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# Chemokine transport dynamics and emerging recognition of their role in immune function

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**Abstract**

Leukocyte migration is critically important during all protective and pathological immune and inflammatory responses. Chemokines play fundamental roles in this process, and chemokine concentration gradients stimulate the directional migration of leukocytes. The formation and regulation of these gradients is poorly understood. These are complex processes that depend on the specific properties of each chemokine and interactions between physical, biological and biochemical processes, including production, diffusion, advection, scavenging, post-translational modification, and extracellular matrix (ECM) binding. While some of these mechanisms have been investigated in isolation or limited combinations, more integrative research is required to provide a quantitative knowledge base that explains how chemokine gradients are established and maintained, and how cells respond to, and modify, these gradients.

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**Abbreviations**

ACKR, atypical chemokine receptor; cCKR, conventional chemokine receptor; CCR, CC chemokine receptor; CXCR, CXC chemokine receptor; DC, dendritic cell; ECM, extracellular matrix; FRC, fibroblastic reticular cell; LEC, lymphatic endothelial cell; LN, lymph node; LV, lymphatic vessel; SCS, subcapsular sinus; SLN, skin-draining lymph node.

## Introduction

An effective immune system requires the functions of a diverse array of leukocytes (white blood cells). The correct localization of these cells is critical, and this is largely governed by a family of secreted proteins called chemokines. Chemokine-directed leukocyte migration controls the development and homeostasis of the immune system, and plays a key role in all protective immune and inflammatory responses. It also contributes to the development and progression of many diseases, including cardiovascular disease, autoimmunity, chronic inflammation and cancer. Moreover, cancer cells can exploit chemokine-directed migration to facilitate their metastatic spread. Understanding the mechanisms that regulate chemokine function therefore has substantial implications in health and disease. Leukocytes sense chemokines via G-protein coupled 'conventional' chemokine receptors (cCKRs). There are more than 40 chemokines, each signaling through one or more of 18 cCKRs [1], and this complexity is required to robustly regulate the diverse leukocyte populations of the immune system [1]. The chemokines are split into four subfamilies (CC, CXC, CX3C and XC) based on the precise arrangement of conserved cysteine residues in the mature protein, with the CC and CXC families being by far the largest with 28 and 16 members, respectively. This subdivision largely aligns with receptor binding: CC chemokines operate primarily through CC chemokine receptors (CCRs), CXC chemokine through CXC chemokine receptors (CXCRs), and so on. Chemokines are named according to a standardized nomenclature in which the subfamily name is followed by the letter 'L' (for ligand), and then a number indicating when the gene encoding that chemokine was identified. Thus, CCL21 is a CC chemokine whose gene was the 21st CC chemokine gene to be characterized.

Chemokines direct leukocyte extravasation from blood and lymph, and control the migratory behavior and positioning of leukocytes within tissues. The spatial distribution of chemokines is therefore critical for their correct functioning. In some contexts, chemokines form concentration gradients that stimulate directional leukocyte migration. These gradients depend on numerous integrated biological and physical processes. First, chemokine is secreted: the type and quantity depends on the identity of the secreting cell and the many environmental signals it receives and integrates.

These signals can include physical parameters: for example, flow-induced wall shear stress upregulates expression of CCL21 by lymph node fibroblastic reticular cells (FRCs) [2] and lymphatic endothelial cells (LECs) [3], while stretch can upregulate expression and release of pro-inflammatory chemokines in alveolar epithelium [4]. Chemokine movement through interstitial spaces occurs through diffusion and advection, and this is profoundly affected by chemokine/ECM interactions [5–7]. Some chemokines bind strongly to ECM components, while others exhibit little or no affinity. These processes will not only shape interstitial gradients, but will also regulate the quantity of chemokine that enters the lymphatic vasculature with the tissue fluid. This is important because lymph-borne chemokines can form flow-regulated intralymphatic gradients [8,9], modify chemokine gradients in downstream lymph nodes (LNs) [10], and reach high endothelial venules to directly control leukocyte recruitment into LNs [11,12]. Further gradient modulation and regulation involves chemokine removal by leukocytes (via cCKRs and non-receptor mediated mechanisms (e.g. pinocytosis) [13–15]), and by specialized chemokine scavengers called 'atypical' chemokine receptors (ACKRs) that are primarily expressed by stromal cells [16]. Migratory cells can also cleave chemokines to dramatically alter their ECM-binding properties [5], and chemokine-driven cCKR regulation means that exposure to chemokine can alter a cell's subsequent migratory properties. Importantly, each chemokine has a unique set of properties that will influence its distribution and therefore the nature of the concentration gradients it can form. Therefore, a complex combination of physical and biological factors determines how chemokine gradients are generated, maintained and regulated, and, importantly, how they direct the migration and interstitial positioning of leukocytes.

