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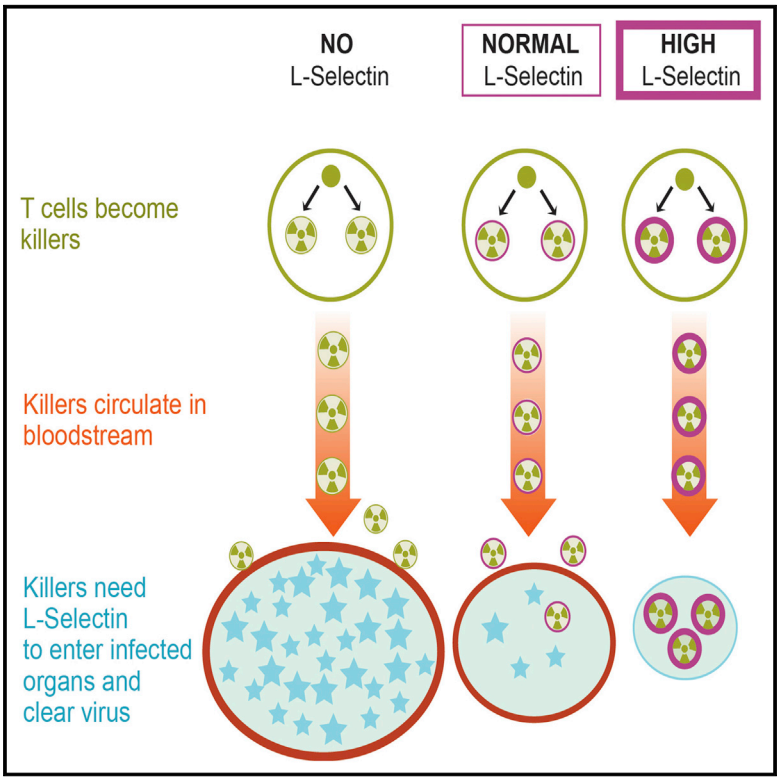
L-selectin Is Essential for Delivery of Activated CD8$^+$ T Cells to Virus-Infected Organs for Protective Immunity

Graphical Abstract



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In Brief

Lymphocyte migration is a key step in the host's immune response against viruses. Mohammed et al. demonstrate that re-expressed L-selectin/CD62L on primed virus-specific CD8$^+$ T cells plays a pivotal role in their recruitment from the bloodstream into virus-infected tissues for protective immunity.

Highlights

- L-selectin is re-expressed on activated CD8$^+$ T cells exiting lymph nodes
- L-selectin does not regulate priming, differentiation, or function of cytotoxic T lymphocytes
- Entry of activated CD8$^+$ T cells into virus-infected tissues is L-selectin dependent
- The level of cell-surface L-selectin determines the extent of anti-viral immunity

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L-selectin Is Essential for Delivery of Activated CD8$^+$ T Cells to Virus-Infected Organs for Protective Immunity

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SUMMARY

Cytotoxic CD8$^+$ T lymphocytes play a critical role in the host response to infection by viruses. The ability to secrete cytotoxic chemicals and cytokines is considered pivotal for eliminating virus. Of equal importance is how effector CD8$^+$ T cells home to virus-infected tissues. L-selectin has not been considered important for effector T cell homing, because levels are low on activated T cells. We report here that, although L-selectin expression is downregulated following T cell priming in lymph nodes, L-selectin is re-expressed on activated CD8$^+$ T cells entering the bloodstream, and recruitment of activated CD8$^+$ T cells from the bloodstream into virus-infected tissues is L-selectin dependent. Furthermore, L-selectin on effector CD8$^+$ T cells confers protective immunity to two evolutionally distinct viruses, vaccinia and influenza, which infect mucosal and visceral organs, respectively. These results connect homing and a function of virus-specific CD8$^+$ T cells to a single molecule, L-selectin.

INTRODUCTION

CD8$^+$ T cells play a prominent role in the host response to infection with a variety of pathogens, most notably, viruses. The activation, proliferation, and differentiation of naive CD8$^+$ T cells into effector cytotoxic T cells have been studied extensively in mice in response to a number of different viruses, using various routes of inoculation (Fung-Leung et al., 1991; Goulding et al., 2014; Zinkernagel and Doherty, 1979). The consensus from these studies is that effector CD8$^+$ T cells are generated from naive CD8$^+$ T cells inside lymphoid organs draining the site of virus inoculation. Following exit from the lymph node (LN) and entry into the bloodstream, effector CD8$^+$ T cells migrate to virus-infected tissues in response to inflammatory stimuli produced by the virus to clear/resolve the infection. Effector CD8$^+$ T cells also migrate to many different non-lymphoid organs that are not infected by virus (Masopust et al., 2004). The widespread dissemination of virus-specific CD8$^+$ T cells to tissues in which they are not needed may limit the number available to clear virus from infected organs and thereby reduce their efficacy. Extensive studies have elucidated the different mechanisms that effector CD8$^+$ T cells use to eliminate virus (Zhang and Bevan, 2011). However, the recruitment of virus-specific effector CD8$^+$ T cells from the bloodstream into tissues in the resolution of a primary infection is equally important to understand.

Intravital imaging has revealed that a key event in the selection of blood-borne leukocytes for recruitment into tissues is their capture, rolling, and arrest on the inside walls of blood vessels. This depends on co-ordinated signaling of different types of adhesion molecule, such as selectins and integrins, as well as chemokine receptors following engagement by their respective ligands on blood vessel endothelial cells. Virus-specific effector CD8$^+$ T cells upregulate the expression of a number of adhesion molecules known to regulate the recruitment of activated or effector T lymphocytes into sites of inflammation, including P-selectin glycoprotein ligand (PSGL)-1, CD44, and the integrins LFA-1 and VLA-4 (Austrup et al., 1997; DeGrendele et al., 1997; Mora and von Andrian, 2006; Oehen and Brduscha-Riem, 1998; Siegelman et al., 2000; Lefrançois and Marzo, 2006; Liu et al., 2006). Depending on whether virus inoculation is via the skin or the mucosa, upregulation of skin homing molecules such as cutaneous lymphocyte antigen (CLA) or the mucosal homing receptor $\alpha4\beta7$ integrin could also impart tissue-specific homing properties to virus-specific effector CD8$^+$ T (Liu et al., 2006). However, direct evidence for any of the homing-associated molecules expressed by activated virus-specific CD8$^+$ T cells regulating their recruitment from the bloodstream into infected tissues is lacking. In fact, a recent study found that the chemokine receptor CXCR3, which is widely implicated in the homing of interferon (IFN)-γ secreting CD8$^+$ T cells, had no role in the recruitment of virus-specific CD8+ T cells from the bloodstream into infected skin (Hickman et al., 2015).

A striking feature of virus-specific effector CD8$^+$ T cells, regardless of the route of virus inoculation, is downregulation of the adhesion molecule leukocyte-selectin (L-selectin)/CD62L. Low expression of L-selectin on effector T cells (Kaech et al., 2002;