

Effector lymphocytes in autoimmunity

Pere Santamaria

Autoimmune diseases result from complex interactions among different T- and B-lymphocyte subpopulations that target a rapidly growing number of autoantigens on different cell types. The etiology of most spontaneous autoimmune disorders, and both the kinetics and hierarchy of the underlying autoimmune responses are poorly understood. However, important advances have been made in recent years in our understanding of how autoreactive lymphocytes cause tissue damage, including the discovery that granzyme B binds to a cell surface receptor on target cells. This review is an attempt to summarize recent developments in this area.

Addresses

Department of Microbiology and Infectious Diseases, Faculty of Medicine, The University of Calgary, 3330 Hospital Drive NW, Calgary, Alberta T2N 4N1, Canada; e-mail: psantama@ucalgary.ca

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Abbreviations

APC	antigen-presenting cell
CTL	cytotoxic T lymphocyte
EAE	experimental autoimmune encephalomyelitis
FasL	Fas ligand
IBD	inflammatory bowel disease
MOG	myelin oligodendrocyte protein
NOD	non-obese diabetic
RA	rheumatoid arthritis
T1D	type 1 diabetes mellitus
TNFR	TNF receptor
TRAIL	TNF-related apoptosis-inducing ligand

Introduction

Most autoimmune disorders arise when cells of specific tissues become the targets of autoantibodies and/or T lymphocytes. In some instances, T lymphocytes effect tissue damage directly through processes of cell-mediated cytotoxicity that involve Fas, perforin, or both. Perforin-mediated lysis requires a cognate interaction between the antigen-specific TCR on a T lymphocyte and the specific antigen (usually a peptide) presented on an MHC molecule on the target cell's plasma membrane (Figure 1). Fas-mediated cytotoxicity involves the ligation of Fas on the target cell by Fas ligand (FasL) on T cells but does not require a cognate interaction between the effector lymphocyte and its target, and thus has the potential to damage innocent bystanders (Figure 1).

In other instances, T lymphocytes kill their targets by secreting cytokines that can ligate pro-apoptotic receptors on the target cell (Figure 1). And yet in other instances, autoreactive lymphocytes kill their targets indirectly, by enhancing their susceptibility to death-effector mechanisms mediated by non-lymphocytes (Figure 1), by promoting the recruitment of additional inflammatory cells

into the target tissue (i.e. cytotoxic macrophages) (Figure 1), or by driving the differentiation of autoreactive B cells into autoantibody-secreting plasma cells.

This review is an attempt to summarize recent developments in this area.

Effector lymphocytes in autoimmune disorders

Much of what is currently known about effector pathways of autoimmunity has been learned from a handful of spontaneous and experimental models of autoimmune disease. Type 1 diabetes mellitus (T1D) in non-obese diabetic (NOD) mice is a prototypic model of spontaneous, organ-specific autoimmunity. NOD mice spontaneously develop a form of autoimmune diabetes, closely resembling human T1D, that results from destruction of the pancreatic β cells by T lymphocytes.

