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In Vivo Modulation of T Cell Responses and Protective Immunity by TCR Antagonism during Infection¹

Lisa L. Lau,²,³ Jiu Jiang,²,⁴ and Hao Shen⁵

Infectious agents are known to express altered peptide ligands that antagonize T cells in vitro; however, direct evidence of TCR antagonism during infection is still lacking, and its importance in the context of infection remains to be established. In this study, we used a murine model of infection with recombinant Listeria monocytogenes and addressed three issues that are critical for assessing the role of TCR antagonism in the modulation of the immune response. First, we demonstrated that the antagonist peptide efficiently inhibited the ability of the agonist to prime naive TCR-transgenic T cells in vivo. Second, we showed clonal memory T cells were antagonized during recall responses, resulting in loss of protective immunity. Lastly, we observed that even in the context of a polyclonal response, TCR antagonism greatly inhibits the agonist-specific response, leading to altered hierarchy of immunodominance and reduced T cell memory and protective immunity. These results provide direct evidence of clonal TCR antagonism of naive and memory CD8 T cells during infection and demonstrate the effect of TCR antagonism on protective immunity. Thus, agonist/antagonist interactions may play an important role in determining the immunodominance and repertoire of T cell targets, and evaluation of immune responses and vaccine strategies may require examination of not only agonists but also antagonists and their interactions during an infection. The Journal of Immunology, 2005, 174: 7970–7976.

T

lymphocytes use TCR to recognize antigenic peptides presented in the context of MHC molecules. Altered peptide ligands with substitutions at TCR contact residues can act as specific TCR antagonists or partial agonists and play a role in thymic T cell development, maintenance of peripheral T cells, and down-modulation of autoreactive T cell responses (1–4). TCR antagonists do not induce phenotypic changes associated with T cell activation but inhibit the T cell response to agonists. This inhibition is independent of competition for binding to MHC molecules and instead is a function of the low-affinity interaction between antagonists and TCR (5). Recent data have shown that stimulation by antagonists induces suboptimal TCR signaling, leading to incomplete phosphorylation of TCR-ζ and lack of Zap70 activation (6–9). This is thought to result from the weak interactions between TCR and antagonist-MHC that are kinetically unstable. It is proposed that in the presence of antagonists, TCR are quickly sequestered away from agonists into short-lived complexes with antagonist/MHC, resulting in inhibition of T cell activation by agonists (10).

Infectious agents are known to express antagonist peptides that inhibit the activation and function of T cells in vitro. In patients chronically infected with hepatitis B virus and HIV, viral variants have been isolated that contain mutations in immunodominant epitopes recognized by CTL. Some of these altered peptides function as antagonists of the wild-type epitope in vitro, inhibiting the ability of T cell lines to lyse target cells and produce IFN-γ (11–13). Antagonistic epitopes have also been identified in cohabiting strains of Plasmodium falciparum and shown to interfere with the induction of de novo responses in an in vitro CTL priming model (14, 15). These data strongly suggest that generation of TCR antagonists by variants of an infectious agent may represent an effective immune evasion mechanism. In vivo inhibition of the T cell response has been observed when an antagonist peptide is expressed endogenously as a self-Ag (16) or injected into mice in peptide/protein forms (14, 17). In contrast, direct in vivo evidence of TCR antagonism during an infection is still lacking. Inflammatory conditions are known to override anergy/tolerance induction by providing appropriate cytokines and costimulatory signals (18). Thus, it is possible that the inflammatory milieu accompanying an infection may render T cells less sensitive to TCR antagonism. In addition, protective immunity is mediated by memory T cells, which are more sensitive than naive T cells to TCR signaling induced by agonist ligands (19–21). It is not known whether memory T cells might be antagonized during an in vivo recall response. Furthermore, the possible impact of clone-specific TCR antagonism in the midst of polyclonal T cell responses to a natural infection is still unclear. Answers to these questions are critical in assessing the role of TCR antagonism in mediating immune evasion, modulating protective immunity to infection, and shaping the complexity of T cell responses.

