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The essential role of chemokines in the selective regulation of lymphocyte homing

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Abstract

Knowledge of lymphocyte migration has become a major issue in our understanding of acquired immunity. The selective migration of naïve, effector, memory and regulatory T-cells is a multiple step process regulated by a specific arrangement of cytokines, chemokines and adhesion receptors that guide these cells to specific locations. Recent research has outlined two major pathways of lymphocyte trafficking under homeostatic and inflammatory conditions, one concerning tropism to cutaneous tissue and a second one related to mucosal-associated sites. In this article we will outline our present understanding of the role of cytokines and chemokines as regulators of lymphocyte migration through tissues.

Keywords: Lymphocyte homing; Chemokines

1. Introduction

The initiation of an effective immune response requires that dendritic cells (DCs), located at the sites of pathogen entry recognize these microorganisms in the context of a danger signal. Thus, in response to inflammatory signals, DCs capture, process and carry antigens from the site of pathogen entry to secondary lymphoid organs where they present peptides derived from the pathogen to infrequent antigen-specific naïve T-cells [1]. These naïve, antigen-inexperienced T-cells circulate continuously through secondary lymphoid organs including spleen, peripheral lymph nodes and mucosal-associated lymphoid tissue. Although it is thought that naïve cells are excluded from non-lymphoid tissue and that only activated memory effector cells can gain access to non-lymphoid tissues, two recent reports have demonstrated that antigen-inexperienced naïve T, including the recent thymic emigrants $CD8^+$ T-cells do migrate to the lamina propria of the small intestine [2,3].

Once their cognate antigen is presented by DCs as a peptide–MHC complex, naïve T-cells differentiate into effector/memory T-cells migrating back to the site of antigen entry via efferent lymphatics where they are able to mount an immune response. Similarly, regulatory T-cells responding to self-antigens acquired by DCs under non-inflammatory conditions may migrate to tertiary tissue, although this point has not been fully resolved. If they actually have the capability of homing to tertiary tissues, Treg may provide immunoregulatory signals thus preventing tissue-targeted effector cells to accumulate in inflamed environments [4]. Alternatively, Treg may remain in secondary organs where they may block the effector activity of responding T-cells. This tropism displayed by effector/memory and regulatory T-cells is mostly determined by the expression on the cell surface of specific tissue-homing receptors and chemokines receptors and of their matching ligands in the postcapillary

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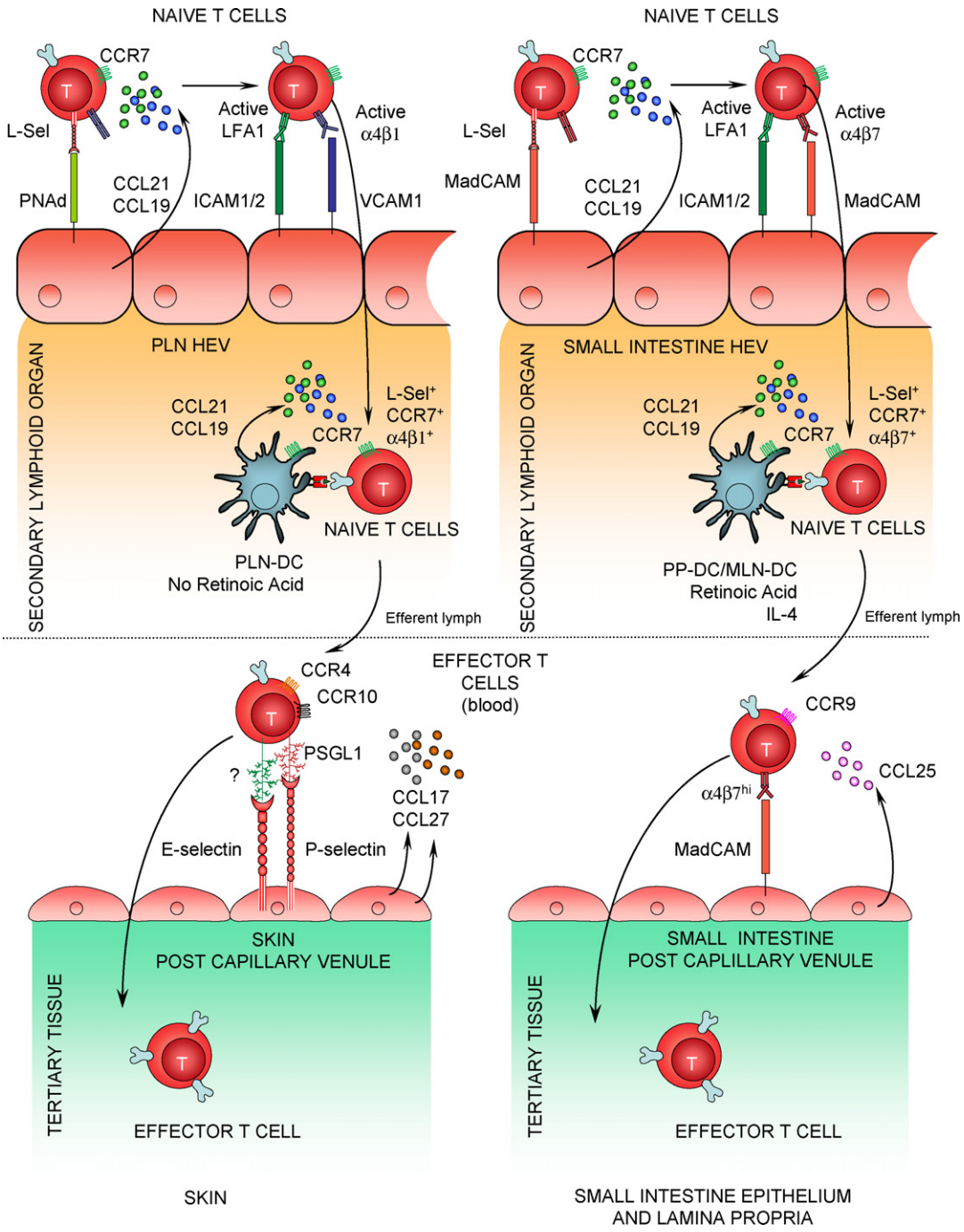

