Review

Chemokines and Chemokine Receptors: Their Manifold Roles in Homeostasis and Disease

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Chemokines are a superfamily of small proteins that bind to G protein-coupled receptors on target cells and were originally discovered as mediators of directional migration of immune cells to sites of inflammation and injury. In recent years, it has become clear that the function of chemokines extends well beyond the role in leukocyte chemotaxis. They participate in organ development, angiogenesis/angiostasis, leukocyte trafficking and homing, tumorigenesis and metastasis, as well as in immune responses to microbial infection. Therefore, chemokines and their receptors are important targets for modulation of host responses in pathophysiological conditions and for therapeutic intervention of human diseases. *Cellular & Molecular Immunology*. 2004;1(2): 95-104.

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Introduction

Phagocytic leukocytes respond to chemoattractants with directional cell migration, activation of integrins, generation of superoxide anions, and release of granule contents. These functions constitute the first-line host defense against invading microorganisms. Over the past decades, a large number of chemoattractants have been identified, which include the "classical" chemoattractants such as the bacterial peptide N-formyl-methionyl-leucyl-phenyl-alanine (fMLF), activated complement components (C3a and C5a), leukotriene B_4 (LTB_4), platelet-activating factor (PAF) (reviewed in 1-3), and a superfamily of newly defined small proteins, chemokines (4-6). Both classical chemoattractants and chemokines activate G-protein coupled seven-transmembrane (STM) receptors expressed not only on cells of hematopoietic origin, but also on other cell types. Classical chemoattractants attract and activate mainly phagocytic leukocytes which express multiple receptors, whereas in addition to acting as inflammatory mediators, some chemokines attract very specific subsets of leukocytes such as immature and mature dendritic cells. Directional migration of receptor expressing cells in response to chemoattractants permits their recruitment to tissue sites of microbial invasion or injury. Furthermore, some chemokines play an essential role in recruiting lymphocyte subsets to specific areas of lymphatic tissues and organs (7-9). There is also growing evidence for the involvement of chemokines or their receptors in development (10, 11), hematopoiesis (12-14), angiogenesis (15, 16), malignancy (17, 18) and HIV infection (19) (Figure 1). This review intends to provide only an introductory overview of the important roles of chemokines and their receptors in homeostasis and disease conditions. Readers can refer to many excellent reviews and original articles for more detailed insights into more specific studies of chemokines and their receptors.

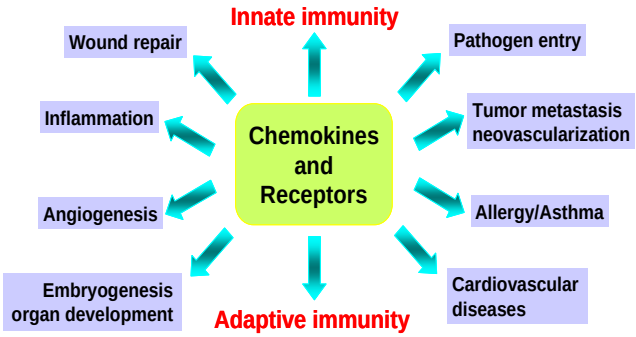

Figure 1. The role of chemokines and receptors in pathophysiologic conditions.

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Abbreviations: fMLF, N-formyl-methionyl-leucyl-phenyl-alanine; STM, seven-transmembrane; LTB_4, leukotriene B_4; PAF, platelet-activating factor; KSHV, Kaposi's sarcoma herpesvirus; NK cell, natural killer cell; DC, dendritic cell; PMN, polymorphonuclear granulocyte; DARC, Duffy antigen receptor for chemokines; HEV, high endothelial venules.

