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The importance of being earnestly selfish

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Abstract

Agonist encounter can divert thymocytes into several unconventional T cell subsets, many of which exhibit regulatory properties. Unexpected findings indicate that agonist selection can drive the differentiation of interleukin 17–producing cells in the thymus.

The perception, first voiced by Ehrlich and Morgenroth, that the immune system is designed to avoid self-destruction, is a fundamental concept in immunology. Together with the notion that the ability of T cells to recognize non-self antigen and the induction of T cell self tolerance are acquired traits initially ‘instructed’ by self antigens during maturation in the thymus, these ideas form some of the most basic principles for understanding adaptive immunity. However, Ehrlich's *horror autotoxicus* theory¹ was initially interpreted to mean that the immune system is inherently unwilling or unable to respond to self. Consistent with that belief, and in line with Jerne's natural selection theory of antibody formation², Burnet proposed the clonal selection theory³, a corollary of which suggested that through discrimination of self versus non-self, autoreactive cells would be eliminated during a process called ‘negative selection’ (Fig. 1). In this issue of *Nature Immunology*, however, Craft and colleagues identify and characterize a subset of self-reactive thymocytes that, instead of being deleted, require encounter with self agonist in the thymus for their further differentiation to become interleukin 17 (IL-17)-producing T helper cells (TH-17 cells)⁴.

These newly identified, self-specific, natural TH-17 cells (nTH-17 cells) acquire specialized functional features during self antigen–based selection in the thymus. However, they are not the first T cell subpopulation identified as requiring self agonist for their thymic selection; they join others, including natural Foxp3+ regulatory T cells (nTreg cells), mucosal CD8 $\alpha\alpha$ + intraepithelial lymphocytes (IELs), invariant natural killer T cells, CD8 $\alpha\alpha$ + natural killer T cells, CD4–CD8– double-negative T cell antigen receptor $\alpha\beta$ (TCR $\alpha\beta$) T cells and subsets of TCR $\gamma\delta$ T cells. Together these cells form the ‘eccentric gang’ of self-reactive thymocytes that do not seem to follow the rules of conventional thymic selection⁵ (Fig. 1).

Some of the early experimental framework for the clonal-selection theory of T lymphocytes came from the group of Kappler and Marrack, which demonstrated that recessive tolerance could be established through clonal elimination of self-reactive T cells⁶ (Fig. 1a). The negative selection idea was further fueled by observations made by von Boehmer and colleagues indicating that conventional thymus-selected $\alpha\beta$ TCRtransgenic cells specific for the male HY antigen (HY-TCR), are absent from the thymus and periphery of male HY-TCR-transgenic mice^{7,8}. The overall concept of thymus selection took further shape with the incorporation of positive selection, in which immature thymocytes that recognize complexes of self peptide and major histocompatibility complex are selected for further maturation into conventional naive T cells specific for nonself antigens⁹ (Fig. 1a). The view that T cell ‘education’ in the thymus initially requires self-recognition further postulated that the signal strength of this interaction is the crucial factor that determines the fate of the maturing thymocyte. Consequently, highavidity interactions would lead to activation-induced cell death, interactions of very low avidity would lead to death by neglect, and intermediate signal strengths would permit the maturation of conventional naive T cells (Fig. 1a).

Eventually, however, it became evident that the clonal-deletion theory was not all-encompassing, as inconsistencies surfaced that challenged the recessive nature of conventional selection. In seminal work using animal models of autoimmunity, Sakaguchi and co-workers indicated that in addition to self-reactive CD4⁺ T cells that could induce autoimmunity, there are also thymus-derived self-reactive CD4⁺ T cells that are crucial for the prevention of autoimmunity¹⁰. These new observations provided some of the initial support for an alternative, dominant self-tolerance hypothesis, which postulated the existence of a pathway that preserves and promotes the differentiation of thymocytes bearing TCRs with strong affinity for complexes of self peptide and major histocompatibility complex (Fig. 1b). The intrathymic alternative lineage commitment of these self-reactive thymocytes during this so-called ‘agonist-mediated positive selection process’ diverts most autoreactive thymocytes out of the repertoire of conventional naive T cells (Fig. 1b). The most compelling evidence supporting the dominant self-tolerance hypothesis has come from various transgenic animal models, in which mice expressing a transgenic TCR together with the cognate antigen in the thymus fail to generate conventional TCR-transgenic T cells but generate ample numbers of thymus-derived TCR-transgenic Foxp3⁺ nTreg and/or CD8 α ⁺ IELs, depending on the TCR-transgenic system used and the tissues analyzed^{11,12}.

Interestingly, using double-transgenic models identical to those shown before to generate self-specific Foxp3⁺ nTreg cells, including the AND TCR α —pigeon cytochrome *c* and the OT-II TCR α —ovalbumin double-transgenic systems, Craft and colleagues now show that some self-specific thymocytes also divert toward an nTH-17 lineage⁴. It could be argued that the accumulation of self-specific nTH-17 cells can be explained by a greater resistance of those thymocytes to clonal deletion, as suggested before for the agonist-dependent nTreg cells¹³.

