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Genetic Circuit Architectures Underlying Cell Fate Choices for Immunity

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Antigen stimulated B cells follow an unusual developmental trajectory that transiently passes through a germinal center state, which promotes receptor affinity maturation and immunoglobulin class switching, before terminally differentiating into antibody secreting plasma cells. It was found that graded expression of the transcription factor IRF-4 regulates cell fate, but the relationship between antigen receptor signaling, the network of interactions with IRF-4, and cell fate was not known. This talk describes models that link ligand-receptor avidity with cell fate. The models have been validated experimentally by directly varying the levels and kinetics of IRF-4 accumulation. Furthermore, signaling through the antigen receptor is demonstrated to control the expression of IRF-4 and in turn the frequency of B cells that undergo class switching before differentiating into plasma cells. These findings provide an explanation for experiments that measure B cell numbers in transgenic mice. The architecture of our regulatory circuit provides a general mechanism for quantitative variations in a signal to be translated into a binary cell-fate choice involving transient expression of one of the two developmental fates. In collaboration with Aryeh Warmflash, Ying Li, Roger Sciammas, and Harinder Singh, The University of Chicago.