Comment on: A Validated Mathematical Model of Cell-Mediated Immune Response to Tumor Growth

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In Response:

Gowal et al. erroneously surmise that in ref. 1, we assume "unrealistic" initial natural killer (NK) cell levels of zero in order to generate the simulations of Fig. 4, and they conclude from their own simulations that NK efficacy is stronger than we indicate. We do not draw conclusions about the efficiency of NK cells from our model. Rather, we use the model equations as a possible description of the different cytolytic mechanisms of NK cells versus $CD8^+$ T cells. These mathematical descriptions of the immune cell dynamics are validated when we show that the simulations can reproduce experimentally observed differences in the efficacy of innate and the tumor-specific responses.

An explicit statement of the initial conditions used was omitted in ref. 1, so we state them here. Figure 4 (*right*) of ref. 1 is a simulation that captures the behavior shown in Fig. 3*D* (*right-most panel*) of ref. 2. The simulation employed a parameter set using a modified scaling of NK parameters from Table 1 of ref. 1 and non-zero NK initial conditions. The same qualitative simulation outcomes can be obtained using the NK parameters in Table 1, with $j(ln) = 6j(nn)$, and with the initial NK count at its steady-state value: $NK_0 = \sigma/f = 3.16 \times 10^5$ cells. The initial $CD8^+$ T count is zero, and the initial tumor challenge is $T_0 = 10^4$ cells, with a re-challenge on day 10 of 10^4 live cells. We note that any values for j are rough estimates because precise values were not to be found in the literature.

We also point out that for the first 10 days of the simulation, the "ligand-transduced" parameter set for the NK cells was used, and from day 10 onward, the "control-transduced" parameter set was employed. This reflects the conditions of the laboratory experiment. We conjecture, based on their simulations, that Gowal et al. neglected to change the parameter set on day 10. We can only reproduce their results when the ligand-transduced parameter set is used for the entire simulation. This naturally results in a much stronger immune suppression of the tumor, but does not reflect the experiment reported in ref. 2.

The image on Fig. 4 (*bottom left*) of ref. 1 represents the outcomes of the experiments of Fig. 2*A* of ref. 2. In this case, only $CD8^+$ T cells were targeted for deactivation. However, because of potential cross-reactions, including the loss of IL-2 production by the T cells, which in turn, could diminish NK differentiation and maturation, we assume that initial NK cell counts were lower than the steady state, but certainly not zero, as conjectured by Gowal and colleagues. Initial NK was $NK_0 = 10^4$ cells, and initial $CD8^+$ T count was zero. The NK source term and death term in our simulations are at the values stated in Table 1 of ref. 1.

The simulations of ref. 1 show that the new functional form for the interaction of the $CD8^+$ T cells with tumor cells was sufficient to capture a range of behaviors observed experimentally, using a biologically reasonable set of initial conditions and system parameters.

1. de Pillis L, Radunskaya A, Wiseman C. A validated mathematical model of cell-mediated immune response to tumor growth. Cancer Res 2005;65:7950–8.
2. Diefenbach A, Jensen E, Jamieson A, Raulet D. Rae1 and H60 ligands of the NKG2D receptor stimulate tumor immunity. Nature 2001;413:165–71.

doi:10.1158/0008-5472.CAN-07-1403