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Taming Tissue-specific T cells: CTLA-4 keeps self-reactive T cells at bay

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Abstract

CTLA-4 is a potent co-inhibitory molecule that is critical for peripheral T cell tolerance. A report in this issue reveals the autoantigen-specific nature of CTLA-4-deficient CD4⁺ T cells within target tissue. *In vivo* studies demonstrate that CTLA-4 expression by self-reactive effector cells is sufficient to limit their infiltration into target tissue and that regulatory T cells expressing CTLA-4 can control autoantigen-specific effector T cells. Thus, these findings provide evidence that CTLA-4 exerts its critical immunoregulatory functions by controlling conventional T cells as well as regulatory T cells.

It has been appreciated for some time that the Cytotoxic T lymphocyte antigen-4 (CTLA-4) receptor, a homolog of CD28, is an indispensable negative regulator of peripheral T cell function¹. The fatal lymphoproliferative phenotype of CTLA-4^{-/-} mice revealed the critical negative regulatory function of CTLA-4 and provided the first evidence that costimulatory receptors could provide negative, as well as positive, second signals^{2,3}. CTLA-4^{-/-} mice develop severe myocarditis and pancreatitis and die within the first month of life. This pathology resembled an autoimmune disease and gave impetus to studies investigating the role of CTLA-4 in T cell tolerance and autoimmunity⁴. While the role of CTLA-4 in regulating peripheral T cell tolerance has become firmly established, there are still many questions regarding how CTLA-4 exerts its key immunoregulatory functions. Among them is the unresolved question of whether or not T cells that infiltrate various tissues in the CTLA-4^{-/-} mice are autoreactive and tissue-specific. In this issue of *Nature Immunology*, Ise *et al.* show for the first time that the hyperproliferative and destructive T cell populations in CTLA-4-deficient mice are not on autopilot, but require specific signals provided by autoantigens to cause tissue damage⁵. Their work points to an important role for CTLA-4 expression by effector T cells in restraining tissue-specific CD4⁺ T cells from infiltrating, expanding and/or surviving in target organs and provides evidence that CTLA-4 can control pathogenicity of self-reactive T cell at multiple levels.

Ise *et al.* were able to analyze the TCR repertoire of CTLA-4^{-/-} T cells by fixing the TCRβ chain of CTLA-4^{-/-} mice (DOβCTLA-4^{-/-} mice). DOβCTLA-4^{-/-} mice exhibited similar, but somewhat delayed, pathology in comparison with CTLA-4^{-/-} mice. The antigen-specific nature of pathogenic CTLA-4^{-/-} T cells was suggested by homing studies where CD4⁺ T cells from the spleen or affected organs of DOβCTLA-4^{-/-} mice were introduced into Rag-2^{-/-} recipients. While transfer of splenic T cells recapitulated the multi-organ CTLA-4^{-/-} phenotype, T cells transferred from affected organs (eg. lungs, heart or pancreas) tended to accumulate in the corresponding organ of the recipient and only caused pathology

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in this tissue. Ise *et al.* identified acinar cell-specific protein disulfide isomerase associated 2 (Pdia2) as a specific autoantigen that drives pancreatic pathology in DO β CTLA-4^{-/-} mice and found anti-Pdia2 antibodies in sera from CTLA-4^{-/-} mice. They cloned a Pdia2-reactive TCR that endowed naïve T cells with pancreas-specific reactivity and compared the functions of CTLA-4^{+/+} and CTLA-4^{-/-} Pdia2-specific T cells

Notably, CTLA-4^{+/+} and CTLA-4^{-/-} Pdia2-specific T cells migrated and accumulated comparably in pancreatic lymph nodes, but CTLA-4 deficiency markedly enhanced infiltration of these T cells into the pancreas. These findings point to a novel function for CTLA-4 expressed by antigen-specific effector T cells in regulating peripheral tolerance at the level of the tissue. Their work indicates that CTLA-4 governs a critical tolerance checkpoint that controls self reactive T cell entry, expansion and/or survival in target tissue. A role for CTLA-4 in modulating the dynamics of T cell-antigen presenting cell (APC) interactions has been previously demonstrated, but the focus has been mainly on interactions within the lymph node, rather than trafficking into tissues⁶. Further studies are needed to understand how CTLA-4 protects the tissues from pathogenic self reactive T cells.