Table 1. *Chemokines*

Chemokines	-ELR-	H/I	Synonyms	Major target cells showing chemotaxis
CC chemokines				
CCL1	NA	I	I-309, TCA3, P500	monocytes, T cells
CCL2	NA	I	MCP-1, MCAF (mouse; JE)	monocytes, T cells, basophils, NK cells, progenitors
CCL3	NA	I	LD78α, LD78β, MIP-1α	monocytes, T cells, NK cells, basophils, eosinophils, dendritic cells, hematopoietic progenitors
CCL4	NA	I	Act-2, G-26, HC21, H400, MIP-1β, LAG-1, SISγ, MAD-5	monocytes, T cells, dendritic cells, NK cells, progenitors
CCL5	NA	I	RANTES	T cells, eosinophils, basophils, NK cells, dendritic cells
CCL6	NA	I	C10 (mouse), MRP-1 (mouse)	macrophages
CCL7	NA	I	MCP-3	monocytes, T cells, eosinophils, basophils, NK cells, dendritic cells
CCL8	NA	I	MCP-2, HC14	monocytes, T cells, eosinophils, basophils, NK cells
CCL9	NA	I	MRP-2 (mouse), MIP-1γ (mouse)	T cells
CCL10	NA	I	CCF18	T cells
CCL11	NA	I	eotaxin	eosinophils, T cells
CCL12	NA	I	MCP-5 (mouse)	monocytes, T cells, eosinophils
CCL13	NA	I	MCP-4, NCC-1, CKβ10	monocytes, T cells, eosinophils
CCL14	NA	I	HCC-1, HCC-3, NCC-2, CKβ1, MCIF	monocytes, hematopoietic progenitors
CCL15	NA	I	HCC-2, NCC-3, MIP-5, Lkn-1, MIP-1	monocytes, T cells, eosinophils
CCL16	NA	I	NCC-4, LEC, HCC-4, LMC, LCC-1,CKβ12	T cells, neutrophils
CCL17	NA	H	TARC	T cells
CCL18	NA	H?	DC-CK1, PARC, MIP-4, CKβ7, DCCK1	naïve T cells
CCL19	NA	H	ELC, MIP-3β, exodus-3, CKβ11	T cells, B cells, dendritic cells, activated NK cells
CCL20	NA	H	MIP-3, LARC, exodus-1, ST38, CKβ4	T cells, B cells
CCL21	NA	H	SLC, 6Ckine, exodus-2, TCA4, CKβ9	T cells, B cells, dendritic cells, activated NK cells, macrophage progenitors
CCL22	NA	H	MDC, STCP-1, DC/B-CK	T cells, eosinophils
CCL23	NA	I	MIP-3, MPIF-1, CKβ8	dendritic cells, osteoclasts
CCL24	NA	I	MPIF-2, CKβ6, eotaxin-2	effector Th2 cells
CCL25	NA	H	TECK, CK15	memory T cells, B cells, immature thymocytes
CCL26	NA	I	eotaxin-3, IMAC, MIP-4α, TSC-1	eosinophils, T cells
CCL27	NA	H	ALP, skinkine, ILC, ESkine, PESKY, CTAK	CLA^+ T cells
CCL28	NA	H	MEC, CCK1	T cells
CXC chemokines				
CXCL1	ELR+	I	GROα, MGSA-α, NAP-3 (mouse/rat; KC, MIP-2, CINC-2β)	neutrophils, endothelial cells
CXCL2	ELR+	I	GROα, MIP-2α, MGSA-β, CINC-2α	neutrophils, endothelial cells
CXCL3	ELR+	I	GROγ, MIP-2α, CINC-2β	neutrophils
CXCL4	ELR-	I	PF4	fibroblasts, endothelial cells
CXCL5	ELR+	I	ENA-78	neutrophils
CXCL6	ELR+	I	GCP-2	neutrophils
CXCL7	ELR+	I	CTAPIII, NAP-2, LA-PF4, MDGF, LDGF, β-TG	fibroblasts
CXCL8	ELR+	I	IL-8, NAP-1	neutrophils, T cells, basophils, endothelial cells
CXCL9	ELR-	I	Mig	T cells, progenitors
CXCL10	ELR-	I	IP-10	T cells
CXCL11	ELR-	I	I-TAC	T cells
CXCL12	ELR-	H	SDF-1, SDF-1, PBSF	monocytes, B cells, hematopoietic progenitors, non-hematopoietic cells
CXCL13	ELR-	H	BLC, BCA-1	B cells
CXCL14	ELR-	I	BRAK, bolekine, MIP-2, BMAC, KS1	neutrophils, NK cells, B cells?
CXCL15	ELR-	H	lungkine	airspace neutrophils
CXCL16	ELR-	?	SR-PSOX, SEXCKINE	dendritic cells
C chemokines				
XCL1	NA	I	lymphotactin, SCM-1, ATAC	B cells, T cells, NK cells, neutrophils
XCL2	NA	I	SCM-1	B cells, T cells, NK cells, neutrophils
CX3C chemokine				
CX3CL1	NA	I	fractalkine, neurotactin	effector T cells

H, homeostatic chemokine; I, inflammatory chemokine; NA, not applicable. For definitions of the various synonyms, see Ref 21.

