The subtle hands of self-reactivity in peripheral T cells

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T cells with increased self-reactivity and marked by high expression of the negative regulator CD5 differ in gene-expression patterns and are poised for greater bursts of proliferation when they encounter foreign antigens.

The interactions of T cells with low-affinity complexes of self peptide and major histocompatibility complex (MHC) are critical for positive selection in the thymus, as well as for peripheral homeostasis[1,2]. It is now well established that the affinity of the T cell antigen receptor (TCR) for a foreign antigen can be used to predict the degree of initial response and that such engagement by a T cell of an antigen-presenting cell displaying foreign peptide–MHC influences subsequent antigen-specific T cell population expansion and differentiation. However, the importance of self peptide–MHC interactions and their effect on the response of a T cell to foreign peptide–MHC remain less clear. An entrée into this question is provided by the discovery that the amount of the surface glycoprotein CD5 on naive peripheral T cells reports the intensity of recent self peptide–MHC engagement[3–5]. In this issue of *Nature Immunology*, Fulton *et al.* report that $CD5^{hi}$ $CD8^+$ T cells exhibit enhanced responsiveness and population expansion upon challenge with foreign antigen, and they extend their findings to a panoply of assays to determine why $CD5^{hi}$ cells dominate a response[6]. Their results are formative insofar as they reveal the breadth of situations in which the effector functions of $CD5^{hi}$ T cells are improved while providing insight into cell-intrinsic properties that emerge from this range of self-reactivity (**Fig. 1**).

Prior to this study, it was understood that $CD5^{hi}$ peripheral T cells exhibit greater sensitivity to homeostatic cytokines and turnover than that of $CD5^{lo}$ T cells, with $CD5^{hi}$ $CD8^+$ T cells having slightly higher expression of cytokine receptors such as IL-2Rβ and IL-7Rα[7–9]. In parallel studies, $CD5^{hi}$ $CD4^+$ T cells also display a heightened response to foreign antigen, with the abundance of CD5 correlating with self peptide–MHC binding[5,10]. So what are the fundamental differences between $CD5^{hi}$ T cells and $CD5^{lo}$ T cells, and how do these affect antigen–specific responses generated by the respective populations?

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Focusing on $CD8^+$ T cells, Fulton *et al.* compare $CD5^{hi}$ and $CD5^{lo}$ populations among $CD44^{lo}$ (non-memory) naive $CD8^+$ T cells and report higher expression of proteins associated with activation and/or memory, such as CD44, CXCR3, XCL1, T-bet and Eomes, in some or all $CD5^{hi}$ $CD8^+$ T cells[6]. Interestingly, there is considerable heterogeneity among $CD5^{hi}$ cells for these markers, which suggests this $CD5^{hi}$ phenotype is a diverse collection of cell types rather than a single distinct one. The authors bolster the argument that these cells are broadly different from 'true naive' T cells by carrying out gene-expression analysis of the populations, in which they detect subtle but distinct differences in the expression of approximately 57 genes. Furthermore, when they conduct analysis within a framework of defined gene cluster sets, they discover that $CD5^{hi}$ T cells in aggregate express a higher proportion of genes linked to cell cycle preparation and division, and a late effector and memory state. Such differences in expression provide evidence that $CD5^{hi}$ $CD8^+$ T cells are generally advantageously positioned, at the level of gene expression, to respond to an immunogenic challenge.

