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There is increasing evidence that the immune response can be inhibited by several T cell subsets, including NK T cells, CD25<sup>+</sup>CD4<sup>+</sup> T cells, and a subpopulation of CD8<sup>+</sup> T cells. Animal model studies of multiple sclerosis have suggested an important role for suppressor CD8<sup>+</sup> T cells in protection against disease recurrence and exacerbation. The molecular lynchpin of CD8<sup>+</sup> suppressive activity is the murine MHC molecule Qa-1, termed HLA-E in humans. Here we summarize findings from work on Qa-1 that have begun to delineate suppressor CD8<sup>+</sup> T cells and their mechanisms of action in the context of self tolerance and autoimmune disease.

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# Qa-1 restriction of CD8<sup>+</sup> suppressor T cells

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**There is increasing evidence that the immune response can be inhibited by several T cell subsets, including NK T cells, CD25<sup>+</sup>CD4<sup>+</sup> T cells, and a subpopulation of CD8<sup>+</sup> T cells. Animal model studies of multiple sclerosis have suggested an important role for suppressor CD8<sup>+</sup> T cells in protection against disease recurrence and exacerbation. The molecular lynchpin of CD8<sup>+</sup> suppressive activity is the murine MHC molecule Qa-1, termed HLA-E in humans. Here we summarize findings from work on Qa-1 that have begun to delineate suppressor CD8<sup>+</sup> T cells and their mechanisms of action in the context of self tolerance and autoimmune disease.**

## Mechanisms of peripheral tolerance

The first stages of T cell development occur in the thymus, where a selection process weeds out potentially autoreactive cells. Successful progression of thymocytes through selection requires expression of TCRs capable of efficient binding to self-MHC products. Although T cell clones bearing TCRs with high affinity for self-peptide MHC products are generally eliminated during this process, the resulting T cell repertoire is still strongly biased toward self reactivity (1). As a result, substantial numbers of peripheral T cells can proliferate in response to self-peptide MHC complexes, and some can differentiate into effector cells in the context of inflammatory stimuli (2–4).

Expansion of autoreactive T cells in peripheral lymphoid tissues is constrained, in part, by abortive TCR signals that lead to T cell elimination or inactivation (5, 6). However, mechanisms of T cell elimination that include activation-induced cell death (AICD) and anergy, an insensitivity to antigens that creates an inability to elicit a normal antigenic response, may not suffice to prevent autoimmune disease (7, 8). The apparent limitations of these mechanisms for eliminating all self-reactive cells have stimulated research into T cells and other cell types, so-called suppressor T cells, that may exert dominant inhibitory effects on expansion of pathogenic autoreactive T cells. One such group of cells is the suppressor CD8<sup>+</sup> T cells.

## Suppressor CD8<sup>+</sup> T cells and Qa-1

The recent resurgence of interest in suppressor T cells has been largely due to the delineation of a CD4<sup>+</sup> sublineage with regulatory activity (9–13). The possibility that CD8<sup>+</sup> T cells might also contain a regulatory sublineage has received much less attention despite the fact that CD8<sup>+</sup> T cells were the initial target of work in this area. Early research used experimental systems that mainly measured *in vitro* antibody responses to complex antigens such as foreign erythrocytes as well as *in vivo* contact hypersensitivity and delayed-type-hypersensitivity reactions. Downregulation of these responses by subpopulations of CD8<sup>+</sup> T cells was then difficult to distinguish from modes of inhibition that were not yet well understood, includ-

ing the impact of regulatory cytokines and AICD on CD4<sup>+</sup> T cells. These difficulties, combined with the inability of molecular genetics to validate early models by identifying genes for suppressor factors and receptors, gave rise to a well-justified skepticism concerning the existence of suppressor CD8<sup>+</sup> T cells. However, some useful information can be gleaned by reexamining these early approaches. For example, the ability of T cell vaccination with pathogenic autoreactive CD4<sup>+</sup> clones to inhibit autoimmune disease (14, 15) has been verified, along with suggestions that protection depends on induction of suppressor CD8<sup>+</sup> T cells (16–18).