Materials and Methods

Mice, bacteria, and viruses

C57BL/6 and P14 (Rag−/−) TCR-transgenic mice from National Cancer Institute and Taconic Farms, respectively, were maintained in Institutional Animal Care and Use Committee-approved facilities. Recombinant Listeria monocytogenes (rLM)⁶ strains secreting agonist, antagonist, or both
peptides within fusion proteins were constructed by chromosomal integration into the wild-type strain 10403S as described previously (22, 23). In rLM-GP33A, GP33-41 (KAVYNFATC) of lymphocytic choriomeningitis virus (LCMV) is expressed as a fusion GFP under the control of the iap promoter (24). In rLM-GP33a, the GP33-41 antagonist (KAVSNFATC) is expressed as a fusion with dihydrofolate reductase (DHFR) under the control of the hly promoter (24). Both fusions contain the hly signal sequence for bacterial secretion and a mAb epitope from influenza hemagglutinin for Western blot detection. Strain rLM-GP33A/a expresses both fusions as convergent transcriptional units. Western blots were performed on electrophoresed TCA-precipitated culture supernatants using mouse anti-hemagglutinin mAb (Roche), peroxidase-conjugated anti-mouse IgG, and ECL detection (Amersham Biosciences). LCMV Armstrong and Clone13 strains were propagated in vitro and quantitated by plaque assay as described previously (25).

Animal experiments

Mice were immunized i.p. with either 2 × 10^5 PFU LCMV Armstrong or i.v. with ~5 × 10^6 CFU rLM. Challenges were performed by i.v. injection of either ~5 × 10^6 CFU rLM or 2 × 10^6 PFU LCMV clone 13. Bacterial titers were determined by plating serial 10-fold dilutions of spleen or liver homogenates in 1% Triton X-100 in PBS. Viral titers were measured from the serum. For adoptive transfer experiments, splenic naive or memory P14 Thy1.1 cells were labeled with CFSE as previously described (26) and injected i.v. into C57BL/6 Thy1.2 mice (0–2 × 10^6 cells/recipient). Memory P14 cells were generated as previously described (27, 28) by transfer of naive P14 Thy1.1 cells into irradiated C57BL/6 Thy1.2 hosts, immuno- nizing the hosts with LCMV Armstrong, and recovering P14 cells from the spleen after 30 days.

Flow cytometry

Splenocytes were stained with Abs (BD Pharmingen) to CD8, Thy1.1, Thy1.2, CD44, and CD62L, or H-2DbGP33 or H-2KbGP34 tetramers (29). Intracellular IFN-γ staining was performed with the Cytofix/Cytoperm kit (BD Pharmingen) after 5 h in vitro stimulation with or without 1 μM GP33-41 (KAVYNFATC) or rLM-GP33A expressing the agonist peptide, as evident by loss of CFSE fluorescence, increase in total number, and display of activation phenotypes (CD44^high and CD62Llow). In mice infected with rLM-GP33A/a expressing both the agonist and antagonist peptides, the proliferative response of P14 T cells was diminished greatly compared with that in rLM-GP33A-infected mice. These results provide direct visualization that antagonist peptides inhibited the priming of clonal naive T cells by agonist peptide during bacterial infection.

We next investigated if TCR antagonism occurs when the agonist and antagonist peptide are expressed in separate microbes. We adoptively transferred naive P14 T cells and infected the recipients with a mixture of rLM-GP33A and rLM-GP33a that express the agonist and antagonist peptide, respectively. The activation and expansion of P14 cells in the spleen were analyzed on day 3 after infection. Compared with rLM-GP33A-infected mice, the response by P14 cells was inhibited in recipients that were infected with a mixture of rLM-GP33A and rLM-GP33a (Fig. 3). However, the inhibition was not as pronounced as that observed when the antagonist and agonist peptides were expressed on the same bacterium. Thus, an antagonist peptide can inhibit the response to an agonist that is not expressed by the same bacterium, although TCR antagonism is more effective when the agonist and antagonist peptides are expressed on the same microorganism.