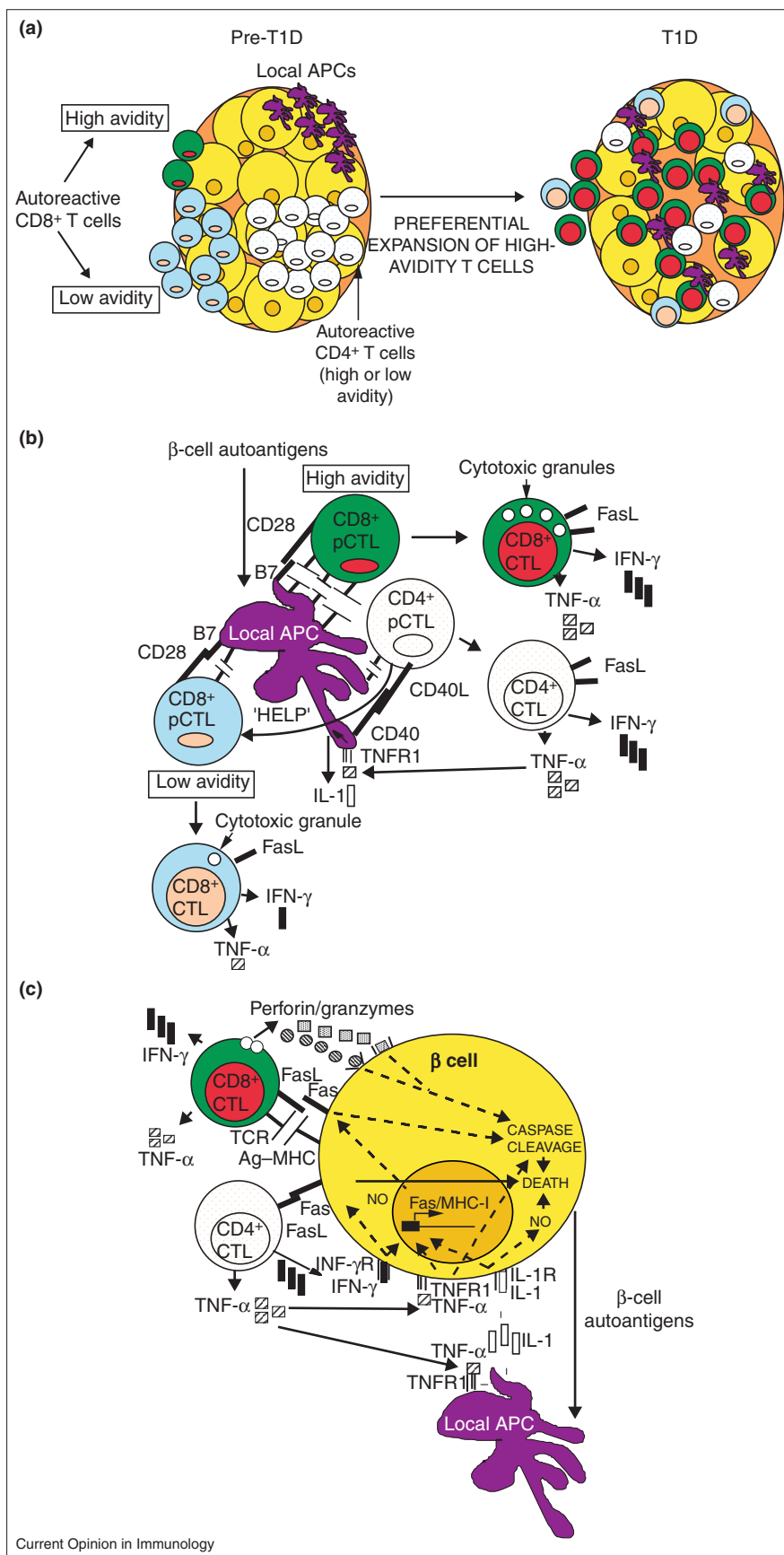
Figure 1 provides a simplified overview of the interplay among β cells, T lymphocytes and antigen-presenting cells (APCs) in the development of T1D. Studies of CD8⁺-T-cell-deficient NOD mice have suggested that the initial β -cell insult in T1D is effected by cytotoxic CD8⁺ T cells in a manner dependent on CD4⁺ T cells (for a review on the role of CD4⁺ T cells, see [1]).

Several transgenic models of T1D have shown that CD8⁺ T cells can readily kill β cells expressing transgenic neo-antigens; however, little is known about the antigenic specificity or specificities of the CD8⁺ T cells that kill β cells in NOD mice. Wong *et al.* [2] have reported that there is a CD8⁺ T-cell subpopulation that recognizes an insulin-derived peptide in the islets of young NOD mice. Although its size is a matter of debate [3], this subpopulation dwindles with age [3] and is replaced, in part, by a subpopulation of diabetogenic CD8⁺ T cells that use highly homologous TCR α chains [4–7]. This subpopulation recognizes a peptide named NRP and a number of variants [8,9], expands in size as the mice age [3] and undergoes a process of 'avidity maturation' that coincides with exponential penetrance of diabetes through the colony [3].

