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L-selectin-negative CCR7$^-$ effector and memory CD8$^+$ T cells enter reactive lymph nodes and kill dendritic cells

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T lymphocytes lacking the lymph node–homing receptors L-selectin and CCR7 do not migrate to lymph nodes in the steady state. Instead, we found here that lymph nodes draining sites of mature dendritic cells or adjuvant inoculation recruited L-selectin-negative CCR7$^-$ effector and memory CD8$^+$ T cells. This recruitment required CXCR3 expression on T cells and occurred through high endothelial venules in concert with lumenal expression of the CXCR3 ligand CXCL9. In reactive lymph nodes, recruited T cells established stable interactions with and killed antigen-bearing dendritic cells, limiting the ability of these dendritic cells to activate naive CD4$^+$ and CD8$^+$ T cells. The inducible recruitment of blood-borne effector and memory T cells to lymph nodes may represent a mechanism for terminating primary and limiting secondary immune responses.

Useful immune responses require the regulated trafficking of T lymphocytes to secondary lymphoid organs, where naive T lymphocytes are activated by antigen-bearing dendritic cells (DCs), and subsequently to inflamed nonlymphoid tissues, where mainly effector T lymphocytes mediate their activity[1]. Many insights into the molecular mechanisms underlying the compartmentalization of the inductive and effector phases of immune responses have been gained over the past decade. Naive T cells selectively migrate from blood to peripheral lymph nodes with a 'three-digit code' in which rolling, sticking and firm adhesion are mediated by the interaction of L-selectin, the chemokine receptor CCR7 and the integrin LFA-1 with their ligands (peripheral node addressin (PNAd), CCL21 and intercellular adhesion molecule 1 (ICAM-1), respectively) on the lumenal surfaces of high endothelial venules (HEVs)[2,3]. Once they have entered the lymph node, naive T cells migrate to the paracortical T cell zone by establishing physical contacts with fibers of the fibroblastic reticular network bearing the CCR7 ligand CCL21 (ref. 4). CCR7 is also required for the migration of maturing DCs from the peripheral tissues to T cell areas of the draining lymph nodes[5], where these DCs seem to integrate into the fibroblastic reticular cell network, positioning themselves for efficient interaction with T cells[4,6]. The migrating naive T cells 'scan' the surfaces of the DCs and establish transient or stable contacts of variable duration depending on the nature of the stimulus[7], eventually undergoing activation, proliferation and differentiation into effector cells.

Most of the effector T cells that emerge from a productive immune response have lost expression of the lymph node–homing receptors L-selectin and CCR7 and therefore the capacity to migrate to lymph nodes. At the same time, they have acquired the expression of a different set of adhesion molecules and chemokine receptors that equip them for migration into inflamed peripheral nonlymphoid tissues[8]. Among these are ligands for E- and P-selectin, CXCR3 (the receptor for the interferon-γ (IFN-γ)–induced chemokines CXCL9, CXCL10 and CXCL11) and CCR5 (the receptor for CCL3, CCL4 and CCL5)[9–12].

The segregation of immune functions by migratory constraints described for naive and effector T cells is maintained in the memory compartment[13]. Indeed, central memory T cells, which are devoid of immediate effector function but rapidly proliferate in secondary responses, express CCR7 and L-selectin and are found in lymph nodes, whereas effector memory T cells, which are characterized by immediate effector function, lack L-selectin and CCR7 and are found in blood, peripheral tissues and spleen but not in lymph nodes[14–16]. The exclusion of effector and effector memory T cells, especially cytolytic CD8$^+$ T cells, from the lymph nodes can be viewed as a mechanism to prevent killing of antigen-presenting DCs and therefore preserve their capacity to trigger sustained primary and secondary

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Descrizione del progetto

Based on functional and homing properties, two subsets of memory T cells have been defined. Central memory T cells (T_{CM} cells) express the lymph node homing receptors CD62L and CCR7, have poor effector function but proliferate efficiently upon antigenic stimulation. Effector memory T cells (T_{EM} cells) do not express CCR7, are mostly CD62L negative and therefore are excluded from lymph nodes, but are able to migrate to the sites of inflammation where they exert immediate effector functions by production of inflammatory cytokines and cytotoxic mediators.

In the present work, the question addressed concerns the capacity of effector and T_{EM} $CD8^+$ T cells to home to the lymph nodes under inflammatory conditions. Strikingly, we found that lymph nodes draining sites of mature DCs or adjuvant inoculation recruit $CD62L^-$ $CCR7^-$ effector and T_{EM} $CD8^+$ cells. $CD8^+$ T cell recruitment requires CXCR3 expression on T cells and occurs through high endothelial venules (HEVs) in concert with HEV luminal expression of the CXCR3 ligand CXCL9. In reactive lymph nodes, recruited T cells establish stable interactions with and kill antigen-bearing DCs, limiting the ability of these DCs to activate $CD4^+$ and $CD8^+$ T cells.

Therefore, the inducible recruitment of blood-borne effector and T_{EM} $CD8^+$ cells to lymph nodes may represent a mechanism for terminating primary and limiting secondary immune responses.