The effect of time-varying antigen dosing schemes on antibody production and its optimal temporal pattern for eliciting stronger immunological memory

by

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Abstract

One of the barriers to rational vaccine design against evolving pathogens is our lack of mechanistic understanding of how innate and adaptive immune response systematically emerge and evolve. Immune response is comprised of dynamic events that require many components to cooperate collectively in a manner that spans a range of scales. These characteristics make it hard to predict mechanisms for immune response based solely on experimental observations. This thesis investigates various aspects of affinity maturation that are relevant to vaccination and therapeutic strategies but are not yet fully understood mechanistically, ranging from the evolution of the heterogeneity of the antibody population with respect to affinity to optimal design parameters for temporal dosing of vaccines. Our approach is to apply computational techniques to mathematically model the immune system, and being synergistic with complementary experiments.

1. As affinity maturation ensues, average affinity of antibodies increase with time while resulting affinity distribution becomes increasingly heterogeneous. To shed light on how the extent of this heterogeneity evolves with time during affinity maturation, we have taken advantage of previously published data of antibodies isolated from individual serum samples. Using the ratio of the strongest to the weakest binding subsets as a metric of heterogeneity (or affinity inequality), we find that after a single injection of small antigen doses, the ratio decreases progressively over time. This is consistent with Darwinian evolution in the strong selection limit. By contrast, neither the average affinity nor the heterogeneity evolves much with time for high doses of antigen, as competition between clones of the same affinity is minimal.

2. What are the aspects of affinity maturation being altered by various temporal patterns of antigen dosing? Certain extended-duration dosing profiles increase the strength of the humoral response, with exponentially-increasing(EI) dosage providing the greatest enhancement. While this is an exciting result, it is necessary to establish a mechanistic understanding of how immune response be enhanced to further engineer and optimize the temporal patterns. From our computational model, the effect is driven by enhanced capture of antigen in lymph nodes by evolving higher-affinity antibodies early in the GC response. We validate the prediction from

independent experimental data, where EI dosage result in promoted capture and retention of the antigen in lymph nodes. To our knowledge, this work is the first to demonstrate a key mechanism for vaccine kinetics in the response of B cells to immunization, and may prove to be an effective method for increasing the efficacy of subunit vaccines.

3. Are there optimal dosing profiles that maximize total protection? That is, lead to the evolution of the most antibodies of high affinity? In extension of mechanistic studies in 2, we propose a stochastic simulation method that can be used as a tool for optimizing dosage protocols for vaccine delivery. Using this tool, we analyze experimental conditions for EI dosage induce suboptimal immune response and investigate two approaches for the optimization. Specifically, reducing the total dosage optimizes affinity of resulting antibodies, while total protection is optimal neither at constant or EI dosage but that corresponding to a “linear-like” dosing profile. Our approach can be extended to broader applications in vaccine design.

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