Review

# Chemokines and chemokine receptors: new insights into cancer-related inflammation

Gwendal Lazennec[1] and Ann Richmond[2,3]

[1] INSERM, U844, Site Saint Eloi - Bâtiment INM - 80 rue Augustin Fliche, University of Montpellier I, Montpellier, F-34090, France
[2] Veterans Affairs Medical Center, Vanderbilt University School of Medicine, Nashville, Tennessee, USA
[3] Department of Cancer Biology, Vanderbilt University School of Medicine, Nashville, Tennessee, USA

**Chemokines are involved in cellular interactions and tropism in situations frequently associated with inflammation. Recently, the importance of chemokines and chemokine receptors in inflammation associated with carcinogenesis has been highlighted. Increasing evidence suggests that chemokines are produced by tumor cells as well as by cells of the tumor microenvironment including cancer-associated fibroblasts (CAFs), mesenchymal stem cells (MSCs), endothelial cells, tumor-associated macrophages (TAMs) and more recently tumor-associated neutrophils (TANs). In addition to affecting tumor cell proliferation, angiogenesis and metastasis, chemokines also seem to modulate senescence and cell survival. Here, we review recent progress on the roles of chemokines and chemokine receptors in cancer-related inflammation, and discuss the mechanisms underlying chemokine action in cancer that might facilitate the development of novel therapies in the future.**

## Introduction

Chemokines are chemotactic cytokines (approximately 8-17 kDa) with the ability to bind G-protein-coupled receptors (Box 1). Chemokines were originally identified as potent attractants for leukocytes such as neutrophils and monocytes, and were generally regarded as mediators of acute and chronic inflammation (inflammatory chemokines). Several chemokines were subsequently found to be constitutively expressed in lymphoid tissues. Moreover, leukocytes also express specific chemokines and their receptors. Accumulating evidence suggests that in addition to inflammation, chemokines are important regulators in development, homeostasis and pathophysiological processes associated with osteoporosis [1], obesity and insulin resistance [2], viral infections [3,4], immune responses [5,6], mobilization of progenitors to the bone marrow [7] and autoimmune encephalomyelitis [8].

More recently, chemokines and their receptors have been identified as mediators of chronic inflammation, which plays a key role in the initiation or progression of cancers of the lung, colon, liver, breast, cervix, prostate, bladder, ovary, esophagus, skin and lymphatics [9–12]. Tumor growth and dissemination is the result of dynamic interactions between tumor cells themselves, and also with components of the tumor environment. In this regard, chemokines are emerging as key mediators not only in the homing of cancer cells to metastatic sites but also in the recruitment of a number of different cell types to the tumor microenvironment.

Several studies have suggested that cancer cells express chemokine receptors that mediate metastasis to target organs expressing their cognate chemokines. Furthermore, recent studies have suggested that chemokines are produced by epithelial cancer cells, leading to the recruitment of TAMs, TANs, lymphocytes, CAFs, MSCs and endothelial cells into the tumor microenvironment. These infiltrating cells provide a secondary source of chemokines that could affect tumor growth, cell survival, senescence, angiogenesis and metastasis. Here, we review the role of chemokines and chemokine receptors in cancer-related inflammation. These novel findings provide a rationale for developing therapies that target chemokines as well as their receptors.

## Sources of chemokines and chemokine receptors in tumors

Early work has shown that cancer cells from a variety of types of solid cancers express high levels of the chemokine receptors CXCR4, CCR7, CCR9 and CCR10 [11–13] (Table 1). This could define the metastatic tropism of each type of cancer, depending on the receptor present at the surface of cancer cells and the chemokines produced at the sites of metastasis. Indeed, the ligand of CXCR4, CXCL12, is expressed at high levels in various organs, including the lung, liver and lymph nodes, which are frequently involved in tumor metastasis. Similarly, CCL21, the ligand of CCR7, is produced by lymph nodes, and CCL27, the ligand of CCR10, is secreted by the skin [14]. This picture became more complex when studies revealed that cancer epithelial cells were producing higher levels of a number of chemokines compared with normal epithelial cells, and were also expressing high levels of a series of chemokine receptors, to establish a tumor-promoting microenvironment, facilitating tumor-associated angiogenesis and metastasis (Table 1). These factors can produce a 'cytokine storm' that amplifies the inflammatory response by recruiting additional inflammatory cells, including macrophages, neutrophils and lymphocytes [15]. This is particularly

*Corresponding author:* Lazennec, G. (gwendal.lazennec@inserm.fr).

1471-4914/$ – see front matter  doi:10.1016/j.molmed.2010.01.003 Available online 15 February 2010

**Box 1. Chemokine families**

Chemokines and their receptors are involved in neutrophil and monocyte cell trafficking [78,79] and are classified on the basis of the presence of variations on a conserved cysteine motif in the mature sequence of the proteins [11,12] (Figure I). The first group of chemokines, named the CC subfamily (so-called because of the juxtaposition of the first two cysteine residues), is composed of 28 members, whereas the CXC subfamily (which possesses a single variable amino acid between the first two cysteines) comprises 17 members. Two smaller subfamilies (one member each) are represented by the CX3C family (three amino acids between the first two cysteines) and the XC family, which lacks the first and third cysteines. The CXC chemokines can be further classified into ELR− and ELR+ subgroups based on the presence or absence of the motif 'glu-leu-arg (ELR)'. ELR+ CXC chemokines (CXCL1, 2, 3, 5, 6, 7 and 8) are angiogenic factors, whereas ELR− members (except CXCL12) function as angiostatic factors to inhibit the formation of blood vessels [80].

