Mathematical modeling dissects maturation kinetics of natural killer cells in response to mouse cytomegalovirus infection

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***Short Abstract* — Deciphering mechanisms of natural killer cell differentiation in response to mouse cytomegalovirus (MCMV) infection is important to understanding NK cell-mediated control of that infection. To this end, we collected mass cytometry (CyTOF) data of splenocytes in C57BL/6 mice at milestone timepoints in the immunological response to MCMV-infection. Simple ordinary differential equation (ODE) and stochastic models to describe these and other single-cell data illustrate important features of natural killer cell proliferation and maturation and quantify kinetic rates of the response to MCMV infection.**

***Keywords* — Ordinary differential equations, ODE, Gillespie, natural killer cells, NK, mass cytometry, CyTOF**

I. Background

STIMULATION of natural killer (NK) cells by the NK receptor Ly49H results in cellular proliferation and differentiation of naïve NK cells into mature effector cells [1]-[3]. This process is uni-directional and occurs in a stepwise fashion, distinguished by the presence or absence of CD11b and CD27. More specifically, these development stages are defined as CD11b-/CD27+ (immature), CD11b+/CD27+ (double-positive), and CD11b+/CD27- (mature) [2],[4]. Whereas immature cells proliferate more robustly, double-positive and fully mature cells produce more effective cytokine and cytotoxic responses [3],[4]. Deciphering the kinetics of the NK cell maturation process is critical to understanding the effectiveness of an NK cell response to pathogenic challenge.

II. Data Collection

C57BL/6 mice were infected with 1000 PFU of mouse cytomegalovirus (MCMV). At 4- and 7-days post-infection, groups of 3 and 4 mice, respectively, were sacrificed and their splenocytes harvested. Another group of 4 uninfected mice were sacrificed for a day 0 timepoint. Mass cytometry (CyTOF), an experimental technique which measures single-cell protein expressions of up to 40 proteins, was performed on these splenocytes. These data were then divided into populations given their expression of the proteins Ly49H, CD11b, and CD27 for further analysis. This provided the percentage of Ly49H+ and Ly49H- cells that were in each maturation stage. Multiplying these values by the total abundance of NK cells at time *t* provided trajectories for the number of different NK cell phenotypes present at time *t*.

III. Results

A. ODE Modeling of CyTOF Data

A simple ordinary differential equation (ODE) model was fit to data quantifying the abundance of each maturation state for both Ly49H+ and Ly49H- cells. Using a model where each of the CD11b/CD27 subsets proliferate at a distinct rate and transition unidirectionally yields two main findings: 1) Ly49H+ cells show faster proliferation rates compared to that of Ly49H- cells, and 2) immature NK cells proliferate at a faster rate compared to the double-positive or mature counterparts.

B. Validation with Stochastic Model

Previously published results indicate that single NK cells stimulated with MCMV can proliferate and form diverse populations ("clones"), and that there is a negative correlation between the number of cells in a clonal burst and the percentage of those cells that are CD27+ [4]. We applied our kinetic estimates from the ODE model to a Gillespie model of many single NK cells and found that this negative correlation is only possible with biologically infeasible parameter values. However, changing the model to one that incorporates a "time delay" in differentiation of immature NK cells leads to a better agreement between experiments. These results offer new potential mechanisms to describe NK cell maturation during MCMV infection.

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