## Murine Qa-1

More recent studies have suggested that a subpopulation of CD8<sup>+</sup> T cells might suppress the response of successfully activated CD4<sup>+</sup> T cells and B cells through an interaction that depends on expression by target cells (or APCs) of the HLA class Ib MHC molecule Qa-1 (19, 20). The Qa-1 protein is a member of the class Ib MHC family. Most class Ib MHC gene products interact with CD8 on the surface of T cells and are expressed on the cell surface along with  $\beta_2$  microglobulin ( $\beta_2m$ ) molecules. Several class Ib molecules are ligands for receptors on NK cells, e.g., Qa-1 is a ligand for the inhibitory CD94/NKG2A or CD94/NKG2C receptors.

The impact of molecular immunology on our understanding of Tregs is evident from research into the murine Qa-1 protein. Early work revealed an inhibitory interaction between CD8<sup>+</sup> and CD4<sup>+</sup> T cells *in vitro* that depended on the expression of the Qa-1 molecule on activated CD4<sup>+</sup> target cells (21). The significance of this observation became clearer after Qa-1 was shown to be a peptide-binding class Ib molecule (rather than an activation-related surface protein); it mapped to the 3' end of the MHC class I region on chromosome 17, the same region that contained other class Ib genes, including thymus leukemia antigen (22–24). The mouse MHC class Ib molecule Qa-1 and its human homologue, the HLA-E protein, form heterodimers with  $\beta_2m$  in lymphoid cells that bind to and present peptides derived from self or foreign proteins (25–28). Although Qa-1 RNA is expressed in many cell types (29), surface expression of the Qa-1- $\beta_2m$  heterodimer is highly constrained by Qa-1- $\beta_2m$  assembly and transport mechanisms that favor expression on activated T and B lymphocytes and dendritic cells (28, 30).

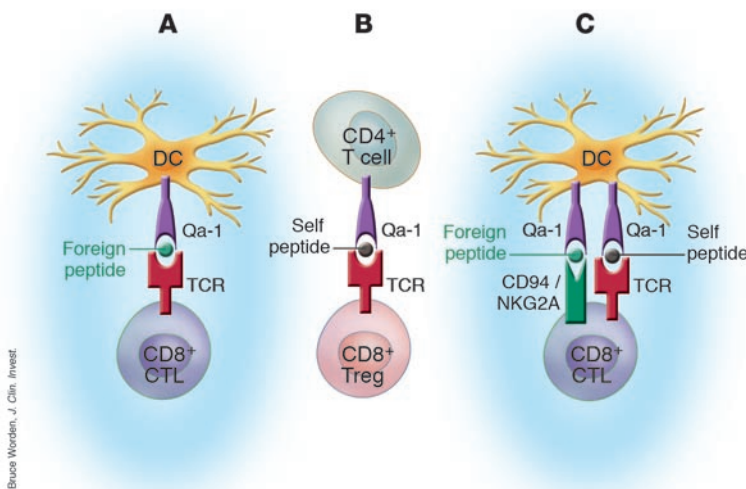
## Qa-1 gene products engage two classes of receptors

Peptide-containing Qa-1 complexes engage two classes of receptors. Qa-1 heterodimers containing peptides derived in a transporter-associated with antigen processing-dependent (TAP-dependent)

**Nonstandard abbreviations used:** AICD, activation-induced cell death; EAE, experimental autoimmune encephalomyelitis; hsp, heat shock protein;  $\beta_2m$ ,  $\beta_2$  microglobulin; MBP, myelin basic protein; PLP, proteolipid protein; Qdm, Qa-1 determinant modifiers; TAP, transporter associated with antigen processing.

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**Figure 1**

Engagement of Qa-1 by the TCR and by CD94/NKG2A. **(A)** Presentation of Qa-1–bacterial GroEL peptide by a DC following *Salmonella* infection to CD8<sup>+</sup> T cells, where the receptor is a TCR, leads to CTL responses. **(B)** Presentation of Qa-1–self peptides by activated CD4<sup>+</sup> T cells to CD8<sup>+</sup> T cells, where the receptor is a TCR, leads to the development of Qa-1–restricted suppressor CD8<sup>+</sup> T cells. **(C)** Engagement of CD94/NKG2A receptors on CD8<sup>+</sup> T cells with a DC can inhibit either TCR-mediated CTL responses specific for Qa-1–foreign peptide ligands and/or TCR-mediated suppressive responses specific for Qa-1–self peptide ligands. This NKG2A-dependent interaction may regulate expression of suppressor or cytotoxic CD8<sup>+</sup> T cells through inhibition of cellular activation or diminished AICD.

fashion from class Ia leader sequences, termed Qa-1 determinants (Qdm), bind to nonclonally distributed CD94–NKG2A, C, and/or E receptors on NK cells and a subpopulation of CD8 cells. The functional outcome of Qdm:NKG2 interactions is generally inhibition of NK or CD8 CTL activity (31). A second class of Qa-1 ligands is comprised of Qa-1:β<sub>2</sub>m heterodimers containing a growing number of peptides, including those derived from TCR V<sub>β</sub>, preproinsulin, bacterial GroEL, and endogenous heat shock protein 60 (hsp60) (27, 32–34). Interaction between this class of Qa-1 ligands and the TCR on CD8 cells can promote CD8 cell activation, expansion, and expression of effector cell activity (35).