Table 2. *Chemokine receptors*

Receptors	Synonyms	Chemokine ligands	Receptor-expressing cells
CCR			
CCR1	CKR1, CC CKR1, CMKBR1	CCL3,5,7,8,13,14,15,16,23	monocytes, immature DCs, T cells, PMNs, eosinophils, mesangial cells, platelets
CCR2	CKR2, CC CKR2, CMKBR2	CCL2,7,8,12,13	monocytes, immature DCs, basophils, PMNs, T cells, NK cells, endothelial cells, fibroblasts
CCR3	CKR3, CC CKR3, Eot R, CMKBR3	CCL5,7,8,11,13,14,15,24,26	eosinophils, basophils, T cells (Th2>Th1), DCs, platelets, mast cells
CCR4	CKR4, CC CKR4, CMKBR4, K5-5	CCL17,22	immature DCs, basophils, T cells (Th2>Th1), platelets
CCR5	CKR5, CC CKR5, ChemR13, CMKBR5	CCL3,4,5,8,11,13,14,20	Th1 cells, immature DCs, monocytes, NK cells, thymocytes
CCR6	GPR-CY4, CKR-L3, STRL22, CRY-6, DCR2, CMKBR6	CCL20	immature DCs, T cells, B cells
CCR7	BLR-2, CMKBR7	CCL19,21	mature DCs, T cells, B cells
CCR8	TER1, CKR-L1, GPR-CY6, ChemR1, CMKBR8	CCL1,4,16	monocytes, B cells, T cells, thymocytes
CCR9	GPR9-6	CCL25	T cells, thymocytes, DCs, macrophages
CCR10	GPR2	CCL27,28	T cells, melanocytes, dermal endothelia, dermal fibroblasts, Langerhans cells
CCR11	PPR1	CCL2,8,13,19,21,25	astrocytes
CXCR			
CXCR1	IL-8RA, IL-8R-I, IL-8R	CXCL2,3,5,6,7,8	PMNs, monocytes, astrocytes, endothelia, mast cells
CXCR2	IL-8RB, IL-8R-II, IL-8R	CXCL1,2,3,5,6,7,8	PMNs, monocytes, eosinophils, endothelia, mast cells
CXCR3	IP10/MigR, GPR9	CXCL9,10,11	T cells (Th1>Th2), B cells, NK cells, mesangial cells, smooth muscle cells, endothelia
CXCR4	HUMSTSR fusin, LESTR, HM89	CXCL12	hematopoietic progenitors, T cells, immature DCs, monocytes, B cells, PMNs, platelets, astrocyte, endothelia
CXCR5	BLR-I, MDRI5	CXCL13	T cells, B cells, astrocytes
CXCR6	Bonzo, STRL33, TYMSTR	CXCL16	memory T cells
XCR			
XCR1	GPR5	XCL1, XCL2	T cells
CX3CR			
CX3CR1	GPR13, V28, CMKBRL1	CX3CL1	PMNs, monocytes, NK cells, T cells, astrocytes
Duffy	DARC	CXCL1,7,8, CCL1,5	red blood cells, endothelia
D6	CCR9,10, JAB61	CCL2,4,5,8,13,14,15	B cells

NK cell, natural killer cell; DC, dendritic cell; PMN, polymorphonuclear granulocyte.

Chemokine and chemokine receptor family

Chemokines are highly basic proteins consisting of 70-125 amino acids with molecular masses ranging from 6-14 kD (5, 20). To date over 50 chemokines have been identified. The superfamily of chemokines is subclassified on the basis of the arrangement of cysteine residues located in the N-terminal region, as designated C, CC, CXC, and CX3C members, in which C represents the number of cysteine residues in the N-terminal region and X denotes the number of intervening amino acids in between the first two cysteines (5, 6, 21) (Table 1). The CXC subfamily is sometimes further classified into ELR^+ and ELR^- types based on the presence or absence of a triplet amino acid motif (Glu-Leu-Arg) that precedes the first cysteine residue in the primary amino acid sequences of these chemokines. The presence of this motif imparts angiogenic function to this subset of CXC chemokines, while the ELR^- chemokines have angiostatic properties (23), with the exception of SDF-1 which is angiogenic (24). In general, the chemokines attract distinct classes of leukocytes: CC chemokines attract one or more classes of mononuclear cells, eosinophils and basophils; ELR^+CXC chemokines attract neutrophils; ELR^-CXC chemokines attract lymphocytes; C chemokine (lymphotactin) attracts T cells and CX3C chemokine (fractalkine) acts on T cells, natural killer cells and monocytes (25). Chemokines are produced by a variety of cell types either constitutively or in response to inflammatory stimuli. Chemokines can be broadly divided into homeostatic and inflammatory categories based on their expression pattern and function in the immune system (20, 21) (Table 1). The homeostatic chemokines are generally those that are "constitutively" expressed. They are involved in homeostatic lymphocyte and dendritic cell (DC) trafficking and lymphoid tissue organogenesis. The "inflammatory" chemokines are upregulated by proinflammatory stimuli and help orchestrate innate and adaptive immune responses. Although most chemokines are present in soluble forms and some may be associated with glucosaminoglycan moieties on the cell surface, two of the chemokines namely CX3CL1 (fractalkine) and CXCL16, have a natural mucin