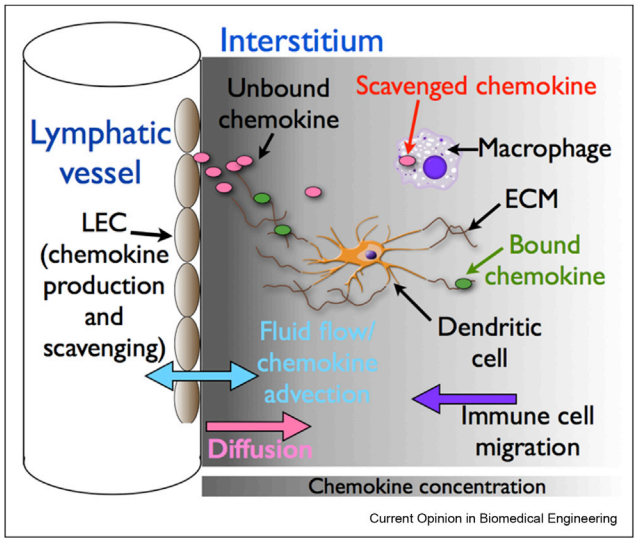
The chemokine biology research literature is vast, and it is not the intent of this review to provide extensive coverage of all background material. Rather, we focus on a subset of those studies that incorporated some aspect of transport mechanisms in the analysis of chemokine gradients and cell actions. The chemokine axis that includes CCL21 and CCL19 has been characterized more extensively than most others, and thus will constitute much of the material of this review. To put these studies in context, we include reference to other key experimental studies even though the importance of transport phenomena may not have been recognized or included in the analysis of the results.

## Quantitative approaches to characterizing chemokine/cell systems

A quantitative knowledge base of chemokine gradients, and the ability to modulate them, requires a tightly integrated, synergistic approach in which experimental and modeling approaches evolve in an interdependent manner. The majority of chemokine research to date comes from biological experiments involving individual chemokine–receptor axes, with some exploration of receptors that bind to multiple ligands. Modeling approaches thus far have similarly taken a reductionist approach. Even under these conditions, evidence of complex behaviors has emerged.

One well-studied example of interstitial chemokine gradients involves those generated by LECs. These cells, which line lymphatic vessels (LVs), form a key microanatomical barrier and play critical roles in regulating the migration, localization and departure of interstitial leukocytes by producing distinct subsets of chemokines and ACKRs which, under homeostatic and inflammatory conditions, create interstitial gradients around LVs. Figure 1 shows the key physical and biological processes that are likely to shape these gradients. The best-studied LEC-derived chemokine is CCL21, which, by interacting with its receptor CCR7, guides dendritic cells (DCs) towards, and into, LVs [17,18]. Interstitial LEC-derived CCL21 gradients can also be exploited by invading cancer cells which up-regulate CCR7 to aid their dissemination to draining LNs. Due

**Figure 1**




**Factors influencing LEC-derived chemokine gradients**. Depending on environmental conditions, LECs release distinct subsets of chemokines (pink and green ovals represent unbound and ECM-bound chemokine, respectively). The distribution of these chemokines within the adjacent tissue (indicated by the grey shading) is likely to be influenced by many physical and biological factors including production rate, diffusion, fluid flow, the nature of the ECM, the chemokine's ECM binding properties, and chemokine scavenging/uptake mediated by ACKRs, cCKRs and pinocytosis by resident tissue cells, such as macrophages and LECs themselves. The ensuing gradients will direct the migration of responsive cell types, such as dendritic cells, which can then modify the gradients by, for example, chemokine scavenging and/or cleavage.