Time Integration of Signal Feedbacks Generates Intensive Scaling of Cytokine Regulation

Karen Tkach[1,2], Debashis Barik[1] , Matt Hathorn[1,2] Jesse Cotari[1,2], Robert Vogel[1,2] Oleg Krichevsky[3], and Grégoire Altan-Bonnet,[1,2]

T cell populations can communicate by secreting and sensing cytokines such as IL-2. We find populations' collective IL-2 output scales with global antigen input, regardless of the number of responding T cells. This result contradicts quantitative predictions based on current understanding of the IL-2 pathway, which project population size dependency and a very limited dynamic range for IL-2 accumulation. Through experimental quantitation and computational modeling, we characterize two new regulations in the IL-2 secretion pathway that are required for population size-independent scaling with antigen dose: an inhibitory cross-talk between antigen and cytokine signaling, and a nonlinear acceleration of IL-2 secretion per cell.

Keywords **— Scaling law, feedback loops, population dynamics, cytokine communication**

I. INTRODUCTION

UNDERSTANDING how collective T cell function emerges from individual responses remains challenging: heterogeneous, digital decisions made on short timescales must be bridged to graded, longer-term population-level outcomes [1]. Previous studies have shown that collective responses to antigens scale with the quality and quantity of pathogenic stimuli [2, 3]. Surprisingly, the scaled magnitude of clonal response is mostly unaffected by the large variability in the initial number of responding lymphocytes [4]. Thus, T cells require mechanisms to create a wide dynamic range of population response, independently of population size.

Cytokines that are secreted upon activation present an elegant solution to scaling population-level lymphocyte responses by translating acute, individual stimulation into a long-term collective readout. We study here interleukin-2 (IL-2), which influences T cell expansion and differentiation and is both produced and consumed by activated T cells [5].

II. RESULTS

We experimentally probed the accumulation of IL-2 for different numbers of T cells exposed to different doses of antigen pulsed on 500,000 antigen presenting cells *in vitro*. At early timepoints such as 12 hours, the accumulated [IL-2] scaled poorly with the quantity of antigen, and was greatly influenced by the number of T cells in the system. However, over days post-activation, we found that IL-2 accumulated non-linearly with time, then abruptly decreased. For each condition, we characterized these dynamics by their apex, $[IL\text{-}2]_{max}$, a quantity which was proportional to the T cell population's total accumulation of [IL-2] over time.

Strikingly, $[IL\text{-}2]_{max}$ varied by more than three orders of magnitude with antigen dose, despite the limited dynamic range of early T cell responses. Furthermore, although smaller populations accumulated IL-2 more slowly, $[IL\text{-}2]_{max}$ was independent of the number of antigen-specific T cells. However, computational simulations of the canonical IL-2 pathway predicted a low saturating threshold and a strong population size dependence for IL-2 output. Our study identified two new regulatory interactions necessary to account for the observed IL-2 scaling law.

IL-2 negatively regulates its own production [6]. We found that antigen-driven inhibition of IL-2 signaling was required to enable the accumulation of cytokine beyond the IL-2 signaling threshold; this cross-talk generated a large dynamic range of IL-2 output that was scaled to antigen input. Furthermore, we found that the rate of IL-2 secretion per cell accelerates over the duration of antigen signaling. This feedback enabled small populations of T cells—which experience greater antigen availability per cell—to achieve higher rates of IL-2 secretion, thereby accumulating similar quantities of IL-2 as equally stimulated larger populations despite amassing fewer IL-2-producing cells. Upon incorporating these two regulatory elements, our experimentally parameterized computational model recapitulated the observed scaling and dynamics of the IL-2 pathway, and predicted IL-2 scaling in a polyclonal reaction.

III. CONCLUSION

We experimentally and computationally characterized two critical regulatory elements—a cross-talk inhibition in cytokine signaling and a non-linear feedback in cytokine production—whose inclusion in the model captured the dynamics and antigen scaling of collective IL-2 accumulation.

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[1]Department of Computational Biology, Sloan Kettering Institute, 1275 York Avenue Box 460 New York NY 10065. E-mail: altanbog@mskcc.org
[2]Weill Cornell Graduate School of Medical Sciences, 1300 York Avenue New York, NY 10021
[3]Physics Department, Ben Gurion University of the Negev, Beer-Sheva 84105 - ISRAËL