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Review

Promotion and prevention of autoimmune disease by CD8+ T cells

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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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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