stalk that adheres onto the membrane of the cells that produce them (26, 27). Their "chemokine" domain is located at the N-terminus of the mucin stalk and can be released by metalloproteinase cleavage. While the soluble, released chemokine domain of CX3CL1 and CXCL16 functions similarly to other secreted chemokines, their membrane bound forms play an important role in mediating leukocyte-endothelial cell adhesion and extravasation.

Chemokines exert their biological effects by binding to G protein-coupled cell surface receptors. Nineteen chemokine receptors have been cloned so far (21, 28) (Table 2), including six CXC receptors (CXCR1-6), eleven CC receptors (CCR1-11), one CX3C (CX3CR1) and one C receptor (XCR1). Chemokine and receptor interactions vary widely in terms of selectivity (Tables 1 and 2). Some chemokines bind only one receptor and vice versa, such as the interactions of CXCR4 with CXCL12 (SDF-1), CXCR5 with CXCL13 (BCA-1), CXCR6 with CXCL16, CCR6 with CCL20 (LARC), and CCR9 with CCL25 (TECK). However, there is also redundancy in chemokine and receptor interactions since some chemokines bind more than one receptor and many receptors recognize more than one chemokine. For example, chemokine CCL5 (RANTES) has been shown to bind at least CCR1, CCR3 and CCR5, while CCR3 also binds CXCL11 (eotaxin), CCL24 (eotaxin-2), CCL26 (eotaxin-3), CCL8 (MCP-2), CCL7 (MCP-3), and CCL13 (MCP-4). Furthermore, two of the chemokine receptor-like proteins, the Duffy antigen receptor for chemokines (DARC) and D6, promiscuously bind many of the CXC and CC chemokines with equal affinity (29-31) (Table 2), but without being activated, presumably acting as sinks that sequester inflammatory chemokines.

Major biological functions of chemokines and receptors

Homeostasis and development

Studies to date have established essential roles for some chemokines in hematopoiesis and organ development. Hematopoiesis is a dynamic process regulated by various cytokines. It is now clear that the chemokine family plays a significant role in this regulatory network. At least 25 chemokines of the CC, CXC and C subgroups have been found to suppress the *in vitro* proliferation of myeloid progenitor cells (12, 13). However, the *in vivo* evidence based on knockout mice studies provides evidence of contrasting hematopoietic effect for only few of the chemokines and their receptors. For example, CCL3 (MIP-1α) inhibits cell cycling and reduces the absolute number of bone marrow progenitor cells when administered in mice (32). Mice depleted of CCR1, a major CCL3 (MIP-1α) receptor, display enhanced lineage-committed myeloproliferation and leukocyte mobilization into the blood stream (33). CXCL12 (SDF-1) is constitutively expressed in bone marrow-derived stromal cells, promotes proliferation of B cell progenitors (34), and mobilizes the emigration of hematopoietic precursors to the bone marrow during embryogenesis (35, 36). Mice deficient in CXCL12 (SDF-1) or its exclusive receptor CXCR4 die perinatally with defects in B lymphopoiesis and myelopoiesis (14). In addition, mice lacking CXCL12 (SDF-1) or CXCR4 suffer other severe developmental abnormalities, such as incomplete development of the cardiac ventricular septum and defective cerebellum development, suggesting the involvement of CXCL12 (SDF-1)/CXCR4 pair in a number of critical developmental processes (10, 11, 14).

The thymus is a critical organ for T-lymphocyte development and expresses mRNA for several chemokines with lymphocyte-attracting properties, including CCL25 (TECK), CCL17 (TARC), CCL21 (SLC), CCL19 (ELC), and CXCL12 (SDF-1α) (37). Thymic T-cell development involves several migratory steps beginning with the influx of immature pre-T cells to their movement from the cortex to the medulla followed by the release of mature T cells into the circulation. Chemokines direct these processes based on a combination of change in the pattern of receptor expression on T cells at different stages of maturation and the production of chemokines in microenvironment. For example, the chemokine CCL25 (TECK) is produced by thymic DCs and is a selective chemoattractant for immature T cells (38). Thus, TECK directs the influx of immature T cells to the thymus where the cells are selected and mature.