Fulton *et al.* next sort $CD5^{hi}$ and $CD5^{lo}$ polyclonal $CD8^+$ T cells and transfer them into recipient mice that they then infect with a recombinant strain of *Listeria monocytogenes* that expresses the H-$2K^b$-restricted vaccinia virus epitope B8R (amino acids 20–27)[6]. They identify B8R–H-$2K^b$–specific T cells by tetramer labeling and find that, consistent with the idea that $CD5^{hi}$ cells are poised for greater reactivity, the transferred $CD5^{hi}$ T cells substantially dominate the response. This 'preferential' population expansion is consistent across other models tested as well. Notably, this expansion is partially dependent on but could not be fully attributed to increased responsiveness to IL-2, as has been reported previously[8]. Notably, given the apparent heterogeneity of the population, the authors take additional measures to eliminate the possibility that a subset of $CD5^{hi}$ T cells drives the overall dominance in expansion. Thus, for example, they are unable to attribute the 'performance gap' between $CD5^{hi}$ cells and $CD5^{lo}$ cells to any one defining marker, such as subcategorical expression of the chemokine receptor CXCR3 by $CD5^{hi}$ cells.

The outstanding question of an over-represented $CD5^{hi}$ subset is ultimately addressed, however, by impressive limiting-dilution single-cell transfer of $CD5^{hi}$ and $CD5^{lo}$ $CD8^+$ cells, in which $CD5^{hi}$ T cells continue to demonstrate proliferative prowess. Through these experiments, Fulton *et al.* establish that $CD5^{hi}$ T cells both respond to infection at a greater rate (as indicated by whether a single cell clonally expands in a given host) and also undergo a greater degree of proliferation (as measured by burst size)[6]. In alignment with these findings, the authors determine that $CD5^{hi}$ T cells are indeed more likely to be among those activated and incorporated early in a primary immune response. However, intriguingly, Fulton *et al.* report that $CD5^{hi}$ and $CD5^{lo}$ $CD8^+$ T cells do not differ substantially in TCR–foreign peptide–MHC interactions, as antigen-specific $CD5^{hi}$ $CD8^+$ T cells and their $CD5^{lo}$ counterparts exhibit similar tetramer-binding affinities[6]. While this result contrasts with those of a published study[5], the authors suggest that this distinction may reflect key dissimilarities between $CD4^+$ T cells and $CD8^+$ T cells.

Thus, these data prompt compelling questions, including a definition of the source of the differences in the responsiveness of naive T cells. As CD5 has been to shown to negatively regulate T cell reactivity[10,11], it is unlikely that CD5 itself is directly responsible. The simplest explanation is that signaling induced by self peptide–MHC essentially 'greases the wheels' for progression through the cell cycle and signaling, and this alone drives the superior response. However, the reasons for the enhanced activation, like the phenotype itself, may be diverse. An intriguing possibility is that there are nuanced differences in a naive T cell's milieu that stem from contact dynamics or the location of a given self peptide–MHC. For example, stronger TCR–self peptide–MHC interactions may result in 'preferential' and continuous retention adjacent to the presenting cells and thus exposure to additional signals from a cytokine-producing antigen-presenting cell presenting self peptide.

It is also very intriguing that a similar spatial mechanism might underlie 'preferential'

