Variability and Robustness in T Cell Activation from Regulated Heterogeneity in Protein Levels

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Abstract —

Stochasticity in protein expression can either interfere with physiological performance or contribute to the useful diversification of biological functions for a clonal population of cells. We developed a single-cell assay to monitor how endogenous variation in the expression levels of signaling proteins influences response variability. Combining this new methodology and computer modeling to study T cell activation, we identified and characterized two key regulators of antigen-induced signaling. The CD8 coreceptor functions as an analog regulator that tunes the activation threshold, while SHP-1 phosphatase acts as a digital regulator whose level determines whether a cell is either responsive or non-responsive. Stochastic variation in the levels of these two proteins generates substantial activation response diversity among cells in a clonal population, but co-regulation in the expression of these molecules limits the extent of this effect. Together, these properties of the signaling network allow T cells to have functional flexibility without sacrificing accurate discrimination between self and foreign antigens.

Keywords **— T cell signaling, phenotypic variability, single-cell measurements, computer modeling, immunology**

I. Purpose

Vertebrate organisms rely on the ability of their adaptive immune system to distinguish self- from non-self agents, to fight efficiently viral or bacterial infections without endangering their own viability [1]. This discrimination between self and non-self agents is fundamental: in the immune system, antigen-presenting cells (APC) constantly process proteins to present on their surface as peptide Major Histocompatibility Complex (pMHC). During an infection, pMHCs' derived from the pathogen are presented by APC to T cells: the immune response relies on the specific activation of T cells upon detecting these non-self (pathogen-derived) pMHCs'. However, spurious activation of T cells by self-derived pMHC must be avoided to prevent auto-immune responses [2]. A major contribution to this pMHC discrimination is the elimination during thymic development of many immature T cells possessing T cell receptors (TCRs') that are highly reactive with self pMHCs. However, this cellular selection itself depends on the capacity of the TCR to make fine distinctions between closely related pMHC structures when transducing signals that regulate cell survival and differentiation, distinctions that also must be made by mature, post-thymic T cells. Hence, at different stages of their lifespan, T cells endowed with a given TCR must be able to perform reliable yet flexible pMHC discrimination.

II. Results

By combining computational modeling and experimental measurements on individual T lymphocytes [3], we tested how ligand discrimination by T cells is controlled by the dynamics of their signaling response. We have shown how two competing feedback loops control a high gain digital amplifier that sets a threshold in terms of the quality of ligand-receptor interaction and defines self/non-self discrimination [4,5]. We show here how heterogeneity of the expression levels of key signaling proteins determines the robustness and adaptability in T cell ligand discrimination. We also demonstrate how coregulation of positive and negative regulators limit cell-to-cell variability in ligand response.

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