### Qa-1–restricted suppression by CD8<sup>+</sup> T cells

As noted above, interest in CD8<sup>+</sup> T cell suppression has been rekindled by studies of experimental autoimmune encephalomyelitis (EAE) in B10.PL mice, which become resistant to disease after initial exposure to myelin basic protein (MBP). Mice deficient in CD8<sup>+</sup> T cells due to a targeted mutation or antibody-dependent depletion do not develop resistance to EAE (36, 37). Resistance requires exposure of CD8<sup>+</sup> T cells to MBP, since replenishment of CD8<sup>+</sup>-deficient mice with CD8<sup>+</sup> T cells from nonimmune donors before a secondary anti-MBP response does not prevent disease recurrence. Additional studies by Jiang, Chess, and colleagues suggest that the inhibitory interaction between CD8<sup>+</sup> Tregs and MBP-reactive CD4<sup>+</sup> T cells involves TCR-based recognition of Qa-1–self-peptide complexes expressed by autoreactive CD4<sup>+</sup> T cells (16, 17, 35).

To develop a clearer understanding of the physiological role of Qa-1–reactive CD8<sup>+</sup> T cells in suppressing immune responses, we recently generated mice that are deficient in Qa-1 gene expression due to a targeted gene mutation (38). Qa-1–deficient animals devel-

op exaggerated secondary CD4<sup>+</sup> T cell responses after viral infection or immunization with foreign or self peptides. In addition, enhanced CD4<sup>+</sup> T cell responses of Qa-1–deficient mice to mouse proteolipid protein (PLP) self peptide are associated with increased susceptibility to recurrence of EAE; this phenotype is remedied by lentiviral-based expression of the correct Qa-1 allele (38). These data indicate Qa-1 is required for an appropriately curtailed CD4<sup>+</sup> T cell response to infection and for autoimmunity resistance.

Analysis of the cellular basis of Qa-1–dependent resistance to EAE indicated that CD8<sup>+</sup> T cells from PLP-peptide immune mice suppressed peptide-specific expansion of CD4<sup>+</sup> T cells; both EAE resistance and the development of suppressor CD8<sup>+</sup> T cells required prior immunization with PLP peptide. These findings indicate that the primary immune response to self peptides may include expansion of Qa-1–restricted CD8<sup>+</sup> T cells that can inhibit expansion of pathogenic autoreactive CD4<sup>+</sup> T cells and consequent autoimmune disease. The impact of CD8<sup>+</sup>-dependent suppression on the clonal composition of MBP-reactive CD4<sup>+</sup> T cells has been ascertained through complementarity-determining region 3 sequence analysis, a PCR-based technique that allows amplification and definition of distinct antigen-binding regions of TCR chains, of CD4<sup>+</sup> T cells after recovery from EAE in the presence or absence of CD8<sup>+</sup> T cells. Depletion of CD8<sup>+</sup> T cells was associated with expansion of several dominant clones of pathogenic autoreactive CD4<sup>+</sup> T

cells in contrast to the more heterogeneous TCR repertoire of CD4<sup>+</sup> T cells, each of limited clonal expansion, that developed after exposure to MBP in the presence of CD8<sup>+</sup> T cells (35).

