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Chemokine-mediated control of T cell traffic in lymphoid and peripheral tissues

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Abstract

Antigen-driven T cell education and subsequent pathogen elimination present particular challenges for the immune system. Pathogens generally enter the body at peripheral sites such as the skin, gastrointestinal tract or lung, areas from which naïve T cells are largely excluded. Instead, naive T cells constantly recirculate through secondary lymphoid organs, such as lymph nodes and Peyer's patches, in search for antigen brought to these locations by means of afferent lymphatic channels. Here, antigen-loaded dendritic cells present antigen–peptide–MHC complexes to clonotypic T cells and provide appropriate co-stimulatory signals for immune response initiation. As a result, short-lived effector T cells and long-lived memory T cells are generated that reach the peripheral tissue for participation in immune responses and immune surveillance.

Effector and memory T cell relocation is non-random, due to tissue-specific "address codes" that allow proper tissue homing. This process involves adhesion molecules, including selectins, integrins, and corresponding vascular ligands as well as the large family of chemokines and their receptors. Here, we discuss the changes in chemokine receptor expression that occur during T cell activation and differentiation, and the ways in which these changes impact on the migration potential of naïve, effector, and memory T cells. We summarize our current understanding of T cell homing to the T zone and B cell follicles within secondary lymphoid tissues and highlight the two chemokine receptors CCR7 and CXCR5 that recognize chemokines constitutively present either in the T zone (CCR7 ligands CCL19/ELC and CCL21/SLC) or follicular compartment (CXCR5 ligand CXCL13/BCA-1). CCR7 is characteristic for naïve and central memory T (T_{CM}) cells whereas CXCR5 distinguishes follicular B helper T (T_{FH}) cells. In addition, we further subdivide long-lived memory T cells into CCR7-negative effector memory T (T_{EM}) cells and peripheral immune surveillance T (T_{PS}) cells. The latter term designates the extraordinarily large subset of memory T cells with primary residence in normal (healthy) peripheral tissues. Our current understanding of T_{PS} cell migration and function is highly fragmentary, but these cells are thought to provide immediate protection locally at the site of pathogen entry. Here, we propose that the tissue distribution of T_{PS} cells is determined by a distinct set of chemokines and corresponding receptors that differs from those operating in secondary lymphoid tissues and inflammatory sites.

Keywords: T Cells; Lymphocyte homing; Chemokines; Chemokine receptors

1. Introduction

Of the approximately 50 human chemokines, the large majority can be categorized as either CXC or CC chemokines (Loetscher et al., 2000; Murphy et al., 2000; Murphy, 2002; Baggiolini et al., 1994, 1997). This division is based on the positioning of cysteine residues within the primary amino acid sequence. In the case of interleukin-8 (CXCL8/IL-8), a prototypical CXC chemokine with potent neutrophil chemoattractant activity, the NH_2-terminal, two of four conserved cysteines are separated by one amino acid. In contrast, these two cysteines are directly adjacent within CC chemokines, as exemplified by the monocyte chemoattractant protein CCL2/MCP-1. In addition, there are two numerically minor structural families, called the C and CX3C

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chemokines. Two chemokine nomenclature systems are used in the literature: the traditional abbreviations dating back to the time of chemokine discovery, such as IL-8 and MCP-1, and a systematic nomenclature that combines structural motifs (CXC, CC, XC, and CX3C) with 'L' (for ligand) and the number of the respective gene, such as CXCL8 for IL-8 and CCL2 for MCP-1 (http://cytokine.medic.kumamoto-u.ac.jp). Chemokine receptors are designated according to the type of chemokine(s) they bind (CXC, CC, XC, and CX3C), followed by 'R' (for receptor) and a number indicating the order of discovery.

An alternative division of chemokines into functional (as opposed to structural) subfamilies has proven to be useful in understanding the biology of chemokines (Sallusto et al., 2000; Loetscher et al., 2000; Moser and Loetscher, 2001; Moser et al., 2004). Inflammatory chemokines are upregulated under conditions of inflammation and are produced by activated leukocytes and tissue cells as well as numerous tumors. They control the recruitment of effector leukocytes and thus, determine the composition of inflammatory infiltrates. Most inflammatory chemokines demonstrate broad target cell selectivity and act on cells of the innate as well as the adaptive immune system. Homeostatic chemokines, in contrast, are produced constitutively at non-inflamed sites. They are responsible for navigating leukocyte precursors during hematopoiesis in the bone marrow and thymus, controlling cellular traffic in spleen and lymph nodes (LNs), and contribute to immune surveillance of healthy peripheral tissues. Importantly, several chemokines are ill defined and cannot be attributed unambiguously to either one of the two functional categories (Moser et al., 2004).