Immunopathological studies of pancreata from human diabetic individuals and pancreas isograft recipients have suggested that destruction of β cells in human T1D may also be effected, at least in part, by CD8⁺ T cells [10,11]. Although CD8⁺ T cells clearly play an important role as effectors in T1D, β -cell loss in spontaneous autoimmune diabetes is also effected by autoreactive CD4⁺ T cells [1].

CD8⁺ T cells are also involved in the development of spontaneous autoimmune diseases of the thyroid. Hashimoto's thyroiditis, for example, results from the destruction of thyroid follicular cells by CD8⁺ T cells [12].

Figure 1



Effector lymphocytes and death-effector pathways in T1D. **(a)** Development of spontaneous autoimmune diabetes in the NOD mouse islet is preceded by a long, protracted period (pre-T1D) of islet inflammation (insulinitis) that involves local professional APCs (B cells, dendritic cells and macrophages; shown in purple), CD4⁺ T cells (white) and CD8⁺ T cells (green or blue). Islet β -cells are shown in yellow and the islet in orange. Progression of insulinitis results in avidity (and affinity) maturation of autoreactive CD8⁺ T cells (and possibly CD4⁺ T cells). This process results in preferential expansion of autoreactive CD8⁺ T cells bearing high-affinity TCRs for autoantigenic peptide–MHC complexes (these cells are shown in green), at the expense of CD8⁺ T cells bearing low-affinity TCRs (these cells are shown in blue). **(b)** High-avidity CD8⁺ pre-CTLs (pCTLs) probably differentiate into CTLs via TCR recognition of target peptide–MHC-class-I complexes on local APCs, in a CD4⁺-Th-independent manner, using co-stimulatory pathways such as CD28–B7. CTLs kill via cytotoxic granules, FasL, TNF- α and IFN- γ (see below). Low-avidity CD8⁺ pCTLs may also require the assistance ('help') of autoreactive CD4⁺ Th cells to differentiate into CTLs, and may expand at a much slower rate than high-avidity CD8⁺ T cells. CD40L–CD40 and TNF- α –TNFR1 interactions may be involved in this process. Autoreactive CD4⁺ pCTLs can also differentiate into CTLs that can kill β cells. **(c)** CD8⁺ CTLs can directly recognize Ag–MHC-class-I complexes on β cells. This triggers the polarized release of perforin and granzymes, and the upregulation of FasL expression on the plasma membrane of the CTLs. Perforin and granzymes are internalized by binding to specific receptors on the target cell's surface and may trigger caspase-dependent and/or -independent forms of β -cell death (the caspase-independent pathways are not shown). As shown in (b) and (c), autoreactive CD8⁺ and CD4⁺ CTLs secrete cytokines such as TNF- α and IFN- γ into the milieu upon antigen recognition. TNF- α enhances autoantigen presentation and β -cell apoptosis by triggering TNFR1 on APCs and β cells, respectively. In addition, TNF- α –TNFR1 interactions promote IL-1 secretion by APCs. IL-1 α , IL-1 β , TNF- α and IFN- γ bind to specific receptors on islet β cells (IL-1R, TNFR1 and IFN- γ R); depending on the cytokine, this can lead to caspase cleavage, nitric oxide (NO) production, and increased Fas and MHC class I (MHC-I) gene expression. NO is responsible for inducing β -cell death by necrosis. Upregulation of Fas marks β cells for Fas-dependent destruction by diabetogenic CD8⁺ and CD4⁺ T cells. The end result is an exponential progression of β -cell death that culminates in insulin insufficiency. Some of the effector mechanisms involved in T1D are also responsible for tissue destruction in other autoimmune disorders.