Analysis of Qa-1–restricted suppression suggests that expression of a TCR on CD8<sup>+</sup> suppressor T cells may be necessary for recognition of expression of suppressive activity (38). Another observation consistent with this idea is that constraints placed on expression of a full TCR repertoire prevent CD8 cells from mediating suppression. Changes in the structure of Qa-1 on target cells that may affect peptide binding also affect susceptibility to suppression of CD8 cells. CD8<sup>+</sup> T cells expressing an incorrect TCR transgene are unable to mediate suppressive activity (38). This finding is consistent with TCR-dependent discrimination of peptide–Qa-1 complexes on target CD4<sup>+</sup> T cells. NKG2-dependent recognition of Qa-1, on the other hand, would not be expected to be affected by allele-specific changes, although without additional analysis of Qa-1 proteins that express defined mutations, this remains uncertain. Since NKG2 receptors on CD8<sup>+</sup> T cells may affect the levels of TCR-dependent suppressive activity, e.g., through regulation of TCR-dependent activation and expansion of these cells (Figure 1), experimental analysis using cells that express mutant Qa-1 molecules that differentially engage the TCR and NKG2 receptors is needed for a full molecular dissection of the contribution of these two Qa-1–binding recognition elements to suppressive CD8<sup>+</sup> activity.

The timing of CD8<sup>+</sup>-dependent inhibitory responses can be contrasted with that of the naturally occurring CD4<sup>+</sup>CD25<sup>+</sup> Tregs, which interrupt expansion of self-reactive T cells during the initial stages of primary responses. Suppressor CD8<sup>+</sup> T cells arise later in the immune response and become apparent experimentally only after restimulation by antigen or superantigen (11, 38, 39). The development of Qa-1–



restricted suppressive activity more closely resembles the kinetics of CD8<sup>+</sup>-dependent cytolytic activity rather than CD4<sup>+</sup>CD25<sup>+</sup> regulatory activity. Both CD8<sup>+</sup>-dependent suppressive and cytolytic responses require primary immunization to generate TCR-dependent lysis or Qa-1-restricted elimination of target cells (38, 39).

The mechanism of Qa-1-restricted inhibitory interactions has not been established. CD8<sup>+</sup> cells that recognize Qa-1 associated with insulin peptide efficiently kill Qa-1<sup>+</sup> lymphoblastoid target cells in the presence of intact soluble insulin after TAP-independent processing and presentation of insulin-derived peptide by Qa-1 (33). Qa-1-restricted inhibitory activity of CD8<sup>+</sup> T cells may reflect lysis of activated CD4<sup>+</sup> T cells that display Qa-1-peptide complexes, perhaps after TCR-dependent signals induce expression of relevant Qa-1 ligands on activated T and B lymphocytes. Although the Qa-1-binding peptides that target CD8<sup>+</sup> responses have not been fully identified, they may represent a relatively restricted set that is efficiently expressed on activated T cells after high avidity TCR-ligand engagement (35). The fate of individual TCRs following ligation with peptide-MHC complexes is thought to depend on peptide affinity, the association/dissociation rate of TCR-ligand formation, and the strength of TCR-dependent signals. Most internalized TCR complexes are degraded in lysosomes (40), but robust TCR engagement may facilitate a proteasome-dependent degradation process that leads to recycling and TAP-independent Qa-1 presentation (41).

### Peptide presentation and selection of CD8<sup>+</sup> T cells by Qa-1

Positive selection of thymocytes that express a TCR transgene specific for foreign peptides associated with Qa-1 depends on interactions with Qa-1 peptides and self peptides expressed primarily by hematopoietic cells (42). Both selection and antigen recognition are TCR-dependent and do not require NKG2 receptors (28). Whether Qa-1-dependent negative selection by self peptides is dependent on TCR engagement or other receptors is unclear. A bacterial GroEL peptide that is almost identical to murine hsp60 peptide (GroEL: GMQFDRGYL; murine hsp60: GMKFDGRGYI) elicits cytolytic CD8<sup>+</sup> T cells that are cross-reactive with the murine hsp60 self peptide. One explanation for high levels of Qa-1-restricted reactivity to this self peptide is that negative selection by Qa-1 is less efficient than negative selection by conventional class I MHC. Alternatively, expression of CD8 reactivity to Qa-1-restricted self peptides may reflect defects in peripheral tolerance mechanisms.

The expression, structure, and processing pathways of Qa-1 are distinct from those of classical MHC class I. Class Ia molecules are widely expressed on most cell types regardless of activation status. Qa-1 is preferentially expressed on activated but not resting T cells and thymocytes, thus protecting unstimulated T cells from the effects of CD8<sup>+</sup>-dependent suppression. Moreover, Qa-1 expression on activated CD4<sup>+</sup> T cells is short-lived, and optimal levels persist for hours rather than days after TCR ligation. Susceptibility of activated CD4<sup>+</sup> T cells to suppression by CD8<sup>+</sup> T cells is thus restricted to a brief window after immunization. Class Ia molecules are the most highly polymorphic human or mouse genes studied to date, but Qa-1 has very limited polymorphisms and has very tight specificity of peptide binding. Qa-1 was first found to bind the Qdm peptide; subsequent studies have shown that this class Ib MHC molecule is capable of presenting a variety of self and foreign peptides to CD8<sup>+</sup> T cells through TAP-dependent and TAP-independent pathways. The latter pathway allows

