ELSEVIER

The role of CD8 T cells in innate immunity and in antigen non-specific protection

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The role of CD8 T cells in adaptive immune responses is well understood. These lymphocytes respond through their T cell receptors to diverse antigens presented by MHC class I molecules by proliferating, secreting cytokines and chemokines, and directly lysing infected cells. Recently, a role for CD8 T cells in the innate immune response has become apparent. Independent of T cell receptor ligation, CD8 T cells can mount a response against pathogens by secreting cytokines and can defend against tumors by directly killing transformed cells. This innate response has been shown to be beneficial in controlling several types of bacterial infections. However, a subset of CD8 T cells that have innate non-antigen-specific capabilities has been implicated in self-reactivity, which could lead to autoimmunity.

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Introduction

The response of CD8 T cells to intracellular pathogens and tumors is generally attributed to T cell receptor (TCR)-mediated signaling events. The specific interaction of peptide–major histocompatibility complex (MHC) with TCRs on these T cells leads to signaling events that in turn result in effector functions. The specific nature of this recognition event is a hallmark of both T cell and B cell activity. However, there are instances in which T cells cross-react against similar peptide sequences derived from either other pathogens or self-peptides. This cross-reactivity can lead to either heterologous immunity, in the case of two different pathogens [1], or molecular mimicry (which can potentially lead to autoimmunity), in the case of a self-peptide that resembles a pathogenic peptide [2]. In both types of cross-reactivity, signals generated through the TCR are required to induce the function of the T cell. Therefore, although these responses are not specific for a given antigen, they do proceed as would any other adaptive T cell response in terms of kinetics, threshold of activation and effector functions [3].

Until recently, it was assumed that triggering through the TCR was the only mechanism whereby T cells could be activated to perform effector functions. However, recent data support a role for CD8 T cells in innate immune responses, independent of TCR specificity. In this review, we make the argument that under certain circumstances antigen-non-specific TCR-independent responses of CD8 T cells play a beneficial role in controlling infections and tumors. Unfortunately, these same types of innate antigen-independent responses might be harmful when they are self-reactive.

Receptors for innate signals on CD8 T cells

Interleukin (IL)-12 and IL-18 are prime examples of cytokines released during the innate response that can cause effector functions independent of TCR cross-linking. Receptors for these cytokines have been shown to be upregulated on effector and memory CD8 T cells, and binding of IL-12 and IL-18 leads to the secretion of interferon (IFN)-γ [4]. Several other cytokine receptors can also play a role in innate functions of CD8 T cells, including those for type I IFNs, IL-2 and IL-15. In addition, a recent report documented the expression of a low-affinity Fc receptor on self-specific CD8 T cells. In the absence of TCR signaling, this receptor functioned as a cytolytic receptor for antibody-dependent cell-mediated cytotoxicity and induced the production of IFN-γ and tumour necrosis factor (TNF)-α [5].

Several innate receptors that transmit activating signals including NKG2D, CD244 and CD94 are upregulated on a subset of CD8 T cells after IL-2 stimulation [6•,7]. Both intrathymically and extrathymically developed self-reactive CD8 T cells have also been shown to respond to IL-2, IL-15 or NK1.1 cross-linking by secreting IFN-γ [8•,9]. The CD94/NKG2C killer lectin-like receptor is expressed on a subset of CD8 T cells. Engagement of this receptor results in cytotoxicity, proliferation and secretion of TNF-α and IFN-γ [10].

Innate IFN-γ secretion by CD8 T cells

One cytokine produced by CD8 T cells through innate signaling is IFN-γ. Several cytokines have been shown to have the capacity to stimulate production of this important effector molecule. In the case of a lipopolysaccharide

stimulus (as would occur with a Gram-negative bacterial infection), one study indicated that IFN-α and IL-12 were at least partially responsible for inducing IFN-γ secretion in $CD44^{hi}$CD8 T cells [11]. By contrast, another study used blocking antibodies against IL-12 and IL-18 to demonstrate that lipopolysaccharide induction of these two cytokines was responsible for IFN-γ secretion in CD8 T cells [12]. T cell activation and survival cytokines such as IL-2 and IL-15 have been shown to increase the number of IFN-γ-secreting CD8 T cells as well as the amount of IFN-γ secreted by CD8 T cells ([13]; REB and JF, unpublished). A report utilizing transgenic mice that overexpressed IL-15 suggested that this cytokine was responsible, in conjunction with IL-12, for inducing non-antigen-specific IFN-γ production in CD8 T cells in response to *Listeria monocytogenes* (LM) infection [14]. Poly(I:C), which is a strong inducer of type I IFN and mimics a viral infection, was also shown to induce IFN-γ secretion in $CD44^{hi}$CD8 T cells [11].