It has also been reported that initiation of iodine-induced thyroiditis in NOD and NOD-H2^{h4} mice requires the contribution of CD8⁺ T cells [13]. As in T1D, development of thyroid autoimmune diseases also involves CD4⁺ T cells.

Experimental autoimmune encephalomyelitis (EAE) is a prototypic experimental autoimmune disease that models human multiple sclerosis and that develops in susceptible rodent strains after immunization with myelin basic protein, proteolipid antigen or myelin oligodendrocyte protein (MOG).

Autoreactive CD4⁺ T cells seem to be major effectors of EAE (reviewed in [14]); however, some evidence suggests that CD8⁺ T cells have a role in disease progression and severity. Myelin basic protein is processed *in vivo* by the MHC class I pathway [15], and a MOG-derived peptide activates encephalitogenic CD8⁺ T cells *in vivo* [16*]. There is also evidence for clonal expansions of CD8⁺ T cells in active multiple-sclerosis lesions [17*].

In many autoimmune disorders, T lymphocytes function as indirect effectors of autoimmunity by driving the differentiation of B lymphocytes into autoantibody-secreting plasma cells or by shedding autoantigens from target cells. These diseases include, among others, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, Graves' disease, Goodpasture's syndrome, myasthenia gravis, pemphigus vulgaris and systemic lupus erythematosus.

Systemic lupus erythematosus is associated with production of pathogenic autoantibodies against double-stranded DNA and ribonucleoproteins, and may be the result of dysregulated B-lymphocyte apoptosis. Fas-deficient, MRL/lpr mice, mice expressing a Bcl-2 transgene in B cells, Bim-deficient mice, and BAFF-transgenic mice produce pathogenic autoantibodies and develop lupus-like syndromes. Bim inhibits anti-apoptotic genes such as Bcl-2 and Bcl-xl [18], and BAFF (a TNF-family member) induces B-cell proliferation by engaging BCMA or TACI receptors (TNF receptor [TNFR]-family members) [19,20*,21*]. Although systemic lupus erythematosus is primarily effected by autoantibody-secreting lymphocytes, cytotoxic T lymphocytes (CTLs) may also contribute to its pathogenesis by killing macrophages and inducing the release of antigenic DNA [22].

T lymphocytes may also be responsible for eliciting the production of pathogenic autoantibodies in other autoimmune diseases, such as rheumatoid arthritis (RA). In one mouse model of RA, recognition of a complex of self-peptide with MHC class II by a clonotypic CD4⁺ T cell triggered the differentiation of B cells into plasma cells producing high levels of arthritogenic antibodies [23].

Effector mechanisms of tissue damage in autoimmunity

Fas versus the granule exocytosis pathways

CTLs can directly kill target cells via two pathways of cell-mediated cytotoxicity: in the perforin pathway, cell death is

caused by the direct effects of perforin and a series of serine proteases (granzymes) on the target cell; in the Fas pathway, a T-cell ligand (FasL) binds a target cell receptor (Fas) that induces apoptosis when ligated. Despite numerous studies, the roles of Fas and perforin in T1D remain unclear.

On the one hand, perforin-deficient NOD mice develop insulinitis (islet inflammation) but rarely become diabetic [24]. In addition, perforin has been found to be a more important effector pathway of β -cell death than Fas in transgenic mouse models of T1D that express viral antigens in β cells [25–27]. Furthermore, Fas-deficient islet grafts are readily destroyed in spontaneously diabetic NOD mice [28] or on transfer of certain mouse β -cell- autoreactive CD4⁺ T cells in a TNFR1-dependent manner [29].

