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The Subtle Hands of Self Reactivity in Peripheral T cells

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Abstract

Strapline—Like Sneetches marked by stars on their bellies, T cells with increased self-reactivity and marked by high CD5 expression appear especially able to join the activation party.

Alternate—T cells with increased self-reactivity and marked by high CD5 expression differ in gene expression patterns and are poised for greater bursts of proliferation when encountering foreign antigens.

T cell interactions with low-affinity self-peptide-MHC (pMHC) complexes 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 TCR for the foreign antigen predicts the degree of initial response and that such engagement of an antigen-presenting cell (APC) displaying foreign-pMHC by a T cell influences subsequent antigen-specific T cell expansion and differentiation. However, the significance of self-pMHC interactions and their impact on a T cell response against foreign-pMHC remain less clear. An entrée into this question is provided by the discovery that the amount of the surface glycoprotein CD5 on naïve peripheral T cells reports the intensity of recent self-pMHC engagement[3,4,5]. In this issue of *Nature Immunology*, Fulton *et al.* report that $CD5^{hi}$ $CD8^{+}$ T cells exhibit enhanced responsiveness and expansion upon foreign antigen challenge, and extend findings to a panoply of assays to determine why $CD5^{hi}$ cells dominate a response[6]. The results are formative insofar as they reveal the breadth of situations in which $CD5^{hi}$ T cell effector function are improved, while providing insight into cell-intrinsic properties that give rise to this range of self-reactivity.

Prior to this study, it was understood that $CD5^{hi}$ peripheral T cells exhibit greater sensitivity to homeostatic cytokines and turnover with $CD5^{hi}$ $CD8^{+}$ T cells expressing slightly higher amounts of cytokine receptors like interleukin 2Rβ (IL-2Rβ) and IL-7Rα[7–9]. In parallel studies, $CD5^{hi}$ $CD4^{+}$ T cells also displayed a heightened response to foreign antigen, with CD5 abundance correlating with self-pMHC binding[5, 11]. So, what are the fundamental differences between $CD5^{hi}$ and $CD5^{lo}$ T cells, and how do these affect antigen-specific responses generated by the respective populations?

Focusing on $CD8^{+}$ T cells, Fulton *et al.* compared $CD5^{hi}$ and $CD5^{lo}$ populations amongst $CD44^{lo}$ (non-memory) naïve $CD8^{+}$ T cells, and report higher expression of proteins associated with activation and/or memory such as CD44, CXCR3, XCL1, T-bet, and Eomes within some or all $CD5^{hi}$ $CD8^{+}$ T cells[6]. Interestingly, there is considerable heterogeneity for these markers within the $CD5^{hi}$ demarcation, suggesting this $CD5^{hi}$ phenotype is a diverse collection of cell types rather than a single distinct one. The authors bolstered the argument that these cells are broadly different from ‘true naïve’ T cells by carrying out gene

expression analysis between the populations, in which they detected subtle but distinct expression changes in approximately 57 genes. Furthermore, when they conducted analysis within a framework of defined gene cluster sets, they discovered that $CD5^{hi}$ T cells in aggregate express a higher proportion of genes that are linked to cell cycle preparation and division, and a late effector and memory state. Such differential expression provides evidence that $CD5^{hi}$ $CD8^{+}$ T cells are generally advantageously positioned, at the level of gene expression, to respond to an immunogenic challenge.

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

The outstanding question of an over-represented $CD5^{hi}$ subset is ultimately addressed, however, by conducting 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 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. Yet, intriguingly, Fulton *et al.* report that $CD5^{hi}$ and $CD5^{lo}$ $CD8^{+}$ T cells do not differ significantly in TCR–foreign-pMHC interactions as antigen-specific $CD5^{hi}$ and $CD5^{lo}$ $CD8^{+}$ T cells exhibit similar tetramer binding affinities[6]. While this result contrasts with a previous study[5], the authors suggest that this distinction may reflect key dissimilarities between $CD4^{+}$ and $CD8^{+}$ T cells.

As such, these data prompt compelling questions including defining the source of the differences in naïve T cell responsiveness. As CD5 has been to shown to negatively regulate T cell reactivity[11,12], it is unlikely that CD5 itself is directly responsible. The simplest explanation is that self-pMHC induced signaling essentially greases the wheels for cell cycle progression and signaling, and this alone drives the superior response. However, the reasons for enhanced activation, like the phenotype itself, may be diverse. An intriguing possibility is that there are nuanced differences in a naïve T cell's milieu that stem from contact dynamics or location of a given self-pMHC. For example, stronger TCR-self-pMHC interactions may result in preferential and continuous retention adjacent to the presenting cells and thus exposure to additional signals from a cytokine-producing self-presenting APC.