TCR antagonism of clonal memory CD8 T cells during infection

To study in vivo TCR antagonism during infection, we introduced into the intracellular bacterium, Listeria monocytogenes (LM), a pair of agonist and antagonist peptides derived from the H-2Dα-restricted GP33-41 epitope of LCMV. The GP33-41 epitope (GP33A: KAVYNFATC) is a strong agonist of CD8 T cells from P14 TCR-transgenic mice (30), and an altered peptide ligand with a Y→S substitution at a key TCR contact residue (GP33a: KAVSNFATC) is known to antagonize P14 T cells (31). We constructed a rLM strain expressing both the agonist and antagonist peptides (rLM-GP33A/a) and, as controls, rLM expressing either the agonist (rLM-GP33A) or the antagonist peptide (rLM-GP33a; Fig. 1). The agonist and antagonist peptides were fused to secreted DHFR and GFP polypeptides, respectively. The expression of the fusion proteins was confirmed by Western blot analysis, with similar levels observed among the three rLM strains (Fig. 1).

The rLM strains were used in an adoptive transfer model to determine whether expression of the antagonist GP33a peptide affects the induction of T cell responses by the GP33A agonist peptide during infection. CFSE-labeled P14 T cells were adoptively transferred into congenic Thy1.1 C57BL/6 mice. Recipients were infected with one of the three rLM strains, and the priming of P14 cells was monitored on day 3 postinfection (Fig. 2). Although P14 cells did not respond to infection with rLM-GP33a expressing the antagonist peptide, they responded rapidly to infection with rLM-GP33A expressing the agonist peptide, as evident by loss of CFSE fluorescence, increase in total number, and display of activation phenotypes (CD44^high and CD62Llow). In mice infected with rLM-GP33A/a expressing both the agonist and antagonist peptides, the proliferative response of P14 T cells was diminished greatly compared with that in rLM-GP33A-infected mice. These results provide direct visualization that antagonist peptides inhibited the priming of clonal naive T cells by agonist peptide during bacterial infection.

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TCR antagonism of clonal memory CD8 T cells during infection

The ability of memory T cells to mount an accelerated response is a hallmark feature of the immune system and the basis of protective immunity. It is not known whether memory T cells can be...
antagonized during an in vivo recall response. Memory T cells differ from naive T cells in their sensitivity to TCR signaling, with a faster response time, a lower threshold for TCR engagement, and less dependence on costimulation for activation (19–21). Thus, it is possible that they may also differ in their sensitivity to TCR antagonism. To address this question, we adoptively transferred naive or memory P14 T cells and analyzed their responses on day 3 postinfection with the wild-type LM (wtLM) or one of the three rLM strains (Fig. 4). Memory P14 T cells were generated as previously described (27, 28) and shown to have the expected memory surface markers (CD44high/CD11ahigh/CD62Llow; data not shown). Although naive P14 cells did not respond to infection with wtLM or rLM-GP33a, a small percentage of memory P14 cells (73% of memory P14 cells dividing compared with 50% of naive P14 cells) were identified by their CD8+/Thy1.2+ phenotype (A, numbers indicate the percentages of total splenocytes that are CD8+/Thy1.2+ P14 cells). Activation and proliferation of transferred P14 cells (gated on CD8+/Thy1.2+ cells) were visualized by analyzing CFSE profile and the surface expression of CD44 (B) and CD62L (C). Shown are plots from one representative mouse of at least three mice per group; similar results were obtained from two additional independent experiments.

FIGURE 2. The antagonist peptide GP33a inhibits priming of naive P14 TCR-transgenic cells by the agonist peptide GP33A during Listeria infection. Splenocytes from P14 TCR-transgenic mice (C57BL/6/Ty1.2, Rag−/−) were labeled with CFSE and adoptively transferred into congenic C57BL/6Thy1.1 mice (2 × 10⁶ GP33-specific P14 cells/recipient). On the following day, recipients were infected with one of three rLM strains (A, 0.1 LD₅₀ or mock infected with PBS. On day 3 postinfection, splenocytes were harvested, and transferred P14 cells were identified by their CD8+/Thy1.2+ phenotype (A, numbers indicate the percentages of total splenocytes that are CD8+/Thy1.2+ P14 cells). Activation and proliferation of transferred P14 cells (gated on CD8+/Thy1.2+ cells) were visualized by analyzing CFSE profile and the surface expression of CD44 (B) and CD62L (C). Shown are plots from one representative mouse of at least three mice per group; similar results were obtained from two independent experiments.