Some chemokines control the development and organization of secondary lymphoid organs. Mice depleted of the gene of CXCL13 (BCA-1) or its receptor CXCR5 have normal mesenteric lymph nodes but are deficient in peripheral lymph nodes and Peyer's patches (39, 40). In addition, both types of knockout mice show a completely disorganized splenic microarchitecture, without segregation of B-cell and T-cell areas in the white pulp. CXCL13 (BCA-1), CCL21 (SLC) and CCL19 (ELC) induce lymphoid neogenesis upon ectopic expression in pancreatic islets of mice (41-43), suggesting these chemokines in conjunction may actively participate in the development of secondary lymphoid organs.

Leukocyte trafficking and homing

Chemokines control lymphocyte recirculation in immune-system homeostasis, as well as in the activation-dependent and tissue-selective trafficking of effector and memory lymphocytes. Lymphocyte homing to lymphoid and nonlymphoid tissues and recirculation between secondary lymphoid organs critically depend on the chemokines present in different sites. CCL19 and CCL21 (which bind to CCR7), and CXCL13 (which binds to CXCR5), are expressed in the lymphatic vessels, high endothelial venules (HEVs) and secondary lymphoid organs, and promote the entry of antigen-presenting cells (APCs), T cells and B cells into these organs (7). Resident DC precursors in peripheral tissues phagocytose microorganisms or cell debris and are activated by pathogens or antigens. These cells then start to mature and express CCR7 which enables them to migrate in response to CCR7 ligands into the draining lymph nodes *via* the lymphatic vessels, and to infiltrate the T-cell zones where they present processed antigen epitopes to T cells. In contrast to DCs, B cells and naïve T cells enter lymph nodes through HEVs. The CCR7 ligands CCL19 and CCL21 produced by the endothelial cells of HEVs are transcytosed to the luminal surface and induce lymphocyte extravasation to the T-cell zones of the lymph nodes (8). CCL19 produced by mature, inter-

digitating DCs facilitates the "scanning" of DCs by naïve T cells in the lymphoid organs in search of their cognate antigens.

B cells express CXCR5 and the ligand CXCL13 is produced by follicular stromal cells in lymph nodes. B cells activated by T cells proliferate in the follicles, giving rise to germinal centers (GC). Activated T cells expressing CXCR5 may also enter the follicles to participate in the T-B interaction. In addition, CCL19 and CCL21 are responsible for the proper positioning of lymphocytes within distinct microenvironments of lymphoid organs. For instance, CCL19 and CCL21, expressed by DCs and stromal cells retain T cells within the T-cell zones of secondary lymphoid organs. On the other hand, CXCL13 expressed by follicular DCs and stromal cells in follicles attracts B cells and some of the T cell subsets into the B-cell areas. Furthermore, the capacity of B cells to respond to CCR7 as well as CXCR5 ligands controls the position of B cells at the boundary of the follicles and T-cell zones in the spleen, where naïve, mature B cells interact with T cells that are newly activated in the adjacent zones (9, 44). Non-activated B cells and T cells then leave the secondary lymphoid organs *via* the efferent lymphatics.

Angiogenesis

Physiological angiogenesis occurs rapidly but transiently and is tightly regulated, whereas pathological angiogenesis, which occurs during chronic inflammation and tumor growth, results from unbalanced production of positive and negative regulators. Chemokines act either as positive or negative regulators of angiogenesis. CXC chemokines containing ELR motif, CXCL8 (IL-8), CXCL5 (ENA78), and CXCL1, 2, 3 (GRO-α, β, γ) induce vessel formation in rabbit cornea (15, 16). In contrast, ELR^- CXC chemokines CXCL4 (PF4), CXCL10 (IP-10) and CXCL9 (MIG) abrogate the angiogenesis induced by ELR^+ CXC chemokines (45, 46). One exception to this structurally based classification of angiogenic versus angiostatic CXC chemokines is CXCL12 (SDF-1), which despite the absence of the ELR motif, acts as an angiogenic factor both *in vitro* and *in vivo* (24). On the other hand, in separate experimental models two ELR^+ chemokines CXCL1 and 2 (GRO-α and GRO-β), also display angiostatic activities (47). Thus, the role of CXC chemokines in agiogenesis and angiostasis is more complex and may be affected by other environmental factors. Chemokines of other subfamilies also are involved in angiogenic processes with CCL1 (I-309), CCL2 (MCP-1), CCL11 (eotaxin), and CX3CL1 (fractalkine) being angiogenic while CCL21 (SLC) is a potent angiostatic factor (48).

