Assessing the role of CXCR4 in the CD8+ T cell response to vaccinia virus with mathematical modeling.

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Abstract

Migration and motility are essential properties of the cellular immune response, playing an important role for development and effective function. Genetic defects affecting chemokine receptor (CR) expression can lead to inappropriate migratory patterns of developing and mature immune cells, resulting in ineffective immune responses, increased sensitivity to infections and autoimmune diseases. Using a mouse model with a gain-of-function mutation in CXCR4 (CXCR4+/1013-mice), we studied the role of this CR on the dynamics of CD8 T-cells responses, following infection with Vaccinia Virus. During the acute phase of infection, we first found that overexpression of CXCR4 leads to a delayed appearance of CD8 T-cells in the blood. By fitting a mathematical model to these data, we estimated that the appearance of CD8+ T cell responses in the blood of CXCR4+/1013-mice was delayed by _˜1 day. Moreover, in the memory phase, we observed a shift in the generation of memory CD8+ T cell subsets, as well as an increased proportion of cells in the bone marrow.
However, considering the difficulties to assess the exact dynamic of cells' circulation in vivo and its consequences on cell differentiation and function we decided to use a formal approach to analyze CD8 responses in this experimental system. Thus, in order to assess the role of CXCR4 in more detail, we developed an agent-based model following individual cell proliferation, differentiation and migration dynamics in the lymph node (LN) and the blood, explicitly accounting for LN structure. Testing different hypotheses our model indicates that the observed altered CD8+ T cell phenotype dynamics in the blood can be explained by a prolonged dwell time of cells within the LN medulla, or a smaller pool of naive T cells within the LN at the start of infection. Further modeling will be used to study the dynamic of CD8 T-cells circulation and homing, during acute and memory phase.
Altogether, this work aims at providing a systematic framework for an integrative analysis of cell differentiation and migration in the context of the CXCR4-receptor.

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