Several newly discovered cytokines have been described recently that have 'IL-12-like' functions. IL-23 and IL-27 belong to the IL-12 family of cytokines and were initially thought to play overlapping, and possibly redundant, roles with IL-12. However, a more complex picture has emerged recently, which brings into question whether or not they function in a similar fashion to IL-12 [15]. Both cytokines have been shown to induce IFN-γ production in natural killer (NK) and CD4 T cells [16–18], which suggests that they might have a similar role in CD8 T cells. Indeed, Gram-negative bacteria have been shown to induce the production of IL-23 and IL-27 in dendritic cells [19], and mice deficient in the IL-27 receptor are highly susceptible to LM infection [20]. IL-21, in synergy with IL-15 or IL-18, has also been shown to enhance IFN-γ production in NK and T cells [21]. In addition, recent data indicate that a combination of IL-21 and IL-15 can induce proliferation of CD8 T cells and can enhance TCR-mediated production of IFN-γ [22]. When combined, these reports suggest that IL-21, IL-23 and/or IL-27 production during infection or inflammation might lead to the secretion of IFN-γ in CD8 T cells in an innate fashion, although this hypothesis remains to be formally proven.

CD8 T cells secrete IFN-γ when triggered through their TCRs. During a primary adaptive response, this secretion occurs after clonal expansion and differentiation. However, several recent studies have demonstrated that ligation of the TCR *in vivo* leads to the rapid production of IFN-γ by CD8 T cells restricted to MHC Class Ib antigens [23]. Our recent data indicate that $CD44^{hi}$CD8 T cells from MHC Class Ia-deficient mice respond rapidly to TCR ligation by secreting IFN-γ [24]. Another study showed that *in vitro* stimulation of CD8 T cells from old mice for four hours resulted in a much higher amount of IFN-γ secretion than when the same experiment was performed on CD8 T cells isolated from young mice [25]. This experiment suggests that the increase in memory phenotype CD8 T cells seen in older mice results in a higher percentage of cells that have the ability to rapidly secrete IFN-γ. Although these IFN-γ responses might not be antigen-independent (owing to TCR involvement), they could be categorized as 'innate' because of their rapid nature of secretion.

Innate immune responses of CD8 T cells against LM

The adaptive immune response of CD8 T cells against the Gram-positive intracellular bacterium LM has been well studied. However, recently several groups, including ours, have established a role for CD8 T cells during the innate immune response against LM [4,13,26,27].

This innate immune response of CD8 T cells is elicited by the concerted actions of IL-12 and IL-18. It is presumed that these cytokines are secreted by infected macrophages and/or dendritic cells and signal CD8 T cells of either a memory or an effector phenotype to secrete IFN-γ. The receptors for both IL-12 and IL-18 appear to be upregulated on effector and memory CD8 T cells, thus providing a mechanism whereby the CD8 T cells can respond rapidly. Importantly, it has been demonstrated that CD8 T cells that are not specific for LM can perform this function [4].

In order to demonstrate a physiological function for these IFN-γ-secreting CD8 T cells, purified memory CD8 T cells specific for ovalbumin (OT-I T cells) were transferred into IFN-γ-deficient hosts that were subsequently infected with LM. Indeed, as few as 0.5×10^6 transferred memory OT-I T cells were able to provide innate protection against a subsequent LM infection [4]. Interestingly, when similar numbers of purified NK cells were transferred into IFN-γ-deficient hosts, little protection was offered. How could this be explained even when the NK cells were shown to secrete IFN-γ? It was demonstrated that memory CD8 T cells localized to the same areas in the spleen and liver where LM replicates. By contrast, in the spleen NK cells were not associated with the LM lesions [28••]. The localization of NK cells in LM-infected liver is currently unknown.

Innate immune responses of CD8 T cells against other pathogens

Cryptosporidium parvum is an intracellular zoonotic parasite that primarily infects the gastrointestinal epithelium. IFN-γ plays an important role in the early innate defense against this parasite. $CD8^+$, $TCR\alpha\beta^+$ intraepithelial lymphocytes isolated from the small intestine at 24 hours post-infection with *C. parvum* were shown to secrete IFN-γ, albeit after a 48-hour stimulation with anti-CD3 and anti-CD28 [29]. However, these levels of IFN-γ were higher than those from uninfected mice.

Burkholderia pseudomallei is a Gram-negative bacterium that causes the disease melioidosis, which results in septicemia and pneumonia. Similar to infection with LM, early production of IFN-γ is required for resistance. Bancroft and co-workers [26] identified CD8 T cells as being important contributors to the rapid IFN-γ secretion. Production of IL-12 and IL-18 in response to *B. pseudomallei* induces IFN-γ secretion from $CD44^{hi}$, memory phenotype CD8 T cells. These data suggest that IFN-γ production from CD8 T cells might play a role in innate protection against *B. pseudomallei*.