Chemokines bind to the chemokine receptor subfamily of class A G-protein-coupled receptors (GPCRs). There are ten CCR family members and seven CXCR family members in addition to XCR1 and CX3CR1 (Figure I). Decoy receptors, which bind ligands with high affinity but do not elicit signal transduction, include D6, DARC and CCX-CKR (Chemocentryx, chemokine receptor) [30]. Many chemokines bind multiple receptors and most receptors bind multiple chemokines (Figure I), suggesting the possibility of functional redundancy, which is also likely to be modulated by both the spatial and temporal control of expression. Several enzymes, in particular proteases, have been described to process chemokines at specific sites generating chemokine isoforms, which sometimes have higher activity than the full-length protein [81]. In addition to GPCRs, chemokines also interact with glycosaminoglycans (GAGs). Although this interaction is not required for *in vitro* chemotactic activity, GAG binding is essential for the presentation of chemokines on endothelial layers and for leukocyte migration *in vivo* [82]. Chemokine GPCRs signal through heterotrimeric G-proteins, which in turn regulate a diversity of signal transduction pathways involved in chemotaxis, including mitogen-activated protein (MAP) kinases, phospholipase-Cβ, phosphoinositide 3-kinase (PI3K) and RAS as well as Rho GTPases [83]. It is interesting to note that chemokine receptors are themselves subject to dynamic phosphorylation events, which could be crucial for their action and constitute another level of regulation.

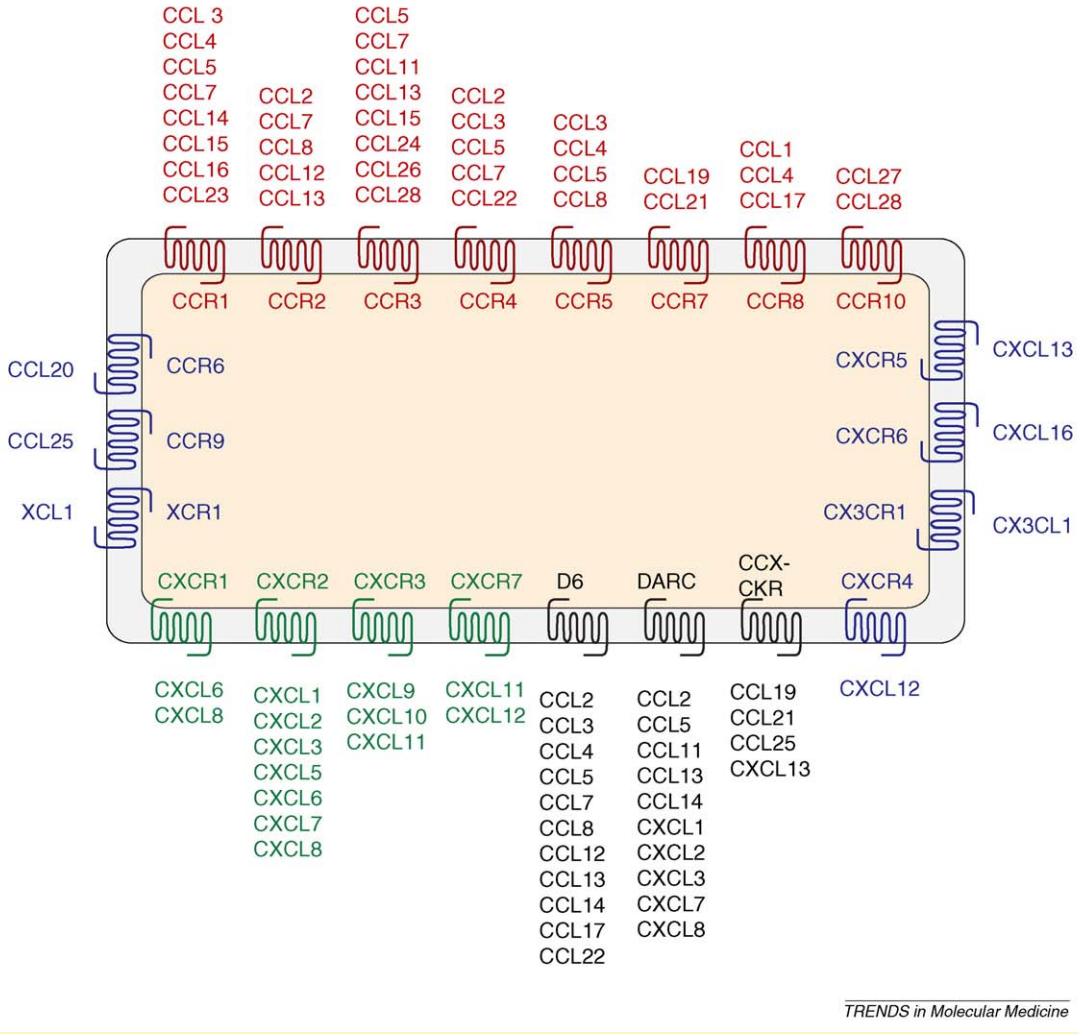


**Figure I**. Chemokines and chemokine receptor families. Most chemokines can interact with multiple receptors, and a single receptor can interact with multiple chemokines. This is the case for most CC (red) and CXC (green) chemokines. Decoy receptors (black) can also bind multiple chemokines. By contrast, a minority of receptors (blue) have only one ligand.

the case with infiltrating leukocytes bearing chemokine receptors such as CXCR1, 2 and CCR2, 4 and 5, and also endothelial cells and CAFs (Table 1). Cells present in the stromal compartment of the tumor constitute another source of chemokines (Table 1), which could alter tumor growth, angiogenesis, metastasis and microenvironment. In the following sections, we will discuss the recent advances in each of these topics.