Angiogenesis is crucial for tumor growth. The ELR^+ CXC chemokine CXCL8 promotes neovascularization and tumorigenesis of ovarian carcinoma (49). A human lung squamous carcinoma cell line that produces little CXCL8 (IL-8) but abundant CXCL10 (IP-10) does not grow in severe combined immunodeficiency (SCID) mice (50). In contrast to tumor cells producing CXCL8, treatment of the mice bearing CXCL8 producing tumors with anti-CXCL8 antibodies or with angiostatic chemokine CXCL10 (IP-10) inhibits tumor growth and metastasis (50, 51). In another study, transgenic mice expressing high levels of IP-10 by keratinocytes are defective in wound healing as characterized by more intense inflammation, a prolonged and disorganized granulation phase, and impaired blood vessel formation (52). These results prompt the proposals to utilize selected chemokines or their inhibitors to manipulate angiogenesis in tumor and wound healing.

It should be noted that most of the results concerning the activity of chemokines in angiogenesis and angiostasis were obtained from *in vitro* or specifically designed experiments in animals. More precise information should probably be derived from knockout models. In this context, mice lacking CXCL12 (SDF-1) or its receptor CXCR4 exhibit defects in cardiovascular development and provide clear evidence of an important role for this chemokine and receptor in angiogenesis during development (10, 14).

Inflammation

The events that lead to an inflammatory response are characterized by recognition of the site of injury by inflammatory cells, recruitment of specific leukocyte subpopulations, removal of offending microbial invaders, "debridement" of injured cells/tissues, and wound repair. Chemokines have been shown to participate in and control the process of a number of acute and chronic inflammatory conditions by promoting the infiltration and activation of inflammatory cells into injured or infected tissues (53).

Several of the CC chemokines including CCL3 (MIP-1α) and CCL5 (RANTES) are expressed in sepsis and exert proinflammatory effects by mediating organ specific leukocyte influx and activation (54, 55). Members of the CXC chemokines are implicated in the pathogenesis of systemic inflammatory response (56, 57). In bacterial pneumonia, CXC chemokine-mediated elicitation of neutrophils is beneficial and necessary for clearance of invading microorganisms (58). To support this notion, overexpression of KC, a murine homologue of human CXCL1 (GRO-α), specifically in the lung, enhances resistance to *Klebsiella* pneumonia (59).

In asthma, the submucosa of small airways is infiltrated by mononuclear, eosinophil and mast cells causing mucous gland hyperplasia and subepithelial fibrosis. Animal models of allergic airway inflammation and asthmatic patients imply a key role for chemokines in regulating lung inflammation (reviewed in 60). The kinetics of production of CCL2, CCL11, CCL17 and CCL22 correlates with the recruitment in airways of specific leukocyte subsets expressing the receptors for these chemokines (61). Chronic obstructive pulmonary disease (COPD) is characterized by progressive development of airflow limitation caused by chronic inflammation with increased recruitment of neutrophils, macrophages and IFN-γ-producing $CD8^+$ T cells in the lung. In COPD patients, the levels of CXCL8 and CXCL10 are increased and correlate with the degree of infiltration by neutrophils and $CD8^+$ T cells that produce IFN-γ. The lung-infiltrating T cells express CXCR3, the receptor for CXCL10 (62), suggesting that CXCR3 may mediate the recruitment of pathogenic Th1 cells into chronically inflamed lungs. Neutralization of CXCL10 also appears to inhibit allergic airway inflammation (63). Thus, in addition to many other chemokines, CXCR3 and its ligands participate in lung inflammation that is not necessarily dominated by Th1 response.