FIGURE 3. The antagonist peptide GP33a inhibits priming of P14 cells by the agonist peptide GP33A that is not expressed by the same bacterium during a mixed infection. Splenocytes from P14 TCR-transgenic mice (Ty1.1) were labeled with CFSE and adoptively transferred into congenic Thy1.2 mice (2 × 10⁶ GP33-specific P14 cells/recipient). On the following day, recipients were infected with rLM-GP33A, rLM-GP33a, or a mixture of the two strains (A, 0.1 LD₅₀ CFU of each strain). On day 3 after infection, splenocytes were harvested, and transferred P14 cells were identified by CD8+/Thy1.1+ staining (B, top panel, gated on live splenocytes). Activation and proliferation of transferred P14 cells were visualized by analyzing the CFSE profile and the surface expression of CD44 and CD62L (A, middle and low panel, gated on donor P14 cells). The ability of the transferred P14 cells to secrete IFN-γ was examined by intracellular cytokine staining (B, gated on total CD8 T cells). Shown are plots from one representative mouse of at least three mice per group; similar results were obtained from two independent experiments.

The antagonist peptide GP33a inhibits priming of P14 cells by the agonist peptide GP33A that is not expressed by the same bacterium during a mixed infection. Splenocytes from P14 TCR-transgenic mice (C57BL/6/Ty1.2, Rag−/−) were labeled with CFSE and adoptively transferred into congenic C57BL/6Thy1.1 mice (2 × 10⁶ GP33-specific P14 cells/recipient). On the following day, recipients were infected with one of three rLM strains (A, 0.1 LD₅₀ or mock infected with PBS. On day 3 postinfection, splenocytes were harvested, and transferred P14 cells were identified by their CD8+/Thy1.2+ phenotype (A, numbers indicate the percentages of total splenocytes that are CD8+/Thy1.2+ P14 cells). Activation and proliferation of transferred P14 cells (gated on CD8+/Thy1.2+ cells) were visualized by analyzing CFSE profile and the surface expression of CD44 (B) and CD62L (C). Shown are plots from one representative mouse of at least three mice per group; similar results were obtained from two independent experiments.

Attenuation of the polyclonal response by TCR antagonism during infection

Because TCR antagonism is clone specific in nature, it remains unclear to what extent it might have an effect on the immune response in the context of a natural infection involving polyclonal T cell responses. To examine this question, we infected C57BL/6 mice with the wtLM or one of the three rLM strains and analyzed the GP33-specific responses by intracellular IFN-γ staining (Fig.
5). The wtLM strain did not induce any detectable GP33-specific response, as expected. Splenocytes from mice infected with rLM-GP33a had very few IFN-γ-producing cells when stimulated with either the GP33A peptide (Fig. 5) or with the GP33a peptide (data not shown), indicating that the antagonist peptide itself was weakly immunogenic. The number of GP33-specific cells induced by rLM-GP33A/a expressing both the agonist and antagonist was ~50% less than that induced by rLM-GP33A expressing the agonist alone. As an internal control, we measured the response to an H2-M3-restricted native LM epitope and found no significant difference between these two strains. Thus, the ~50% reduction of GP33-specific responses was because of specific inhibition by the antagonist peptide, leading to significantly reduced CD8 T cell memory. To further examine this inhibition, we challenged rLM-immunized mice with a virulent strain (clone 13) of LCMV and assessed the GP33-specific recall response and protective immunity (Fig. 5). Mice immunized with rLM-GP33A mounted a strong GP33-specific response and cleared the LCMV virus. In contrast, mice immunized with rLM-GP33A/a responded poorly and failed to control LCMV infection, similar to mice immunized with wtLM and rLM-GP33A. Thus, the presence of the antagonist inhibited the polyclonal response to the agonist and reduced immunological memory to a level below the threshold required for protective immunity.}

