Signaling heterogeneity and feedback regulation for the cytokine IL-2 enforces self/non-self discrimination in the immune system

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In the immune system, lymphocytes discriminate between non-self antigens, to which they respond vs. self molecules, which they must ignore. Antigen discrimination being noisy on short timescales (min) when T cells respond to ligands in an all-or-none fashion, the immune system must rely on proofreading mechanisms to enforce self/non-self discrimination at the population level on longer timescales (days). A critical cytokine that can regulate clonal expansion and quorum-sensing type of responses among T cells is IL-2. Here we use a combination of theoretical *in silico* computer modeling and experimental quantification of signaling molecules at the single cell level to demonstrate how ligand discrimination can be enforced by regulation of IL-2. We document experimentally how signaling heterogeneity for the IL-2 receptor (IL-2R) and feedback regulation (for the production/secretion of IL-2 and the expression of IL-2R) generates a tunable quorum-sensing threshold within populations of T cells. In particular, we demonstrate how regulatory T cells (a subset of T cell that is critical to maintain tolerance to self antigens) can efficiently deplete IL-2 away from effector cells (another subset that rely on their own secreted IL-2 to expand and respond to non-self antigens). We quantify how this IL-2 tug-of-war can critically regulate the balance between response and tolerance. We test predictions from our model and *in vitro* measurements with manipulations of immune responses *in vivo.*