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Quantitative modeling of the terminal differentiation of B cells and mechanisms of lymphomagenesis

Germinal centers (GC) are follicles of B cells that undergo proliferation, differentiation and DNA rearrangement, both through somatic hypermutation and class switch recombination, after presentation of an antigen. GCs are the main sources of memory and plasma cells that produce high-affinity antibodies necessary to protect the body against invading microorganisms. Yet, the mechanisms controlling the molecular switch governing terminal differentiation into either memory or plasma cell are still poorly characterized.

In this work we create a quantitative kinetic model of the transcriptional regulatory module that controls the exit from GCs and the terminal differentiation into plasma cells and memory B cells. Or model recapitulates the dynamics of three key gene regulators of the process, BCL6, IRF4 and BLIMP, and integrates the signals arising from the B cell receptors (BCRs), that sense antibody binding affinity, and de CD40 signaling pathway, that responds to T cell-mediated stimulation. We use gene expression profile data from mature human B cells at several stages of their linage specification to determine appropriate model parameters. Despite a compact structure, the module dynamics are highly complex due to the presence of several feedback loops and self-regulatory interactions, and understanding its dysregulation, frequently associated with lymphomagenesis, requires robust dynamical modeling techniques.

Our model predicts the existence of two different cycles of hysteresis that direct B cells through an irreversible transition towards a differentiated cellular state. Upon stimulation with BCR and the CD40 signaling pathways, B cells experience a transition that leads to a change of state in a bi-stable subsystem, representing a differentiated stage. We show that the interplay between both signaling pathways makes the transition irreversible under normal biological conditions.

Furthermore, by synthetically perturbing the interactions in this network, we can elucidate known mechanism of lymphomagenesis and suggest new candidate tumorigenic alterations, indicating that the model is a valuable quantitative tool to simulate B cell exit from the germinal center under a variety of physiological and pathological conditions.