Fig. 1. Schematic representation of chemokine involvement in T cell homing. Chemokines contribute to naïve T cell entrance to secondary lymphoid organs through high endothelial venules (HEVs) at peripheral lymph nodes (PLN) or at mucosal sites at the small intestine (mesenteric lymph nodes, MLN; Peyer's patches, PP). Cells at HEVs within the T cell zones secrete chemokines CCL19 and CCL21 that attract naïve T-cells expressing CCR7. Also, CCR7-expressing dendritic cells are draw via afferent lymphatics to neighboring sites within secondary lymphoid organs. L-Selectin on the surface of T-cells recognizes peripheral node addressing (PNAd) on PLN and mucosal addressin cell-adhesion molecule-1 (MAdCAM-1) on small intestine HEVs. MAdCAM-1 can also interact with integrin $\alpha_4\beta_7$. Chemokines such as CCL19 and CCL21 rapidly activate integrins to promote strong adhesion of rolling lymphocytes. At PLN, lymphocyte function-associated molecule-1 (LFA-1) and integrin $\alpha_4\beta_1$ bind with high affinity to ligands ICAM-1 and 2 and VCAM-1 respectively, while at intestinal sites, activated $\alpha_4\beta_7$ binds with high affinity to MadCAM-1. These interactions result in T-cell arrest and endothelial transmigration that positions naïve T-cells at the T cell zones of the respective secondary lymphoid organs; PLN in one case and MLN or Peyer's patches in the other. T-cells that recognize their cognate antigen presented as MHC–peptide by dendritic cells differentiate into effector/memory T-cells and remodel their homing and chemokine receptors. Activation of T-cells by PLN-DCs results in a decrease in L-selectin expression and the upregulation of ligands for P- and E-selectin and of chemokine receptors 4 (CCR4) and 10 (CCR10). Secretion of chemokines 17 and 27 (CCL17 and CCL27) attract these cells to inflammed skin. T-cells activated by MLN-DCs or PP-DCs decrease L-selectin expression and upregulate integrin $\alpha_4\beta_7$, that binds to MAdCAM-1 and chemokine receptor 9 (CCR9) that responds to CCL25 produced by cells in the small intestine. These activated T-cells migrate to the epithelium and lamina propria of the small intestine. Besides chemokines, other factors such as retinoic acid (RA) and IL-4 participate in the targeting of T-cells to the small intestine. Other various arrangements of homing and chemokine receptors guide activated T-cells to tertiary organs other that skin and the gut (not depicted).