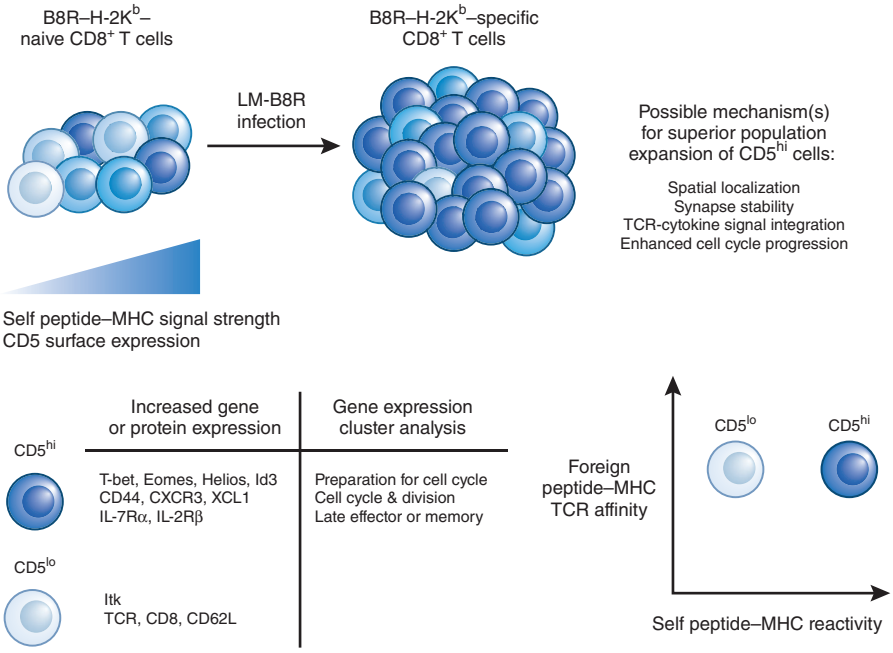

Figure 1 A model for the 'preferential' population expansion of CD5^{hi} cells following a prototypical challenge with foreign antigen. Among the pool of naive CD8$^+$ T cells that recognize a given foreign peptide–MHC complex, there exists a spectrum of CD5 surface expression that correlates with self peptide–MHC signal strength. CD5 abundance also corresponds with differences in the expression of genes and proteins key to the function, proliferation and differentiation of T cells. Upon challenge with a foreign antigen, CD5^{hi} T cells display a greater capacity to become activated and clonally expand. This is probably not due to differences in the affinity or sensitivity of TCR–foreign peptide–MHC but instead is probably due to preexisting cell-intrinsic properties. LM-B8R, recombinant *L. monocytogenes* that expresses B8R.

recruitment into and population expansion during an immune response. Chemokine factors that are generally overexpressed in these cells, such as CXCR3 and XCL1, are known to facilitate expedited T cell contact with antigen-presenting cells[12–14]. Although the authors demonstrate that CXCR3 alone does not fully account for the dominance of CD5^{hi} cells[6], coordinated expression of these chemotactic molecules within a collection of responding clones may act in synergy to rapidly assemble an activating niche within the lymph node. Entering such a niche earlier than other responder cells might be beneficial in that such cells would be the first to gain access to antigens and/or cytokines as they undergo division and differentiation. However, under alternative circumstances, T cells may be more susceptible to activation-induced cell death[15]; this is a possible explanation for the apparent discrepancy, as measured by cell number, between this work and published studies of CD5^{hi} CD4$^+$ cells[5,10,16]. In the future, these spatial parameters might be addressed, for example, by intravital lymph node imaging.

The broad idea that CD5^{hi} T cells are especially good at integrating cues is also hinted at by evidence from Fulton *et al.* in which they show that supplemental inflammation, concurrent with immunization with dendritic cells, boosts the proliferation of antigen-specific CD5^{hi} cells while having little effect on the population expansion of CD5^{lo} cells[6]. Whether this ability of CD5^{hi} T cells to harness inflammatory signals stems from differences in cellular reactivity and/or access to the cues themselves remains to be determined. In sum, the reasons for the dominance of CD5^{hi} CD8$^+$ T cells may be a combination of many of the differences characterized by these authors.

A direct relationship between responsiveness to self antigen and to foreign antigen broadly draws attention to the functional purpose and effect of thymic and peripheral self peptide–MHC interactions. Beyond merely promoting and maintaining the survival and turnover of naive CD8$^+$ T cells[1,2], self peptide–MHC interactions seem to create a range of basal reactivity among T cells that recognize the same foreign peptide–MHC complex. Of critical importance is whether this diversity is beneficial for the host. While CD5^{hi} CD8$^+$ T cell populations expand more robustly than their CD5^{lo} counterparts in this study, there may be conditions under which CD5^{lo} CD8$^+$ T cells coordinate a more effective antigen-specific immune response, as has been illustrated by some CD4$^+$ T cell clones[10,16]. Further investigation will be needed, however, to determine if pertinent examples exist.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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