It is also very intriguing to consider a similar spatial mechanism that might underlie preferential recruitment into and 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 APCs[13–15]. Although the authors demonstrated that CXCR3 alone could not fully account for $CD5^{hi}$ cell dominance[6], coordinated expression of these chemotactic molecules within a collection of responding clones may synergize to rapidly assemble an activating niche within the lymph node. Entering such a niche earlier than other responders may be beneficial in that these cells are the first to gain access to antigens and/or cytokines as they undergo division and differentiation. Yet, under alternative circumstances, T cells may be more susceptible to activation-induced cell death[16] and this is a possible explanation for the apparent discrepancy as measured by cell number, with this work and previous studies of $CD5^{hi}$ $CD4^{+}$ cells[5,10,11]. 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 dendritic cell immunization, boosts antigen-specific $CD5^{hi}$ proliferation while having little effect on $CD5^{lo}$ expansion[6]. Whether this $CD5^{hi}$ T cell capacity to harness inflammatory signals stems from differential cellular reactivity and/or access to the cues themselves remains to be determined. In sum, the reasons for $CD5^{hi}$ $CD8^{+}$ T cell dominance may be a combination of many of the differences characterized by these authors.

A direct relationship between responsiveness to self- and foreign-antigen broadly draws attention to the functional purpose and impact of thymic and peripheral self-pMHC interactions. Beyond merely promoting and maintaining naïve $CD8^{+}$ T cell survival and turnover,[1,2] self-pMHC interactions appear to create a range of basal reactivity among T cells that recognize the same foreign-pMHC complex. Of critical importance is whether this diversity is beneficial for the host. While $CD5^{hi}$ $CD8^{+}$ T cells 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[10,11]. Further investigation will be required, however, to determine if pertinent examples exist.

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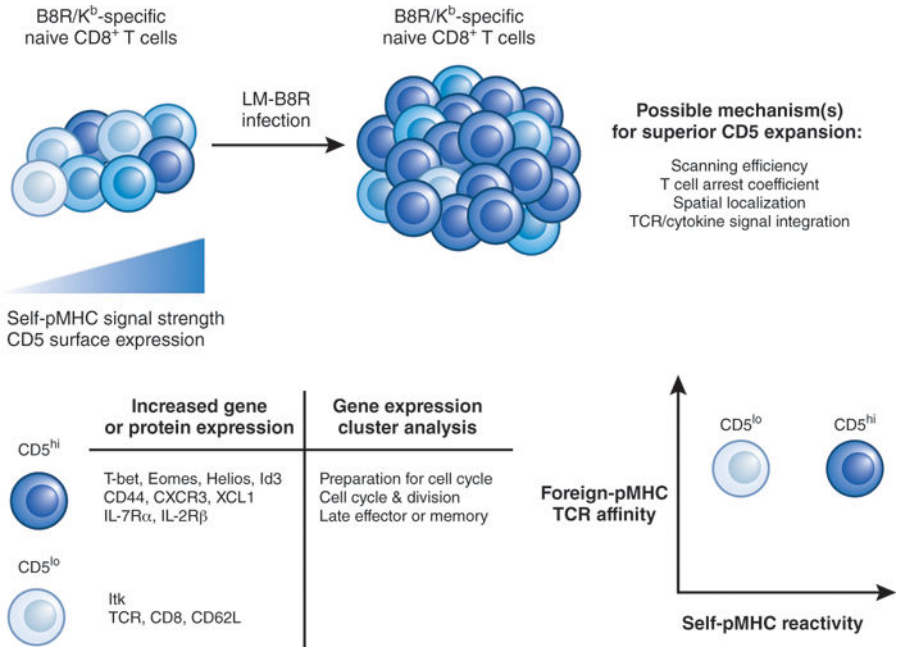

Figure 1. A model for preferential CD5^{hi} expansion following a prototypical foreign antigen challenge

Among the pool of naive CD8+ T cells that recognize a given foreign-pMHC complex, there exists a spectrum of CD5 surface level expression, which correlates with self-pMHC signal strength. CD5 abundance also corresponds with differential expression of genes and proteins key to T cell function, proliferation, and differentiation. Upon infection with a foreign antigen, CD5^{hi} T cells display a greater capacity to become activated and clonally expand. This is likely not due to differences in TCR-foreign-pMHC affinity or sensitivity, but instead pre-existing cell-intrinsic properties.