We next examined whether the presence of an antagonist peptide has any impact on the in vivo recall response of a polyclonal memory population. C57BL/6 mice were immunized with a sublethal dose of wtLM or one of the three rLM strains. Two months after immunization, GP33-specific responses were measured by intracellular IFN-γ staining following 5 h of in vitro stimulation with the GP33-41 peptide (A and D). As an internal control, the H2-M3-restricted response to a native LM epitope (5MIGWII) was also measured (B and E). Another group of wtLM- and rLM-immunized mice was challenged with LCMV clone 13. On day 8 post-LCMV infection, spleens were harvested to assess GP33-specific memory response by intracellular IFN-γ staining (C) and to determine virus titers as a measure of protective immunity (F). Dot plots in A–C show staining with anti-IFN-γ mAb and the isotype control Ig, with the numbers indicating the percentage of CD8 T cells that stained positive for IFN-γ. D and E, The frequency of epitope-specific cells per 1 × 10⁶ CD8 T cells from individual mouse with the short bars indicating the means of each group.
Armstrong immunization, we challenged LCMV-immune and naive control mice with rLM-GP33A and rLM-GP33A/a and assessed bacterial growth and GP33-specific recall responses (Fig. 6). Although the wtLM strain grew to similar levels in LCMV-immune and naive mice (data not shown), LCMV-immune mice had 100-fold fewer rLM-GP33 in the spleen compared with naive mice on day 1 and cleared rLM-GP33A infection by day 2. When challenged with rLM-GP33A/a LCMV-immune mice had ~10-fold less bacteria than naive mice on day 1 and still harbored 10^3 CFU in the spleen on day 2. Thus, GP33-specific memory CD8 T cells in LCMV-immune mice provided a lower level of protection against rLM-GP33A/a than against rLM-GP33A, and this difference correlated with a reduced GP33-specific recall response in rLM-GP33A/a infected mice. On day 2 postchallenge, ~15% of CD8 T cells in the spleen of rLM-GP33A-infected mice were specific to the GP33 epitope, as measured by the intracellular IFN-γ staining. In contrast, mice challenged with rLM-GP33A/a had only ~7% of CD8 cells specific to the GP33 epitope. In addition to the H-2D^β-restricted GP33-41 epitope, there exists an overlapping epitope, GP34-41, that is presented by H-2K^b (33). We took advantage of this feature and used D^b/GP33 and K^b/GP34 tetramers to visualize whether antagonism was specific to the H-2D^β-restricted response because the GP33a peptide used is known to antagonize H-2D^β-restricted CD8 T cells (31). Most of the GP33-specific response was H-2D^β-restricted in rLM-GP33A-infected mice; ~8.9% of CD8 T cells stained positive with D^b/GP33 tetramer, whereas ~1.2% were positive with K^b/GP34 tetramers. Remarkably, the H-2D^β-restricted response was much lower (~3.7% of CD8 T cells) in mice challenged with rLM-GP33A/a, and as a result, the H-2K^b-restricted response became a dominant response (~4.5% of CD8 T cells). Thus, the antagonist peptide in rLM-GP33A/a specifically inhibited the H-2D^β-restricted but not the H-2K^b-restricted response induced by the agonist peptide, resulting in a shift of immunodominance.