Shigella flexneri is a Gram-negative bacterium that is responsible for bacillary dysentery. A mouse pulmonary model of shigellosis demonstrated that both NK and αβ T cells could provide early (day four) protection against infection by secreting IFN-γ [30]. Although it was not demonstrated, it seems probable that CD8 T cells are responsible for this protection. Indeed, IL-12 was shown to be produced at early time points post-infection [30]. The generation of this cytokine, in conjunction with IL-18, could then lead to the early production of IFN-γ from previously activated CD8 T cells.

Innate immune responses of CD8 T cells against tumor cells

In addition to responding to pathogens in an innate fashion, CD8 T cells have been implicated in antigen-independent tumor responses. Self-reactive CD8 T cells (described below) express high levels of NKG2D. It has been shown that this receptor can induce killing of target cells using a redirected lysis assay [6•]. Furthermore, activation of $CD44^{hi}$CD8 T cells using IL-2 resulted in significantly higher levels of killing of a syngeneic target compared with $CD44^{lo}$CD8 T cells [7]. Expression of the NKG2D ligand Rae-1δ resulted in increased killing of the syngeneic targets. As the expression of Rae-1δ is associated with tumors, it seems plausible that a subset of innate CD8 T cells activated with IL-2 could directly lyse tumors using NKG2D, independent of TCR specificity. Another report characterized CD8 T cells in cancer patients receiving IL-12, showing that a subset of CD8 T cells expanded and displayed enhanced MHC non-restricted cytotoxicity *in vitro* [31]. This study once again suggests that cytokines can stimulate subsets of CD8 T cells, independent of TCR signaling, to lyse tumors.

Innate immune responses of self-reactive CD8 T cells

The previous sections have focused on the beneficial effects of antigen non-specific CD8 T cells. However, several groups have also uncovered a potential negative role for innate CD8 T cells. Benoist and co-workers [8•] have described a population of thymic-derived CD8αα T cells in male TCR transgenic mice specific for the HY antigen that are self-reactive and express several innate receptors. Interestingly, although signaling through the TCR on these lymphocytes leads to rapid secretion of IFN-γ, no real autoimmunity is seen in these animals. Signaling through the NK1.1 molecule on this population of CD8 T cells also leads to the rapid production of IFN-γ, leading the authors to speculate that a combination of TCR and NK-like receptors might allow these innate cells to respond to subtle changes in MHC expression [8•]. Using the same HY mouse model, another group has also described the presence of self-reactive CD8 T cells, although in this case the cells are extrathymically derived [9]. These CD8 T cells can be induced to secrete IFN-γ by IL-2 or by IL-15, with marked enhancement by IL-12. A third group used the HY mouse model to analyze these self-reactive CD8 T cells [6•]. A non-antigen-specific proliferation of self-reactive CD8 T cells was seen upon infection with LM. This result suggests that production of cytokines such as IL-2 or IL-15 at early stages of LM infection could lead to proliferation of this small subset of self-reactive CD8 T cells. IFN-γ production was also noted, although a brief TCR stimulation was required *in vitro* [6•]. Collectively, these studies suggest that self-reactive CD8 T cells that do not appear to induce harmful autoimmunity might play a role in responding to pathogens through cytokine and NK-like receptors.

Two recent reports have implicated CD8 T cells in celiac disease, which is an autoimmune condition characterized by the infiltration of T cells into the small intestine. CD8 T cells that express high levels of the activating receptor NKG2D were induced by IL-15 to kill epithelial cells expressing the stress-induced ligand MHC class I-related chain A (MICA). This killing was suggested to be independent of TCR specificity [32••,33••].

