, lack murine MHC class I molecules but express a chimeric MHC class I molecule that carries the murine H-2Db cytoplasmic, transmembrane and α3 domains, and the HLA-A*0201 α1 and α2 (peptide-binding) domains covalently linked to the human β2m chain(38). Since these mice lack murine MHC class I molecules, they can only export HLA-A*0201-restricted CD8+ T cells into the peripheral immune system. As a result, islet-derived CD8+ T cells from NOD.β2mnull.HHD mice can be used as probes to identify potential HLA-A*0201-restricted antigenic epitopes(38). Using this approach, CD8+ T cell responses to three HLA-A2-restricted, murine IGRP-derived peptides, IGRP228-236, IGRP265-273, and IGRP337-345, were described(39). Of these, the IGRP265-273 epitope was found to be shared by human and mouse IGRP, and human IGRP228-236 differed from the murine sequence at two amino acid residues(39). Another group of investigators immunized NOD.β2mnull.HHD mice with antigen-encoding plasmid vectors and screened the mice for vaccination-elicited CD8+ T cell responses. This approach led to the identification of several candidate epitopes within the 65 KD glutamic acid decarboxylase (GAD65) autoantigen, including GAD114-123 and GAD36-545, as well as an epitope in the insulinoma-associated protein (IA-2), IA-2b05-813, all of which were validated in humans, using PBMCs from newly-diagnosed diabetic patients(39).

CD8+ T cells in MS. Multiple sclerosis is a chronic inflammatory demyelinating disease of the central nervous system (CNS) characterized by lesions infiltrated by CD4+ and CD8+ T cells. EAE has been extensively used as an animal model of MS. EAE is induced by active immunization of genetically susceptible strains with defined components of the myelin sheath, together with complete Freund’s adjuvant. Animals induced to develop EAE display demyelinated, lymphocyte-infiltrated CNS lesions and progressive ascending paralysis.

The role of CD4+ T cells in EAE has been studied extensively. They were thought to have a Th1 phenotype, until recent data suggested that they produce IL-17 and represent a novel Th subset (Th17)(39). Because myelin-reactive CD4+ T cells can transfer disease, EAE (and by extension, MS) was widely considered to be a CD4+ T cell-mediated autoimmune disease. A major role for CD4+ T cells in MS is consistent with the fact that HLA-DQ and HLA-DR polymorphisms, especially at the DRB1 locus, are strongly associated with disease susceptibility and resistance(40). However, increasing evidence supports a pathogenic role for CD8+ T cells in both EAE and MS. Transgenic expression of CD86 on microglial cells can induce a spontaneous, T cell-mediated demyelinating disease in the absence of CD4+ T cells(41). Furthermore, CD8+ T cells specific for components of myelin, including myelin oligodendrocyte glycoprotein (MOG) and myelin basic protein (MBP) can transfer EAE to healthy recipients(42-44).
MS is clearly associated with MHC class I gene polymorphisms. The HLA-A*0301 allele, for example, appears to increase the risk of MS independently of DRB1, while certain HLA-A and HLA-C alleles are negatively associated with MS, suggesting a protective effect. There is also clinical evidence to support the contention that the pathological features of MS are not exclusively mediated by CD4+ T cells. For example, treatment of MS patients with CD4+ T cell-depleting monoclonal antibodies did not ameliorate disease. Furthermore, analyses of the mononuclear cell infiltrates in CNS lesions of MS patients have documented an enrichment for CD8+ T cells. There is some evidence suggesting that these CD8+ T cells undergo clonal expansion in situ, that they interact directly with demyelinated axons, and that they are capable of lysing neurons, at least in vitro, in a MHC class I-restricted manner. In addition, it has been shown that CD8+ T cells specific for different myelin-derived antigenic epitopes are present in both healthy individuals and in MS patients. Although the use of HLA-A*0201-transgenic mice has enabled the characterization of some of these CD8+ T cell specificities, the mechanisms through which encephalitogenic CD8+ T cells are activated and contribute to disease progression in MS and EAE remain largely unknown.

