A predictive model of immunodominance hierarchies in influenza infection

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Short Abstract — **We present a model to account for the cellular phenomenon of immunodominance—the differential expansion of antigen-specific populations in response to infection. Specifically, our model addresses CD8+ T cell immunodominance in influenza infection. This model is based on experimental data and is responsive to two main parameters—the epitope density of antigen presented on the cell surface of infected or presenting cells and the precursor frequency of the responding T cell population. Novel methods for accurately quantifying both of these parameters are presented and the ability of the model to account for observed immunodominance phenomeneon is discussed.**

Keywords **— CD8+ T cell responses, influenza, immunodominance, antigen presentation, precursor frequency**

I. Purpose

Immunodominance is the phenomenon of differential expansion of antigen-specific lymphocyte populations. It is observed in B cells as well as CD4+ and CD8+ T cells, often with a single specificity dominating 70-80% of the total response [1]. This phenomenon has direct implications for vaccine design and the control of highly mutable pathogens, which may be able to escape from the dominant response. Several efforts have been made to model immunodominance, though none have been experimentally verified [1]. Our model system, influenza infection in C57BL/6 mice, contains a strong immunodominance structure in the CD8+ T cell response, mirroring those seen in humans. We have attempted to model this response and rigorously quantify the parameters in the model, with the aim of developing a robust method for predicting immunodominance hierarchies and rationally designing vaccines.

II. Experimental Design

There are equivalent numbers of the immunodominant D^bNP_{366}, D^bPA_{224} and K^bPB1_{703} specific responses in the memory phase following primary influenza infection, but challenge of such memory mice establishes a dramatic immunodominance hierarchy, with the D^bNP_{366} response expanding to 10-fold the size of either the D^bPA_{224} or K^bPB1_{703} responses [2]. Deletion of the D^bNP_{366} and D^bPA_{224} responses by mutation of the viral peptide sequence to prevent MHC binding enables immunodominant expansion of the $D^bPB1\text{-}F2_{62}$ response to levels almost equivalent to the D^bNP_{366} response following secondary challenge. Deletion of the D^bNP_{366} and D^bPA_{224} epitopes also allows extensive expansion of two normally extremely minor responses [3]. We have sought to understand these data in light of a theory that the principle determinants of immunodominance are precursor frequency and epitope density on the cell surface [2]. An ODE-based model recapitulates this immunodominance hierarchy without reference to any "immunodomination entity"; the compensatory responses arise purely from delayed antigen clearance and/or increased access to the MHC compartment. The difficulty with testing and refining this model is the ability to accurately and precisely measure precursor frequency and epitope density on the cell surface. To measure precursor frequency, we have employed an ecological approach based on sequencing TCR V-regions on a single-cell level. This approach has allowed us to make rough estimates of the precursor frequency in naïve mice, but we are still technically refining our analyses to enhance the accuracy of this method. To address epitope density, we have developed a novel detection protocol involving ion trap-mass spectrometry using internal isotopic standards that allow quantitative measurement of MHC peptides. This has allowed us to quantify the levels of MHC presented peptides with accuracy previously unattainable. We are currently moving this quantification from an *in vitro* method to directly *ex vivo* samples. These data are being used to evaluate our proposed model in both lab strain and highly pathogenic H5N1 avian influenza viruses, with a final goal of developing a fully predictive algorithm for immunodominance hierarchies.

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