Dynamic competition for cytokine between effector and regulatory T cell subsets sharpens *in vivo* responses to antigen quantity

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The cytokine Interleukin-2 (IL2) is secreted by activated T-cells, spurring T-cell proliferation and differentiation during infection. We observed that access to IL2 during *in vivo* challenge with different antigen quantities sharpened T-cell decisions to either proliferate robustly or in a curtailed manner. In an IL2$^{-/-}$ setting, T-cells from animals immunized with low antigen quantity showed accelerated proliferation relative to wild-type counterparts, suggesting IL2 can also negatively regulate T-cell activation when antigen is scarce. Therefore IL2 can promote or restrict T-cell activation when antigen quantities are high or low, highlighting a novel mechanism to prevent exuberant reactivity to low antigen concentrations.

Keywords **— Interleukin-2, regulatory T cells, cytokine competition, adaptive immunity**

I. Introduction

The emergence of adaptive immunity was a significant event in the evolutionary history of vertebrates. The unique processing of genes coding for T and B-cell antigen receptors endow them with the potential to recognize a vast repertoire of self and foreign peptides. This feature makes it nearly impossible for pathogens to evade T and B-cells, yet can lead to attack of host tissues if not carefully regulated. Our research interests focus on the dynamic interplay between effector (pathogen-specific) and regulatory (immune-suppressive) T-cells during the immune response. Effector T-cells are activated following recognition of peptide presented by antigen presenting cells. Activated effectors secrete the T-cell growth factor Interleukin-2 (IL2) and proliferate robustly. In contrast, regulatory T-cells do not produce IL2, but constitutively express moderate levels of the IL2 receptor [1]. Sensing IL2 leads to initiation of a positive feedback loop that increases expression of the IL2 receptor. Previous work from our lab has shown that the total IL2 produced is proportional to the initial quantity of antigen screened by effectors [2]. Therefore, IL2 can communicate the cumulative antigen load to both regulatory and surrounding effector T-cells. We hypothesized that the dynamic competition for IL2 between effector and regulatory T cells would scale the magnitude of the proliferative response to antigen.

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II. Results

To test this hypothesis *in vivo*, animals were first adoptively transferred with IL2$^{-/-}$ or wild-type (WT) antigen-specific T-cells, immunized with different doses of cognate antigen, and effector cell proliferation was quantified. WT T-cells showed slightly enhanced proliferation relative to IL2$^{-/-}$ cells following immunization with high quantities of peptide, consistent with higher levels of the IL2 receptor on effector versus regulatory T-cells in these animals. However, following immunization with low quantities of peptide, IL2$^{-/-}$ T-cells showed accelerated proliferation relative to their WT counterparts. This was correlated with a lower ratio of IL2 receptor expression on regulatory to effector T cells. Since IL2 can boost both regulatory and effector T cells, we propose the following model: during challenge with high quantities of antigen, more IL2 is produced by effectors, leading to robust autocrine sensing and increased IL2 receptor expression relative to regulatory T cells. However, when antigen quantities are low, IL2 is produced at much lower levels leading to reduced expression of the IL2 receptor. In this regime, regulatory T cells consume a majority of the IL2, boosting their suppressive capabilities. When IL2 is absent, regulatory T cells cannot be boosted following immunization with low quantities of antigen, and effectors remain capable of proliferation. Future studies will reveal the quantitative nature of *in vivo* competition for IL2 and incorporate a mathematical model describing these dynamics. These analyses reveal how the competition for cytokine can sharpen T cell decisions to proliferate based on the magnitude of the infectious insult and offer a potential explanation for how the organism can limit exuberant responses to low quantities of antigen.

References

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