Mechanistic and Probabilistic Models of B Cells During Immune Responses

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Understanding the dynamics of B cell populations and their responses to pathogens is imperative for the development of therapies focused on enhancing antibody-mediated protection and improving vaccine effectiveness. This study focuses on marginal zone (MZ) and follicular (FO) populations, each playing a vital role in the immune response. Typically, FO B cells respond to T-dependent (TD) antigens and differentiate into activated Germinal Center (GC) B cells, which further diversify into either memory or antibody secreting plasma B cells. However, recent studies promote the concept of flexibility in B cell differentiation trajectories during immune responses and demonstrate de novo development of MZ B cells from activated B cells. The underlying dynamics of MZ B cell generation during immune responses are unclear. To investigate this, we will combine mathematical modeling with data derived from a novel antigen-inducible reporter mouse model to map differentiation pathways of B cells during immune responses. One model will assume direct activation of MZ B-cells, another will propose a branched pathway where activated FO cells bifurcate into both MZ and GC cells, and a third model will capture a linear trajectory of GC B cells differentiating into MZ cells. Within these models, we will explore time and/or density dependent variation in MZ B cell generation or their loss. We will validate and compare these models using a robust statistical framework to identify the model that receives the strongest support form the data. Subsequently, we will develop a probabilistic approach to predict the dynamics of antigen-specific clones in the MZ B cell population during the course of immunization. Our study will identify the processes regulating the reconfiguration of the MZ B cell population post immunogenic perturbations. By leveraging these insights, we can enhance our understanding of how the B cell receptor repertoire evolves across the lifespan.