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CXC Chemokine Receptor 5 Expression Defines Follicular Homing T Cells with B Cell Helper Function

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Abstract

Leukocyte traffic through secondary lymphoid tissues is finely tuned by chemokines. We have studied the functional properties of a human T cell subset marked by the expression of CXC chemokine receptor 5 (CXCR5). Memory but not naive T cells from tonsils are $CXCR5^+$ and migrate in response to the B cell–attracting chemokine 1 (BCA-1), which is selectively expressed by reticular cells and blood vessels within B cell follicles. Tonsillar $CXCR5^+$ T cells do not respond to other chemokines present in secondary lymphoid tissues, including secondary lymphoid tissue chemokine (SLC), EBV-induced molecule 1 ligand chemokine (ELC), and stromal cell–derived factor 1 (SDF-1). The involvement of tonsillar $CXCR5^+$ T cells in humoral immune responses is suggested by their localization in the mantle and light zone germinal centers of B cell follicles and by the concomitant expression of activation and costimulatory markers, including CD69, HLA-DR, and inducible costimulator (ICOS). Peripheral blood $CXCR5^+$ T cells also belong to the $CD4^+$ memory T cell subset but, in contrast to tonsillar cells, are in a resting state and migrate weakly to chemokines. $CXCR5^+$ T cells are very inefficient in the production of cytokines but potently induce antibody production during coculture with B cells. These properties portray $CXCR5^+$ T cells as a distinct memory T cell subset with B cell helper function, designated here as follicular B helper T cells (T_{FH}).

Key words: chemokines • CXC chemokine receptor 5 • lymphocytes • B cell follicle • antibodies

Introduction

T cell–dependent immune responses to pathogens are initiated in specialized lymphoid tissues, including LNs, Peyer's patches (PPs),[1] and the spleen. The outcome of these defensive mechanisms relies on the finely tuned traffic of T and B cells as well as antigen-presenting cells, suggesting that chemokines may be involved in the recruitment and proper positioning of leukocytes within these compartments. Chemokines comprise a large family of structurally related chemoattractant proteins that regulate the composition of cellular infiltrates at sites of inflammation or, alternatively, the physiological leukocyte migration during hematopoiesis, antigen sampling in secondary lymphoid tissues, and immune surveillance (1–6). This report focuses on a particular subset of T cells with homing selectivity for B cell follicles in secondary lymphoid tissues.

Chemokines shown to be produced in LNs, PPs, or the spleen include secondary lymphoid tissue chemokine (SLC; CCL21) (systematic nomenclature for human chemokines available at http://cytokine.medic.kumamoto-u.ac.jp/), EBV-induced molecule 1 ligand chemokine (ELC; CCL19), B cell–attracting chemokine 1 (BCA-1; CXCL14), stromal cell–derived factor 1 (SDF-1; CXCL12), and monocyte-derived chemokine (MDC; CCL22 [6–8]). In addition, several typical inflammatory chemokines are upregulated in inflamed rather than resting LNs, which may reflect an enhanced T cell activation status. In contrast to SDF-1 and MDC, the role of SLC and ELC in controlling cellular traffic in secondary lymphoid tissues is well es-

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[1]*Abbreviations used in this paper:* BCA-1, B cell–attracting chemokine 1; CCR7, CC chemokine receptor 7; CXCR5, CXC chemokine receptor 5; DIG, digoxigenin; ELC, EBV-induced molecule 1 ligand chemokine; HEV, high endothelial venule; HPF, high power field; ICOS, inducible costimulator; PP, Peyer's patch; SDF-1, stromal cell–derived factor 1; SLC, secondary lymphoid tissue chemokine; TBS, Tris-buffered saline.

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