Atherosclerosis is widely accepted as an inflammatory

disease (64), in which chemokines play a central role in leukocyte recruitment, angiogenesis, and more intriguingly in the proliferation of vascular smooth muscle cells and their migration into plaques (65). Atherosclerotic lesions express a number of chemokines including CCL2, CCL3, CCL4, CCL5, CCL11 and CXCL8. The cellular sources of chemokines within atherosclerotic lesion are multiple and include endothelial cells, smooth muscle cells and infiltrating leukocytes. There is overwhelming evidence to support the involvement of CCL2/CCR2 chemokine-receptor pair in atherosclerosis. CCL2 is essential for monocyte recruitment, has angiogenic activity and also causes smooth muscle cell proliferation and migration. Many factors known to promote atherosclerosis such as plasma cholesterol, hypertension and diabetes, stimulate chemokine release by atheromatous lesions. Adhesion of leukocytes to endothelial cells also augments chemokine release in the pathogenic process of atherosclerosis. Therefore, chemokines and receptors become important molecular targets for circumventing the formation and development of atherosclerotic lesions. In human, CX3CR1 gene polymorphism in the coding region confers individuals with protection against atherosclerosis (66, 67). An M280 mutation in CX3CR1 results in loss of function of CX3CR1 since cells transfected with this mutant receptor exhibit a markedly reduced response to CX3CR1 ligand CX3CL1 (68). When ApoE transgenic mice, an atherosclerosis model, were crossed with $CX3CR1^{-/-}$ mice, the severity of atherosclerotic lesion was significantly reduced with lower macrophage infiltration (69). This provides an excellent example of the importance of a functional chemokine receptor in contributing to the progression of atherosclerosis.

Rheumatoid arthritis (RA) is characterized by a mixed Th1-type inflammatory cell infiltration (Th1 cells, neutrophils, monocytes) in synovial space of the joints, in association with cartilage destruction and bone remodeling. Chemokines produced in the inflamed joints attract leukocytes across the endothelial barrier to initiate and maintain active RA (70, 71). Among CXC chemokines, high concentrations of CXCL8, CXCL5, CXCL1 are detected in the sera, synovial fluids, and synovial tissues of RA patients (70, 71). These chemokines attract neutrophils and promote angiogenesis (70, 71). Abundant production of CC chemokines CCL2, CCL3 and CCL5 which attract mainly monocytes is also found in RA (70, 71). On the other hand, CXCL12 expressed in the rheumatoid synovium, recruits CD4 memory T cells, which express increased levels of CXCR4, at the RA site (72). CXCL12 also blocks T cells from undergoing activation-induced apoptosis, thus further increasing the accumulation of T cells in the rheumatoid synovium. Interestingly, CXCL12 may induce the migration of DCs from blood stream into the rheumatoid area, implying its potential role in amplifying a detrimental autoimmune response.

Multiple sclerosis (MS) as a chronic inflammatory demyelinating disorder of the central nervous system (CNS) is thought to be caused by an autoimmune response directed against self-myelin-associated antigens. The immune cells infiltrate in CNS lesions of MS patients consist of CD4, CD8 T cells and macrophages (73). Many chemokines are detected in active lesions in the CNS of MS patients and the cerebrospinal fluids of relapsing patients contain elevated levels of CCL3 (74, 75). In MS, infiltrating macrophages express CCR2 and CCR5, while T cells and reactive astrocytes in active lesions express CXCR3 and CCR5 (76, 77). Similar chemokine expression patterns are found in experimental autoimmune encephalomyelitis (EAE), an animal model more related to MS. In EAE, increased expression of CCL2, CCL3, CCL4, CCL5 and CXCL10 correlates with the severity of the disease (78). Neutralizing antibodies to selected chemokines either inhibit the onset or reduce the severity of the EAE (79, 80). A more definitive correlation between chemokines and EAE was established by experiments with CCR1- and CCR2-deficient mice, in which a reduction in disease incidence and severity were clearly documented (81, 82).

Tumorigenesis and metastasis

Many chemokines play multiple roles in tumor growth, invasion and metastasis by inducing cellular transformation, angiogenesis, secretion of proteinases, and organ specific metastasis. The notion that chemokines participate in malignant transformation is supported by studies with a chemokine receptor-like molecule encoded by Kaposi's sarcoma herpesvirus (KSHV). KSHV encodes a G protein-coupled receptor (GPCR) similar to CXCR2. KSHV-GPCR is in a constitutively activated state and is further activated by binding of CXC chemokines such as CXCL8 (IL-8) and CXCL1 (GRO-α). Overexpression of KSHV-GPCR in mice results in the development of lesions that resemble Kaposi's sarcoma (83). A point mutation of CXCR2 causes constitutive activation of the receptor and cells transfected with the CXCR2 mutant undergo malignant transformation (84). The mechanisms by which an active chemokine receptor promotes malignant transformation are not fully understood. It is possible that in selected cells, certain receptors may respond to autocrine or paracrine stimulation by the ligands that provide direct or indirect growth signals to the cells. This hypothesis was corroborated by earlier observations that CXCR2 in melanoma cell lines serves as an essential receptor for the growth stimulatory activity of CXCL1 (85).

