

Chemokines: Introduction

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Chemokines are a family of **chemoattractant cytokines** (small proteins secreted by cells that influence the immune system) which play a vital role in cell migration through venules from blood into tissue and vice versa, and in the **induction of cell movement** in response to a chemical (chemokine) gradient by a process known as **chemotaxis** (**Figure 1**). In addition, chemokines also regulate lymphoid organ development and T-cell differentiation, mediate tumour cell metastasis, and have recently been shown to have a function in the nervous system as neuromodulators.

In order for a cell to respond to a chemokine it must express a complementary **chemokine receptor**. Chemokine receptors belong to the vast family of **G-protein coupled receptors (GPCRs)**: seven transmembrane receptors which bind extracellular ligands and consequently initiate **intracellular signalling**. When a chemokine binds its receptor a calcium signalling cascade is created, resulting in the activation of small GTPases. This then has downstream effects such as activation of integrins (molecules involved in cell adhesion) and actin polymerisation, resulting in the development of a pseudopod (cellular projection), polarised cell morphology and ultimately cell movement.

Chemokines are grouped and named according to their amino acid composition, particularly on the first two cysteine residues of a conserved tetra-cysteine motif. The **CC** and **CXC chemokines** form the two largest groups. The molecules CX3CL1, XCL1 and XCL2 are also regarded as chemokines. There are forty-seven known chemokines and nineteen chemokine receptors (**Figure 2**), and this numerosity results in a high degree of specificity. In fact, the particular molecules expressed on a cell determine which tissue a cell will migrate into. For example, cells expressing the chemokine receptor CCR7 migrate to lymph nodes, where their ligands, CCL19 and CCL21, are expressed.

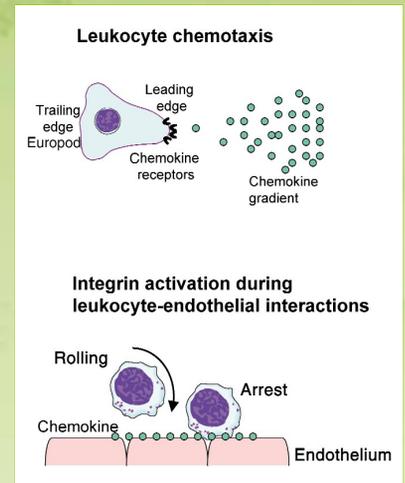
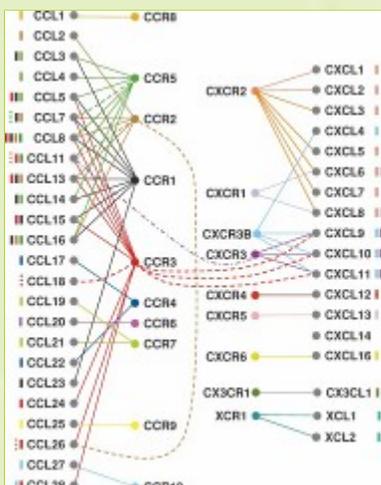


Figure 1. Key functions of chemokines. Adapted from: Mackay CR. *Nat Immunol.* 2001 Feb;2(2):95-101.

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Chemokines may also be grouped according to their function, such as whether they are inflammatory or homeostatic. **Inflammatory chemokines** are produced when inflamed tissue releases cytokines such as **tumour necrosis factor (TNF)**, and they function to recruit leukocytes. Homeostatic chemokines are expressed constitutively and play a key role in lymphocyte migration to, and the development of, lymphoid organs. Furthermore the CXC chemokines can be grouped as to whether they are angiogenic or angiostatic. The CXC chemokines containing the ELR amino acid motif (CXCL1-3, 5-8, 14 and 15) tend to be angiogenic, whereas ELR negative CXC chemokines are mainly angiostatic, with CXCL12 being a possible exception.

Figure 2. Chemokine:receptor interactions. Solid lines represent receptor:agonist interactions and dotted lines receptor:antagonist interactions. Adapted from: Rot A. *Ann Rev Immunol.* 2004;22:891-928