**ACTIVATION OF CD8+ T CELLS**

The activation of autoreactive CD8+ T cells requires recognition of cognate antigen epitopes presented by MHC class I molecules on professional APCs. Because most target cells in organ-specific autoimmune diseases lack professional APC properties (i.e. they do not express essential immune co-stimulatory molecules), the target tissue/organ alone is unlikely to trigger an autoimmune response all by itself. A recent study using transgenic NOD mice in which most APCs were MHC class I-deficient showed that beta cells are capable of lysing neurons, at least in vitro, in a MHC class I-restricted manner. In addition, it has been shown that CD8+ T cells specific for different myelin-derived antigenic epitopes are present in both healthy individuals and in MS patients. Although the use of HLA-A*0201-transgenic mice has enabled the characterization of some of these CD8+ T cell specificities, the mechanisms through which encephalitogenic CD8+ T cells are activated and contribute to disease progression in MS and EAE remain largely unknown.

Multiple factors affect the efficiency of cross-presentation and activation of autoreactive CD8+ T cells, such as, for example, the antigen dose, the presence of immune-complex forming antibodies, or the frequency of effector cells being presented to. A recent study using the RIP-mOVA model of autoimmune diabetes showed that anti-OVA IgG antibodies enhanced OVA-specific CD8+ T cell priming through the formation of Fcγ receptor-binding immune complexes. Target cell death itself fosters cross-presentation. One of the consequences of cell death is the release of so-called endogenous adjuvants, such as heat shock proteins and uric acid. These molecules promote DC activation and thus can fuel the inflammatory process. Indeed, the inflammatory milieu of the target tissue has a significant impact on the outcome of cross-presentation. For example, inflammation in the target organ, such as the pancreas, is associated with increased chemokine production and MHC class I expression, leading to enhanced T cell recruitment and accumulation. Along these lines, it has been shown that activation of Toll-like receptor molecules can augment autoimmunity.

Another important factor to consider in the activation of autoreactive CD8+ T cells is the requirement for CD4+ T cell help. In the absence of CD4+ T cells, naïve IGRP206-214-reactive T cells cannot efficiently accumulate in pancreatic islets despite undergoing activation in the PLNs. This was demonstrated in studies of mice expressing a transgenic IGRP206-214-reactive TCR in a ng2-deficient background. 8.3-NOD.rag2/- mice, which export autoreactive CD8+ T cells in a CD4+ T cell-deficient environment, develop diabetes at a significantly slower rate and decreased frequency than their ng2-competent counterparts. This observation is consistent with the finding that CD8+ splenocytes from...
Figure 1. Dual role of autoreactive CD8+ T cells. (0.) Professional APCs ferry self antigens from the target organ to the regional lymph nodes, where they prime autoreactive CD4+ and CD8+ T cells. (1.) CD8+ T cells are activated by engaging peptide/MHC class I via their TCRs and costimulatory molecules CD80/CD86 via CD28, a process that is enhanced by pro-inflammatory signals, such as those provided by CD4+ T helper cells (CD40/CD154 interaction), and by occupation of the TLR with TLR ligands. These CD8+ T cells undergo clonal expansion and differentiation into CTLs, and they mediate cell damage in the target organ through various means (cytolytic granules, Fas/FasL, secretion of IFNγ and TNFα) (2.) A different outcome of cross-priming is the induction of tolerance (also referred to as cross-tolerance). In the absence of co-stimulatory signals, naïve CD8+ T cells become tolerized via apoptotic deletion or induction of anergy. Ligation of negative costimulatory molecules PD-1 and CTLA-4 by their respective ligands (PD-L and CD80, CD86) on the dendritic cells or target cells also abrogates T cell responses. In some cases, subsets of DCs are rendered tolerogenic through the up-regulation of IDO, an enzyme involved in tryptophan catabolism. (3.) Subsets of autoreactive CD8+ T cells, in addition to the classical CD4+CD25+ Tregs, are shown to down-regulate autoimmune responses, presumably by acting on APCs or directly on the pathogenic T cells.
diabetic donors cannot transfer diabetes in NOD.scid mice in the absence of CD4+ T cell co-transfer. However, not all autoreactive CD8+ T cell specificities require CD4+ T cell help to trigger diabetes.

