A systems biology approach to understanding antigen presentation capacity in a lymph node

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Dendritic cells (DCs) ingest foreign material (antigen) present during infection, process antigen for display on their cell surface, and migrate to T cell zones of lymph nodes (LNs) where millions of circulating T cells are present. A small fraction of these T cells (cognates) have receptors that bind to the displayed antigen on the DCs, initiating a cascade of events leading to priming. These primed T cells then return to the site of infection to lead the body's defense. Recent studies employing two-photon microscopy have significantly advanced our knowledge of T cell motility and the behavior of cognate T cells in the presence of antigen-bearing DCs within LNs, but many unanswered questions remain. We developed a 3 dimensional (3D) agent-based model representing the T cell zone of LNs, allowing for rapid *in silico* simulation of T cell zone function. In addition, monkey LNs were cross-sectioned and fluorescently labeled to reveal the size and shape of T cell zones, density of T cells, and distributions of high-endothelial venules (HEVs) which serve as T cell entry and cortical and medulary sinuses which connects to efferent lymphatics (ELs) and serve as T cell exit ports, respectively. These and other data were used to parameterize an agent-based model in C++ on a 3D toroidal lattice populated with T cells and DCs that interact according to prescribed stochastic rules. We used the model to explore the effect of T cell zone morphology on LN efficiency and used uncertainty and sensitivity analysis to predict which mechanisms contribute significantly to the production of primed T cells. T cells in model simulations exhibit motility in close accord with experimental data, moving at an average speed of about 13 μm/min with a motility coefficient of 45 μm2/min, and an average transit time of about 18 hrs. Introduction of antigen-bearing DCs induces an *in silico* immune response, leading first to the production of effector CD4+ T cells followed by the production of effector CD8+ T cells. Results of our analyses show that the cognate frequency of T cells and the lifespan of DCs, after licensing by effector CD4+ T cells, have a significant influence on T cell differentiation. Analysis of simulations also suggests that LNs have the capacity to accommodate efficient priming of cognate naïve T cells even when cognate frequency is substantially higher than physiological. Our systems biology approach provides a platform not only to understand immune function and suggesting future wetlab experiments, but also to guide manipulation of LN function in the context of infection.