Discussion

Previous studies have identified viral escape mutants and parasitic variants that carry mutations in immunodominant epitopes of CD8 T cells. These epitope variants have been shown to antagonize the T cell response to the wild-type epitopes in vitro (11, 12, 14, 15). These results strongly suggest that generation of TCR antagonists by infectious agents may represent an effective mechanism of immune evasion. However, several questions have remained unanswered that are critical to ascertain the in vivo relevance of TCR antagonism in modulating the immune response to infection. First, it is not known whether antagonist peptides expressed by infectious agents can inhibit the T cell response in vivo. Direct evidence of TCR antagonism during infection has thus far been lacking, and it is possible that T cells may become refractory to antagonism under inflammatory conditions that are known to override anergy/tolerance induction. Second, TCR antagonism of memory T cells has not been studied either in vitro or in vivo. Protective immunity is mediated by memory T cells, which are more sensitive to TCR signaling induced by agonist ligands and thus might be less sensitive to TCR antagonism. Finally, it is not clear to what extent clonal TCR antagonism may have an effect on a polyclonal T cell population responding to infection. In this study, we provide direct in vivo evidence for clonal TCR antagonism of naive and memory CD8 T cells during bacterial infection. Even in the context of a natural infection involving polyclonal responses, our data show that TCR antagonism can have a profound effect on the primary and recall response, leading to reduced memory and diminished protective immunity. Thus, these results conclusively demonstrate the in vivo effects of TCR antagonism in modulating the immune response to infection.

Our results demonstrated the potential of TCR antagonism to attenuate a polyclonal response and shift the hierarchy of immunodominance. These effects are remarkable considering the clone-specific nature of TCR antagonism. How might a single antagonist have such a profound effect on the polyclonal response? The GP33a peptide is known to antagonize P14 cells that express a Vβ8.1 TCR. Subunit. Following LCMV infection, >40% of the GP33-specific response is comprised of the Vβ8.1 ~ cells with conserved CDR3 domains (33). This population of Vβ8.1 ~ cells likely represents one or a few clones that might be sensitive to antagonism by the GP33a peptide. Consistent with this possibility, we have observed that >30% of GP33-specific T cells from LCMV immune C57BL/6 mice are antagonized in vitro by the GP33a peptide (data not shown). These data indicate that the GP33a peptide can antagonize a significant portion of the GP33-specific, polyclonal population, thus providing support to our in vivo results. It is unlikely that our findings are unique to the GP33 epitope we studied but are generally applicable. In several other systems, altered peptides have been identified that antagonize the
majority (>80%) of T cell clones to a given Ag (12, 34–36). Recent studies have shown that the T cells responding to individual epitopes often consist of oligoclonal populations that make up the bulk of the response, which in some cases are further enriched during the secondary response and in persistent infection (17, 33, 37–39). Therefore, TCR antagonism of these dominant clones is predicted to have a significant impact on the composition of the responding T cell population and a measurable effect on the overall magnitude of a polyclonal response.

Viruses and parasites have been shown to evade T cell recognition using various mechanisms, including TCR antagonism (11, 12, 14, 15). In contrast, bacterial escape of T cell recognition has not been described previously. Most of the known T cell targets in bacteria are encoded within virulence factors and thus are less tolerant of mutations. However, bacteria are known to evade Ab recognition by antigenic variation through gene duplications with subsequent rearrangements and mutations (40). These specialized, active mechanisms allow bacteria to acquire mutations at high frequencies and generate antigenic diversity while maintaining a functional copy of the original genes. It is conceivable that a similar mechanism will allow bacteria to generate altered peptide ligands that can antagonize T cell responses. This mechanism would allow the same bacterium to express an antagonist against an endogenous Ag. Furthermore, unlike a virus with a limited genome, bacteria and parasites synthesize thousands of proteins that are processed into numerous peptides for presentation by MHC molecules. This provides a broad spectrum of TCR ligands, including potential antagonists against endogenous bacterial Ags or foreign Ags expressed in bacterial vaccine vectors. Thus, it is conceivable that a pair of antagonist and agonist can be expressed by the same microbe that would have profound effect on the T cell response, as indicated by our results. These considerations, combined with our in vivo results, suggest that agonist/antagonist ligand interactions may play an important role in determining the immunodominance and repertoire of T cell targets. In light of this concept, evaluation of immune responses and vaccine strategies may require examination of not only agonists but also antagonists and their interactions during an infection.

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Disclosures

The authors have no financial conflict of interest.

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