**CROSS-TOLERANCE AND AUTOREACTIVE CD8+ T CELLS**

Cross-presentation of self-antigens to CD8+ T cells may lead to another outcome: T cell tolerance (also referred to as “cross-tolerance”). Cross-tolerance may occur in the thymus, or in the periphery. Negative co-stimulatory molecules of the CD28 family have been shown to be critical for peripheral cross-tolerance. One well-studied example is the CTL-associated antigen 4 (CTLA-4). Ligation of CTLA-4 on activated T cells by CD80 and CD86 on DCs serves to downregulate/terminate T cell responses. Loss of CTLA-4 results in lymphoproliferative disease and multi-organ autoimmunity, and in vivo blockade of CTLA-4 augments autoimmune responses in EAE. Programmed death-1 (PD-1) is another inhibitory receptor that is up-regulated on activated T cells, B cells, and myeloid cells. The interaction of PD-1 with its ligands, PD-L1 and PD-L2, on multiple cell types, including DCs, macrophages, and lymphocytes, and parenchymal cells such as pancreatic beta cells, results in a negative signal that aims to terminate T cell immune responses. Recent studies have shown that the interaction of PD-1 on CD8+ T cells and PD-L1 on DCs and pancreatic beta cells is important for inducing and maintaining peripheral CD8+ T cell tolerance to self antigens. Keir and coworkers found that loss of PD-1 lowers the threshold of activation of PD-1-deficient OT-1 CD8+ T cells, allowing these T cells to efficiently transfer diabetes to RIP-OVA hosts (unlike their PD-1-wild type counterparts). It was also shown that abrogation of the PD-1/PD-L1 interaction fostered CD8+ T cell-mediated autoimmunity, including type 1 diabetes in NOD mice. There is some evidence suggesting that whereas PD-L1 expression in PLN DCs negatively regulates the priming of diabetogenic T cells early on in the disease process, PD-L1 expression in islet cells inhibits islet destruction at a later phase in diabetes progression. Of note, similar to CTLA-4, the PD1/PD-L1 pathway could potentially be exploited to treat autoimmune diseases. Fife and coworkers have shown that reversal of diabetes upon systemic administration of an anti-CD3 mAb or antigen-coupled APCs is a PD-1 and PD-L1-dependent phenomenon. Furthermore, stimulation of PD-1 with a dimeric PD-L1 Ig fusion protein, in conjunction with CD154 co-stimulation blockade, prolonged the survival of islet allografts.

**CD8+ T CELLS AS NEGATIVE MODULATORS OF AUTOIMMUNE DISEASES**

CD8+ T cells with immune regulatory activities have also been identified. These cells, which naturally co-exist with their pathogenic counterparts, can be activated and/or expanded by specific immuno-therapeutic strategies. Qa-1 (HLA-E)-restricted CD8+ T cells, Qa-1 (the murine counterpart of HLA-E) is a non-classical MHC class I b molecule that forms a heterodimer with β2-microglobulin (β2m) and can present peptides from both self- and foreign antigens. Qa-1-deficient mice develop exaggerated CD4+ T cell responses upon viral infection and immunization with self peptides, and display increased susceptibility to EAE induction. The regulatory role of the Qa-1/CD8 TCR interaction was first demonstrated in studies involving vaccination with autoantigen-reactive CD4+V8.2+ T cells (TCV), which protected mice from subsequent induction of EAE, through a Qa-1-restricted, CD8+ T cell-dependent mechanism. It was found that TCV-induced CD8+ T cells selectively killed activated CD4+ T cells in a Vβ-specific manner. One way this could occur was through the recognition of a Vβ8.2-derived peptide presented in the context of Qa-1 molecules on the surface of activated CD4+ T cells. Jiang and coworkers provided evidence that Qa-1-restricted CD8+ T cells selectively delete the high-affinity CD4+ T cell clonotypes, sparing their lower-affinity counterparts. Of note, a similar population of CD8+ regulatory T cells was documented in patients treated with glatiramer acetate (GA), an approved therapy for MS. Untreated MS patients were found to have defective CD8+ T cell-mediated immune suppression, as compared to healthy untreated controls. Treatment with GA might induce HLA-E-dependent, GA-specific cytotoxic responses with suppressive properties.

