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Regulation of T cell expansion by the dynamics of antigen presentation

***Short Abstract* — During an immune reaction, specific lymphocytes proliferate multiple times to form a large pool of effector cells. Adoptive cell transfer experiments have recently demonstrated that the magnitude of T cell expansion is related to the initial number of cells via an inverse power law [1]. Here, we show that such a relationship arises naturally from models in which T cell expansion is limited by decaying antigen availability, and we relate the power law exponent to the proliferation rate of lymphocytes and the rate of antigen decay. Our model identifies the dynamics of presented antigen as a key regulator of the size of an immune response.**

I. Background

THE rapid expansion of specific immune cells forms the basis of the effectiveness of the adaptive immune response despite the low initial number of cells specific to any particular antigen. The proliferation of cells in response to antigenic stimulation is one of the key dynamic processes shaping the immune repertoire, whose composition determines how well an organism is protected against various pathogens. Understanding how this expansion is regulated is thus an important question, with applications, e.g., in the design of vaccines. Recently, adoptive cell transfer experiments, in which transgenically labeled T cells are transferred between mice, have provided new quantitative data to study the regulation of T cell expansion in controlled conditions [1-3]. Quiel et al. have found that fold expansion upon stimulation with cognate antigen depends on the number of transferred T cells as a power law with exponent ~ -1/2 over four decades [1]. In this work we present a physically motivated model to explain this striking observation.

II. Results and Discussion

In our model an exponentially growing number of T cells compete for an exponentially decaying number of antigens. This model incorporates two experimental observations: First, the continued proliferation of T cells is dependent on sufficient signaling from presented antigens [4]. Second, there is antigen turnover, so presented antigen levels decay over time [5]. The model closely fits experimental data for the dependence of fold expansion on initial cell numbers (Fig.1A) and for the time course of expansion (Fig.1B).

In the model, proliferation proceeds until the number of T cells reaches some relative level with respect to the number of presented antigens. From this we derive the key result that fold expansion is proportional to some power of the ratio of the initial number of presented antigens and the initial number of T cells. Using experimental data on antigen turnover rate and T cell proliferation rate, our theory predicts an exponent consistent with the observed exponent.

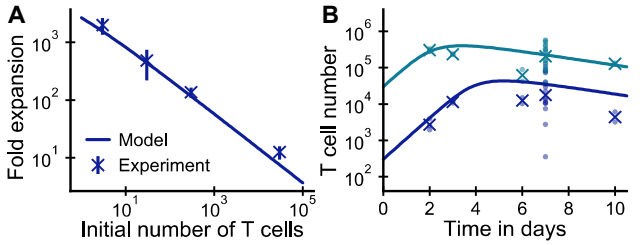

Figure 1: Comparison of experimental data from [1] with model predictions. (A) Factor of expansion at day 7 as a function of the initial number of T cells. (B) T cell number versus time for 300 and 30,000 initial T cells.

Using the same model we quantitatively explain the dependence of T cell expansion on antigen affinity [2] and the influence of antigen dosing kinetics on expansion [3] observed in other adoptive transfer studies.

III. Conclusion

Our model provides a simple explanation for the experimentally observed dependence of T cell expansion on initial cell numbers, supplementing those provided elsewhere [6, 7]. Importantly, the new model dispenses with the need for fine-tuned parameters to explain the power law relationship. Our results suggest that T cell expansion might be regulated by the dynamical turnover of presented antigens across a range of conditions.

Acknowledgements: We thank A. Perelson, and R. de Boer for helpful discussions, and Z. Grossman, and G. Bocharov for providing original data.

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