Chemokine receptors belong to a large family of seven-transmembrane domain receptors, which signal via heterotrimeric GTP-binding proteins (G proteins) (Loetscher et al., 2000; Murphy et al., 2000; Murphy, 2002; Thelen, 2001; Proudfoot, 2002). The currently known 18 human chemokine receptors include six CXCRs, 10 CCRs, one XCR, and one CX3CR. The major downstream second messengers of G protein signaling are phospholipase Cβ (PLCβ) isoforms, Ser/Thr-kinases, phosphatidylinositol 3-kinase-γ (PI3Kγ) and c-Src-related non-receptor tyrosine kinases (Loetscher et al., 2000; Thelen, 2001). Cellular responses to chemokines are typically rapid in onset and transient in duration. Response abrogation is elicited through the activity of Ser/Thr-kinases, which prevent further G protein-coupling by phosphorylation of Ser/Thr residues within the C-terminal region of chemokine receptors (Ferguson, 2001). In a process known as homologous desensitization, G protein-coupled receptor kinases selectively phosphorylate chemokine-occupied receptors, leading to endocytic uptake of chemokine-receptor complexes. Alternative kinases may phosphorylate ligand-free (non-engaged) chemokine receptors, which prevents G protein coupling by a process called heterologous desensitization. Importantly, receptor desensitization allows the continuous redistribution of chemokine receptors on leukocytes for maintaining polarized chemokine sensing and therefore, is an integral requirement of directional leukocyte migration.

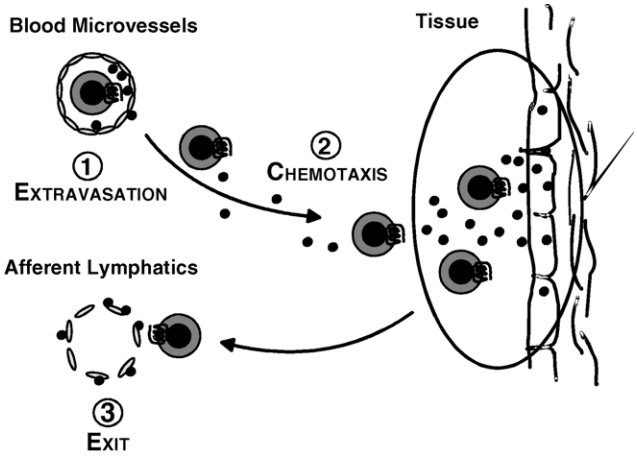

Fig. 1. Recruitment, localization, and tissue exit of circulating leukocytes. The leukocyte recruitment process (1) involves two distinct and sequential processes, termed vascular adhesion and transendothelial migration. Before extravasation, blood leukocytes interact with adhesion molecules on the luminal side of blood vessels. To resist shear forces, integrin function is upregulated by means of chemokine receptor signaling, which leads to firm attachment of leukocytes to the blood vessel wall and their subsequent migration across the endothelium. Perivascular leukocyte may reside at this location, or in the event that they are equipped with the appropriate chemokine receptor(s) may respond to local chemokine gradients and chemotax (2) toward the cellular source of chemokine(s). Eventually, by an unknown process, leukocytes exit the tissue via afferent lymphatic vessels (3), pass through local LNs and return to blood.

2. Chemokines control leukocyte adhesion and tissue migration

The recruitment of circulating leukocytes from the blood stream into tissues depends on three distinct processes: vascular attachment of leukocytes to the luminal side of blood vessels, extravasation (transendothelial migration) and cell migration (Fig. 1). These are highly complex processes, which are controlled by "outside-in" and "inside-out" signaling events during cellular interactions with chemokines and adhesion ligands (Butcher et al., 1999; Von Andrian and Mempel, 2003). Initial contact between blood leukocytes and microvascular endothelial cells involves "loose" interactions mediated by selectins, β1-integrins and their respective vascular ligands, resulting in a "rolling" motion of weakly adherent leukocytes. This process does not require chemokines; however, a number of chemokines have recently been shown to destabilize the rolling of lymphocytes on L-selectin ligands, suggesting that chemokines are capable of regulating the rolling process (Grabovsky et al., 2002). The rolling leukocytes either succumb to blood shear forces and are washed away, or arrest and become firmly attached. Firm adhesion of leukocytes fully depends on chemokine receptor ("outside-in") signaling, which results in the necessary