Qa-1 on dendritic cells to cross-present peptides to CD8<sup>+</sup> T cells, and similar trafficking machinery may allow Qa-1-dependent cross-presentation of peptides by activated CD4<sup>+</sup> T cells. If so, this mechanism would allow the presentation of self peptides derived from the TCR or hsp60 in activated CD4<sup>+</sup> T cells to CD8<sup>+</sup> T cells. The observation that activated lymphoid cells can efficiently process and present intact exogenous insulin associated with Qa-1 is consistent with this mechanism. Findings that engagement of the TCR by peptide ligands can lead to endocytosis of the TCR also suggest a mechanism that may allow TAP-independent endosomal loading of TCR-derived peptides onto Qa-1 molecules.

What about the contribution of non-TCR receptors to Qa-1-restricted activation of CD8<sup>+</sup> T cells? Although CD94/NKG2 receptors are expressed by less than 2.5% of CD8<sup>+</sup> T cells in humans (43), they are upregulated after TCR engagement or stimulation by cytokines, including TGF- $\beta$  and IL-15 (44, 45). CD94/NKG2A expression is also induced shortly after T cell activation following *lymphocytic choriomeningitis* or *Listeria monocytogenes* infection. Regulatory CD8<sup>+</sup> T cells may express both clonally distributed TCR  $\alpha\beta$  receptors for Qa-1-self peptide (19, 20, 35) and nonclonally distributed NKG2<sup>+</sup> coreceptors for Qdm-Qa-1 (46). Interactions between Qa-1-peptide ligands and the TCR  $\alpha\beta$  receptor may stimulate clonal expansion of CD8<sup>+</sup> T cells and development of suppressive or effector activity, while interactions between Qa-1-Qdm and CD94-NKG2 receptors on CD8<sup>+</sup> T cells may downregulate expansion and/or protect against AICD (32, 47) (see Figure 1). According to this model, differential engagement of these two classes of Qa-1 receptors may regulate the expansion and activation of suppressor CD8<sup>+</sup> T cells.

### CD8<sup>+</sup> T cell suppression and self tolerance

The potential role of Qa-1-restricted CD8<sup>+</sup> T cells in clinical or animal models – aside from murine EAE – has not been investigated. However, experimental analysis of other animal models of autoimmune disease and organ transplantation have suggested a potential role for inhibitory CD8<sup>+</sup> T cells and/or T cells that may recognize conserved Qa-1-peptide ligands. Vaccination with self or foreign hsp60 can inhibit development of adjuvant-induced arthritis, and transfer of hsp65 peptide-primed T cells can afford protection against disease development in adoptive hosts (48, 49). Analysis of the protective activity of hsp-derived peptides in murine adjuvant-induced arthritis (50) and in some mouse models of type 1 diabetes (51) in animals deficient in Qa-1 expression may help to clarify the contribution of Qa-1-restricted CD8<sup>+</sup> T cells to disease protection.

Studies of transplantation tolerance have also suggested a possible role for suppressor CD8<sup>+</sup> T cells. Early experiments first suggested that Qa-1-specific transplantation tolerance could prevent generation of alloreactive CTL (52) as well as the generation of suppressor T cell activity in anti-Qa-1 immune responses (53, 54). CD8<sup>+</sup> T cells may contribute to the inhibitory effects of pretransplant donor-specific blood transfusion since elimination of this subset before blood transfusion can result in graft rejection (55). The potential role of Qa-1/HLA-E-restricted CD8 cells in these responses is not currently understood.

### Concluding remarks

Definition of the role of CD8<sup>+</sup> T cells that suppress the response of CD4<sup>+</sup> T cells expressing Qa-1-peptide target ligands has important implications for understanding immunoregulation in the context of self tolerance. Further investigation of animal models of arthritis, autoimmune type I diabetes, and organ transplantation is needed to





delineate the regulatory role of the Qa-1/HLA-E-restricted mechanisms defined in this review. The availability of Qa-1 deficient mice represents a new experimental approach to evaluation of the potential role of Qa-1-restricted suppression in these disorders.

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