**CD8+ CD122+ T cells** - Suzuki and co-workers observed that IL-2/IL-15 receptor β-chain (CD122)-deficient mice spontaneously accumulate activated T cells, resulting in the abnormal and exhaustive differentiation of B cells into antibody-secreting plasma cells. This phenotype of abnormal T and B cell activation could be reversed by the transfer of purified CD8+CD122+ T cells, or higher numbers of CD4+CD25+ T cells. In the same study, CD8+CD122+ T cells were shown to play a crucial role in the regulation of CD8+CD122+ T cells, in an APC-independent manner. A subsequent study found that CD8+CD122+ T cells could suppress the proliferation of their CD122+ counterparts by secreting IL-10 into the culture medium. The protective role of CD8+CD122+ T cells has been documented in other autoimmune disorders. In a model of Graves’ disease, a B cell-mediated, T cell-dependent autoimmune disease of the thyroid gland, in vivo depletion of CD122+ cells via the systemic administration of monoclonal anti-CD122 antibodies resulted in an elevated incidence of...
showed that depletion of CD8+CD122+ T cells resulted in an increase in CNS-infiltrating T cells and cytokine production, while transfer of CD8+CD122+ regulatory T cells resulted in a decrease in disease symptoms, particularly in the recovery phase of EAE. The mechanism(s) through which CD8+CD122+ T cells regulate autoimmunity remain(s) to be determined.

**CD8+CD28- T cells**. CD8+CD28- T cells isolated from humans were shown to suppress alloreactive CD4+ T cell responses in vitro, suggesting a regulatory role for this particular CD8+ T cell subset. Najafian and coworkers showed that depletion of CD8+ T cells prior to EAE induction with MOG led to heightened disease progression, similar to what has been described in CD8-deficient mice. The adoptive transfer of CD8+CD28- T cells into CD8-deficient hosts reversed this phenotype and significantly decreased disease severity. At the cellular level, CD8+CD28- T cells suppressed the proliferation of MOG-specific CD4+ T cells both in vitro and in vivo. It was shown that suppression was mediated through a MHC class I-restricted, contact-dependent mechanism that required the presence of APCs. The CD8+CD28- T cell/APC interaction led to downregulation of several costimulatory molecules, including CD80, CD86 and CD40, on APCs. In another study, CD8+CD28- T cells were shown to exert regulatory activity in an animal model of myasthenia gravis (MG), an autoimmune disease characterized by antibody-mediated blockade of acetylcholine receptors (AchR) at neuromuscular junctions. Ben-David and coworkers showed that treatment with an APL consisting of two tandemly-fused myasthenogenic peptide analogs suppressed MG-associated autoimmunity through the induction of a group of CD8+CD28- cells that also express FoxP3. These CD8+CD28 FoxP3+ T cells were shown to produce immunosuppressive cytokines such as IL-10 and TGF-β, and could transfer protection into MG-prone animals. Another study showed that antigen-primed CD8+CD28- T regulatory cells could suppress up-regulation of the inhibitory receptors immunoglobulin-like transcript 3 (ILT3) and ILT4 on APCs, rendering them tolerogenic. A recent report suggests that suppression of ILT3/ILT4 upregulation on endothelial cells may enhance heart allograft survival.

Additional types of regulatory CD8+ T cells have also been described. Regulatory CD8+ T cells induced by a tolerogenic anti-DNA IgG-derived peptide in murine systemic lupus are found in both the CD28+ and CD28- subsets and suppress autoimmune antibody responses in a Foxp3-dependent and TGF-β-dependent manner. Another study documented the induction of regulatory CD8+ T cells in lupus-prone animals treated with a nucleosomal histone peptide. The induced CD8+ T cell population expressed glucocorticoid-induced tumor necrosis factor receptor (GITR) and TGFβ, and suppressed autoantibody production by secreting TGFβ, in a contact-independent manner. Another subset of CD8+ (and CD11c+) T cells with regulatory properties has been described in an animal model of collagen-induced arthritis. This subset of T cells was shown to produce large amounts of IFNγ, which induced indoleamine 2,3-deoxygenase activity in DCs and monocytes, resulting in the suppression of antigen-specific CD4+ T cell responses.

**CONCLUSIONS**

There is now no doubt that, in autoimmunity, CD8+ T cells play important roles as both effectors of tissue damage and immunoregulators. Pathogenic CD8+ T cells mediate tissue damage through their cytotoxic activity, as well as through the secretion of cytokines that further fuel inflammation. However, when the suppressive activity of autoreactive T cells targets pathogenic immune cell types, it suppresses autoimmunity. Thus, advances in our understanding of the biology of autoreactive CD8+ T cells, coupled to antigenic epitope discovery and characterization, may accelerate the discovery of novel antigen-specific therapeutic strategies to prevent and/or blunt autoimmune responses.

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**DISCLOSURES**

The authors declare no financial conflicts of interest.

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