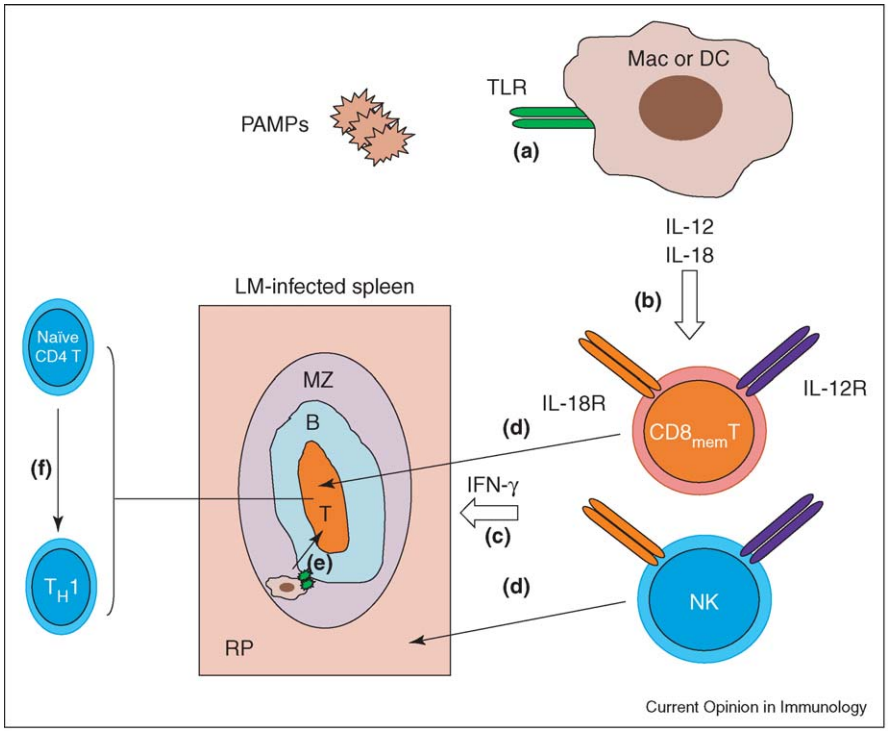
Suppression of immune responses by innate CD8 T cells

Another potential function of innate CD8 T cells is the suppression of other immune responses. Marsland *et al.* [34•] recently described an experimental model in which influenza-specific CD8 T cells were generated that remain in the lung after pathogen clearance. This finding was expected, but the fact that these CD8 T cells could reduce allergen-induced inflammation in the lungs was not predicted. IFN-γ production by CD8 T cells in an antigen-independent manner was shown to be required for this reduction in the allergic response. IL-12 and/or IL-18 were suggested to be the inducing factors for production of IFN-γ by CD8 T cells in response to the airway allergen [34•].

Conclusions

Although the contribution of CD8 T cells to innate immune responses is becoming apparent, the question remains why these lymphocytes that are usually exquisitely specific in their responses would secrete cytokines in an antigen-non-specific manner. Independent of their specificity, memory CD8 T cells are distributed

Figure 1



CD8 T cells are more efficacious than NK cells in the innate response to *Listeria monocytogenes* (LM). **(a)** Pathogen-associated molecular patterns (PAMPs) interact with Toll-like receptors (TLR) on host cells, which results in secretion of IL-12 and IL-18. **(b)** IL-12 and IL-18 bind to their complementary receptors (IL-12R and IL-18R) on 'innate' $CD8_{mem}$ T and NK cells. **(c)** Cytokine-activated $CD8_{mem}$ T and NK cells secrete IFN-γ. **(d)** During the innate response, $CD8_{mem}$ T cells localize to the T cell area of the splenic white pulp (T), whereas NK cells localize to the red pulp (RP). **(e)** LM-infected marginal zone (MZ) macrophages (Mac) relocalize to the T cell area of the white pulp, which is where bacterial replication takes place. **(f)** Naïve CD4 T cells differentiate into T_H1 cells; this is potentially aided by polarizing signals from $CD8_{mem}$ T cells. B represents B lymphocyte area.

ubiquitously throughout organs of the body ready to respond to specific antigenic challenge [4,35]. The activation of Toll-like receptors by interaction with pathogen-associated molecular patterns allows for the immediate secretion of innate cytokines from host cells. This is likely to allow bystander CD8 T cells to respond rapidly in an innate manner before the antigen-specific T cells undergo clonal expansion to carry out the specific phase of the immune response.

We suggest that the same signals that attract specific CD8 T cells to sites of infection allow for a similar localization of antigen-non-specific T cells, and that this localization allows these cells to mount a protective innate response (Figure 1). Using the example of an LM infection, non-antigen-specific memory CD8 T cells localize to the areas of the LM-infected lesions in both the spleen and liver. Stimulation by IL-12 and IL-18 allows these CD8 T cells to secrete IFN-γ and to protect against infection. NK cells also secrete IFN-γ, but their lack of co-localization with the LM renders them less-effective in control of infection (Figure 1). It is possible that this innate CD8 T cell response is designed to bridge a gap between an immediate and an adaptive response. For both innate and adaptive responses of CD8 T cells there must be tight control in order to avoid destructive immunopathology. For TCR-mediated responses, it is known that most of the responding T cells are destined to die by way of apoptosis once the pathogen is eliminated. However, for the non-antigen-specific responses described above, the control phase of the response has not been described. Understanding how to manipulate such innate responses of CD8 T cells should allow researchers to harness these lymphocytes to aid in the control of infectious diseases.

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