However, using the same double-transgenic system used in the agonist-dependent nTreg studies, Craft and co-workers show that TCR transgene-expressing nTH-17 cells are higher in percentage as well as in absolute number in mice expressing the cognate antigen⁴, which would indicate that exposure to self agonists in the thymus promotes the actual generation and differentiation of self-reactive thymocytes. Because the generation of TH-17 cells and Foxp3⁺ cells is reciprocally regulated¹⁴, it is possible that the reported lack of an agonist-dependent increase in Foxp3⁺ nTreg cells in the double-transgenic mice might have been due to an alternate conversion or revision of self-reactive thymocytes to the nTH-17 subset. The striking direct correlation between the differentiation of these self-specific nTH-17 cells and TCR–cognate ligand affinity further indicates that the process of differentiation of thymocytes through agonist-driven selection crucially depends on the high-avidity recognition of self antigen (Fig. 1b).

The fact that all specialized self antigen–reactive T cell subsets depend on agonist selection for their differentiation suggests a developmental relationship or common functional purpose for these cells (Fig. 1b). However, they are by no means ‘look-alikes’, and, therefore, in addition to high-affinity interactions, other factors may have a role in driving the differentiation of each agonist-dependent T cell subset. It is notable that the nTH-17 cells described by Craft and colleagues are generated under the influence of the same agonist that drives the differentiation of Foxp3⁺ nTreg cells. Furthermore, they show that the nTH-17 cells depend on transforming growth factor- β and IL-6 for their differentiation, which could indicate that these cytokines might have a crucial role in the balanced differentiation of nTreg and nTH-17 cells in the thymus, similar to the peripheral differentiation of these subsets from naive T cells. It is not known which cell types provide these cytokines during thymic selection; however, we have observed *in vitro*, in the presence of transforming growth factor- β with or without IL-6, that thymic dendritic cells have the

unique ability to drive TH-17 differentiation, whereas they fail to induce the differentiation of Foxp3⁺ Treg cells (D.M., Y. Park and H.C., unpublished observations). This would suggest that selecting and accessory cells in the thymus might serve a key role in driving the differentiation of specific agonist–selected thymocyte subsets.

In normal conditions, agonist-selected T cells, although autoreactive, are not autodestructive. Consistent with that notion, Craft and colleagues find that the AND TCR $\times$ pigeon cytochrome *c* double-transgenic mice—which have larger numbers and percentages of nTH-17 cells—did not develop signs of autoimmunity even when observed for more than 1 year. This is probably due in part to the presence of a substantial subset of nTreg cells in these double-transgenic mice. Nevertheless, in addition to the Foxp3⁺ nTreg cells, almost all self-specific agonist–selected T cell subsets, including the CD8 $\alpha\alpha$ ⁺ IELs¹⁵, show some degree of regulatory ability. Consistent with that, Craft and colleagues show that the transgenic nTH-17 cells provide unique agonist-dependent protection against inflammation-induced liver toxicity by secreting IL-22. It is also possible, however, that in inflammatory conditions, selfreactive agonist–selected T cells modify their protective function and instead contribute to the proinflammatory responses¹⁶. When uncontrolled, such altered autoimmune responses could induce and/or promote autoimmunity and self-destruction.

In summary, the nTH-17 cells described by Craft and colleagues underscore the importance of the ‘selfish’ thymus not only for weeding out self-reactive cells and positively selecting cells with intermediate reactivity for self but also for the critical shaping and ‘education’ of ‘earnestly’ self-reactive T cells that contribute to the establishment and maintenance of self-tolerance (Fig. 1). It is clear that the identification of these T cells brings a new appreciation of thymus self antigen–mediated selection and underscores the need to refine the foundation of concepts on which immune tolerance and adaptive immunity have been erected.

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Figure 1.

The classical and alternative selection pathways in the thymus. **(a)** Classical thymic selection. During thymic differentiation, thymocytes will undergo positive and negative selection and generate naive conventional T cells that reach the periphery and further differentiate in response to encounter with cognate non-self antigen. Nevertheless, some of these conventional effector T cells may have escaped negative selection and might respond to self antigen during inflammation. This model is called ‘recessive tolerance’. DN, double-negative; DP, double-positive; CTL, cytotoxic T lymphocyte. **(b)** Agonist-driven thymic selection. In addition to development by the conventional positive selection pathway in **a**, specialized T cell subsets develop from thymocytes that bind with high avidity to self antigens in the thymus; these cells leave the thymus as antigen-experienced T cells. This agonist-driven selection process diverts cells into a variety of subsets, such as Foxp3⁺ nTreg cells, double-negative TCRαβ⁺ cells, CD8αα⁺ TcRαβ⁺ IELs, invariant natural killer T cells (iNKT) and the newly identified nTH-17 cells. This model is referred to as ‘dominant tolerance’.