On the other hand, NOD.*lpr* mice develop neither diabetes nor insulinitis [30], and mice heterozygous for the FasL mutation *gld* do not develop diabetes [31]. Furthermore, both insulin- and NRP-reactive CD8⁺ T cells kill NOD β cells exclusively via Fas, even though they express perforin [32,33]. CD4⁺ CTLs bearing a highly diabetogenic, I-A^{g7}-restricted β -cell-reactive TCR (4.1-TCR) also kill β cells exclusively via Fas [34], although this requires prior stimulation of the β cells with IL-1 α , IL-1 β , TNF- α and/or IFN- γ [34].

Interestingly, Fas is expressed on most β cells in inflamed human islets [35]. When taken together, these paradoxical observations suggest that perforin and Fas play crucial roles at different stages in the disease process: T1D might be initiated by CTLs that lyse β cells exclusively via Fas, and amplified by CTLs that can kill via other death-effector pathways, including perforin.

It should be noted that Fas- and perforin-mediated cytotoxicity can be triggered independently according to the nature of the target peptide–MHC complex [36], and possibly to the avidity with which molecular targets on tissue cells are recognized by cognate TCR molecules on a given CTL. An alternative, but not mutually exclusive, possibility is that β cells undergo changes in their ability to bind and/or internalize perforin [37] or granzyme B [38**] in response to inflammatory stimuli as the disease progresses.

Fas–FasL interactions also seem to play a vital role in the induction and progression of EAE [39–42], albeit apparently not in its effector phase [43*]. Interestingly, bone marrow chimeras expressing Fas and FasL on T cells but not radioresistant tissues (i.e. ocular tissues) develop experimental autoimmune uveitis with normal intensity and incidence, but expression of Fas and FasL is indispensable [44]. This observation suggests that the role of Fas in experimental autoimmune uveitis (and perhaps EAE as well) is dissociated from its pro-apoptotic activity, or that it somehow enhances presentation of antigen [45]. The latter possibility is compatible with the observation that disrupting Fas–FasL interactions inhibits the production of

autoantibodies in pristane-induced lupus, which usually target autoantigens that cluster in apoptotic blebs [46*].

Fas and its ligand may also be crucially involved in Hashimoto's thyroiditis. It has been reported that thyrocytes constitutively express FasL, and that IL-1 β -induced upregulation of Fas leads to thyrocyte death in Hashimoto's thyroiditis [47]. But it has also been shown that normal thyrocytes do not express FasL on their surface [48,49], and that Fas-dependent cytotoxicity can be readily induced with IFN- γ and either TNF- α or IL-1 β , but not by IFN- γ or IL-1 β alone [12]. Fas-FasL interactions may also play a role in certain immune-mediated skin disorders. Eczematous dermatitis, including atopic dermatitis and allergic contact dermatitis, involves T-cell-mediated, Fas-dependent apoptosis of keratinocytes stimulated by IFN- γ [50].

TNF- α and TNFRs

TNF- α plays an important role in the development of T1D. Although TNF- α is both cytostatic and cytotoxic for β cells *in vitro*, production of transgenic TNF- α *in situ* does not cause diabetes in the absence of T cells. Therefore, the role of TNF- α as effector cytokine *in vivo* remains unclear. When expressed in the islets of pre-diabetic NOD mice, TNF- α enhances the presentation of β -cell autoantigens to autoreactive T cells by ligating TNFR1 on APCs [51]. β cells express low levels of TNFR1 constitutively, but can be induced to express both TNFR1 and TNFR2 during inflammation [52]. This pro-immunogenic effect of TNFR1 signaling in T1D has been also observed in experimental myasthenia gravis after immunization with the *Torpedo* acetylcholine receptor [53].

TNF- α can damage the myelin sheath and can induce oligodendrocyte apoptosis, suggesting that TNF- α -TNFR1 interactions have an effector role in the pathogenesis of EAE and multiple sclerosis. In fact, TNFR1-deficient mice do not develop MOG-induced EAE [54,55,56*].