The work of Ise *et al.* also addresses the controversial question of whether expression of CTLA-4 is important only on regulatory T cells (Treg) or whether conventional T cells (Tconv) also require expression of this molecule. Treg act in *trans* to control the responsiveness of Tconv and other components of the immune system. A role for CTLA-4 in facilitating Treg function was first suggested by bone marrow chimera studies⁷. Recently, specific deletion of CTLA-4 in FoxP3⁺ Treg and sophisticated blastocyst chimera experiments unambiguously demonstrated the crucial role for CTLA-4 in Treg biology^{8,9}. However, a lack of CTLA-4 on Treg does not fully account for the phenotype of CTLA-4 null mice, as Foxp3-specific CTLA-4 deficiency results in a fatal inflammatory pathology that is delayed in onset and more restricted as compared to CTLA-4 null mice⁸.

Ise *et al.* provide evidence to support a role for CTLA-4 in controlling Tconv, exclusive of its role on Treg. CTLA-4-expressing, Pdia2-specific T cells were studied in a Rag-2^{-/-} environment and did not express Foxp3, suggesting that CTLA-4 expression on Tconv is sufficient to prevent these cells from becoming pathogenic. However, CTLA-4-expressing Treg could also suppress the pathogenicity of CTLA-4-deficient Pdia2-specific T cells. Thus, this work points to dual functions for CTLA-4, acting both on Tconv and Treg.

The work of Ise *et al.* suggests that particular self-reactive T cells that escape negative selection must either express CTLA-4 themselves or become subject to peripheral control by Treg that also depend on CTLA-4 for their function (Figure 1). It is not yet settled whether CTLA-4 acts directly on the T cell that expresses it, or acts on the APC, either by binding of B7 by CTLA-4, which leads to back signaling into APC^{10,11} or by down-modulating B7 expression⁸. The finding that CTLA-4 governs a critical tolerance checkpoint that controls T cell entry into and accumulation within target organs opens a novel area of investigation. It will be important to understand how CTLA-4 regulates the balance between pathogenic effector and protective Treg responses within non-lymphoid organs. Since B7-1 (CD80) and B7-2 (CD86) can be expressed on some non-hematopoietic cells, as well as hematopoietic cells, there may exist as yet unappreciated cellular interactions by which CTLA-4 defends tissues from pathogenic self reactive T cells, which would provide insights into immunoregulation in specific tissue microenvironments.

Further understanding of how CTLA-4 regulates tolerance has therapeutic as well as fundamental importance. The critical role of CTLA-4 in human autoimmune disease is underscored by genome-wide association studies that have identified CTLA-4 as a key gene associated with risk of developing multiple human autoimmune diseases¹². In addition,

CTLA-4 is an important therapeutic target in cancer immunotherapy¹³. The work of Ise *et al.* suggests a new means by which CTLA-4 may contribute to the multiple barriers that prevent anti-tumor responses and shield tumors from immune eradication. Better understanding of the levels at which CTLA-4 exerts its inhibitory functions will facilitate design of therapeutic strategies that target CTLA-4 to treat cancer, autoimmunity, graft rejection and infectious diseases.

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Figure 1.

CTLA-4 limits autoantigen-specific T cells at multiple checkpoints. Self-antigen-specific T cells that escape negative selection must either express CTLA-4 themselves or become subject to peripheral control by Treg that also depend on CTLA-4 for their function. As well as restraining activation events in the lymph node, CTLA-4 also prevents T cell infiltration, expansion and survival at the level of the target tissue.