Mechanistic insights into how collective effects mediate the T cell response

By Rose Yin

T cells are a crucial branch of the adaptive immune system. We each have billions of T cells. Most T cells have a distinct receptor on their surface (TCR) that bind to antigens displayed on antigen-presenting cells (APCs). If the TCR displayed by a T cell binds to antigen displayed on an APC strongly enough, the T cell can be activated. In healthy people, T cells do not mount an immune response towards host tissue antigens displayed on APCs. During an infection, T cells activated due to interactions with pathogen-derived antigens proliferate and mount an immune response.

T cell development in the thymus helps train T cells to discriminate between self and non-self antigens. However, thymic development is not perfect, and so we all have autoreactive T cells. How do T cells correctly mount a response against foreign pathogens while avoiding autoimmune responses when autoreactive T cells are activated? Regulatory T cells (Tregs) suppress conventional T cell responses by absorbing cytokines necessary for T cell proliferation, and this is an important reason why autoimmune responses are suppressed. However, how they suppress autoimmune T cell responses, but not those against pathogens remained unclear. A general framework that has emerged based on theoretical considerations and experimental data is that T cells mount an immune response by a mechanism related to bacterial quorum sensing. This mechanism states that a threshold number (a quorum) of T cells must be activated in a localized environment for T cell proliferation to occur, thus enabling a T cell-mediated immune response. This is because a quorum of activated T cells can produce cytokines required for proliferation and beat out the suppressive effects of Tregs.

In my thesis, I strive to understand how the quorum threshold arises and its determinant factors. With collaborators, we use analytical and computational models to understand how the existence of a quorum threshold allows for acute infections to be cleared without inducing autoimmunity, and how this threshold introduces robustness to the adaptive immune system in the face of negative perturbations that should otherwise increase the risk of autoimmunity; these perturbations include decreased self-antigen presentation during thymic selection or increased self-antigen presentation due to damage by inflammation during infection. However, these models also show how robustness against autoimmunity conferred by the quorum threshold can be outweighed by the effects of perturbations, if large enough. Under persistent or major infection, the T cell quorum threshold is less effective at preventing autoimmunity due to increased probability of the sampling of rare self-antigens that activate many T cells and activation of cross-reactive T cells.

I also strive to understand how the quorum threshold arises dynamically. By developing a population dynamics model, I show how, and under what conditions, a T cell quorum threshold emerges. Dynamical steady states corresponding to an effective immune response or an inadequate are separated by a separatrix determined by key parameters. The existence of the separatrix corresponding to the quorum threshold is robust to randomized parameter variations.

Thesis supervisor: Arup K. Chakraborty
Title: John M. Deutch Institute Professor