TNF- α also has an effector role in inflammatory bowel disease (IBD) and RA. TNF- α can induce apoptosis of intestinal epithelial cells [57] and, in a T-cell transfer model of IBD, CD4⁺CD45RB^{hi} cells induce colitis by stimulating the production of TNF- α by non-T cells of the colonic mucosa [58]. Furthermore, TNFR2-Ig fusion proteins and humanized anti-TNF- α mAbs can inhibit IBD and RA [59–61].

The cytopathic effect of TNF- α in autoimmunity is not always direct. TNF- α is able to upregulate expression of Fas on target cells (see above) and is a powerful paracrine inducer of other cytotoxic cytokines such as IL-1 α and IL-1 β that are expressed by activated macrophages. IL-1 β enhances the activity of the inducible form of nitric oxide synthase (iNOS) in β cells and augments the endogenous production of nitric oxide, causing necrosis of β cells [62].

The contribution of free-radical damage to β -cell loss in T1D is supported by the observation that β cells from

ALR/Lt mice, which express high systemic levels of molecules associated with dissipation of free-radical stress, are unusually resistant to cytotoxic cytokines and diabetogenic CTLs [63*]. Thus, although triggering a death receptor induces cell death primarily by apoptosis, TNF-TNFR interactions can also lead to necrosis. This phenomenon is not unique to β cells: IL-1 β can degrade joint cartilage in autoimmune arthritis [61].

TRAIL and RANKL

TRAIL (TNF-related apoptosis-inducing ligand) can induce cell death, and in particular the death of tumor cells, but its role in T-lymphocyte-mediated autoimmunity is unclear. On the one hand, TRAIL and TRAIL receptors have been shown to be expressed in intra-thyroidal lymphocytes and in cytokine-stimulated thyroid follicular cells [64], suggesting that they have a role in autoimmune thyroid disease. On the other hand, systemic administration of TRAIL can prevent autoimmune disorders such as collagen-induced arthritis [65] and EAE [66].

The RANK (receptor activator of nuclear factor κ B) ligand (RANKL, also known as TRANCE or osteoprotegerin ligand) — a TNF family member that is secreted by activated T cells — can trigger bone erosion in the joints of arthritic patients by triggering osteoclastic bone resorption [67].

Other cytokines

IL-6, which can be produced by CD4⁺ T cells, is elevated in *ex vivo* organ cultures of inflamed colonic mucosa from patients affected with either ulcerative colitis or Chron's disease. IL-6 is thought to contribute to the pathogenesis of disease by increasing the production of cytopathic cytokines such as IL-1 β and TNF- α , and matrix metalloproteinases, as well as by inhibiting apoptosis of T cells [68*]. IL-6 may also be involved in the pathogenesis of EAE, as IL-6-deficient mice are resistant to EAE (reviewed in [69]).

Although usually associated with protection from autoimmunity, IL-4-producing Th2 cells can be effectors of autoimmunity. For example, these cells have a pathogenic role in oxazolone-induced colitis and contribute to the pathogenesis of IBD in TCR α -deficient mice, perhaps by increasing permeability of the intestinal epithelium and neutrophil adhesion to epithelial layers [70,71]. IL-17 — which is produced by CD4⁺ T cells in the affected joints of RA patients — is, independently of IL-1, an effector of joint destruction in collagen-induced arthritis [72].

Conclusions

The effector mechanisms of tissue destruction in autoimmunity are highly complex and involve several immune cell types, antigenic specificities and pathways of cell- and cytokine-mediated cytotoxicity. The importance of a given pathway in a given autoimmune disease is influenced by a number of factors, including the nature of target autoantigens, the type of effector lymphocytes involved and the genetic background of the affected individuals or animal

models. This complexity is probably compounded by changes in the susceptibility of target cells to different death-effector pathways during the progression of disease, which results from an upregulation or downregulation in expression of death receptors and signaling intermediates in response to a myriad of inflammatory stimuli. Enormous progress has been made in recent years in this area, but solutions to current controversies will surely have to await the development of additional reductionist models of increasing complexity that are relevant to human disease.

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