A major finding about the role of chemokines in the progression of malignant tumors in recent years was provided by experiments with a mouse lymphoma variant that preferentially metastasizes to the kidney. In fact, mouse kidneys and mesangial cells produce chemoattractant activity for metastatic tumor cells and biochemical purification revealed the identity of the chemoattractant as JE, the mouse homologue of CCL2 (86). A number of subsequent observations revealed that the expression of specific chemokine receptors could be essential for the metastasis of many human cancers. For instance, CXCR4 and CCR7 are highly expressed in human breast cancer cell lines, malignant breast tumors and metastatic foci. On the other hand, the ligands for these receptors, CXCL12 (SDF-1) and CCL21 (SLC) are highly expressed in organs to which tumor cells metastasize (87). Other examples of chemokine and receptor involvement in tumor metastasis include melanoma, acute myeloid leukemia, acute T cell leukemia, chronic lymphoblastic leukemia, chronic lymphocytic leukemia, non-Hodgkin's B-cell lymphoma, ovarian cancer, and pancreatic cancer

(88-92). Thus, it is conceivable that anti-chemokine therapy will be added to the arsenal of cancer therapeutics to improve control of metastasis.

Microbial infection

One of the major areas of chemokine study is the relationship of chemokines and receptors to microbial infection. In fact, chemokines are expressed at high levels in virtually every kind of microbial infection examined. The dilemma appears to be that some chemokines and receptors are essential for host resistance while others are exploited by pathogenic microbes as gateways for invasion or to disarm the host defense.

In human monocytes, rapidly and most potently induced cytokines by bacterial products are chemokines CXCL8, CXCL2, CCL3 and CCL4 as determined by cDNA array (93). CCL2 and CCL22 protect mice from lethality of peritoneal sepsis (94, 95). In murine *Pseudomonas aeruginosa* pneumonia, neutralization of CXCR2 results in a markedly increased mortality that is associated with reduced neutrophil recruitment to the lung and the subsequent bacterial clearance (96). However, not all chemokines are beneficial in bacterial infection. In fulminant hepatic failure induced by *Propionibacterium acnes* in mice, CCL17, a CCR4 ligand was responsible for recruitment of host $CCR4^+CD4^+$ T cells into the liver and the ensuing inflammatory responses resulted in lethal organ failure (97).

Viruses have evolved ways to corrupt the normal functioning of the chemokine network in the host by production of proteins with homology to chemokines or resemblance to chemokine receptors. Some viruses secrete chemokine-binding proteins that competitively absorb chemokines produced by host and interfere with their recognition by cognate host receptors. More than 30 distinct virally encoded chemokine and chemokine receptor mimics have been identified so far, all of which are encoded by strains in herpesvirus, poxvirus and retrovirus families. Among these viruses, at least six are clinically important: HIV, human cytomegalovirus, human herpesviruses 6, 7 and 8, and molluscum contagiosum virus (98). Although the exact function of viral chemokine and receptor mimics remains to be fully understood, it is proposed that viruses may use these molecules to elude the protective mechanisms of the host to the advantage of their own survival and replication (98, 99). This view of point is obviously supported by the discovery of chemokine receptors CCR5 and CXCR4 as essential coreceptors for HIV entry into host cells. The present model of HIV infection holds that the HIV-1 envelope protein gp120 forms a trimolecular complex with host cell CD4 and either CCR5 or CXCR4. This results in the exposure of a cryptic fusogenic peptide of gp41 from the HIV-1 envelope protein, which mediates fusion between the viral envelope and host cell membranes (100, 101). CCR5 is utilized by macrophage tropic HIV strains to infect mononuclear phagocytes, primary T cells and DCs, while CXCR4 is used by HIV strains that infect $CD4^+$ T lymphocytes. Mutations in the coding region of CCR5 change the susceptibility of the host to HIV-1 infection. A prominent example is that homozygous inheritance of a defective allele CCR5Δ32—which encodes a truncated form of CCR5 not expressed on cell surface—is strongly correlated with HIV resistance (102-104). Utilization of chemokine receptors for host entry appears to be a popular strategy for lentiviruses. At least 7 chemokine receptors could be used by some strains of simian immunodeficiency virus, and the feline immunodeficiency virus uses CXCR4 (19). The utilization of chemokine receptors by HIV for infection has not only greatly expanded the functional scope of these host molecules, but also provided a novel approach to the development of anti-HIV-1 strategy.

Conclusion

Chemokines are distinct from other cytokines in their structure, cell surface receptors and unique pattern of activities. The seemingly promiscuous nature of many chemokines and receptors suggest the redundancy of these molecules in pathophysiological conditions. However, experiments with gene depletion and antibody neutralization suggest each chemokine and receptor may have a special position on the stage of orchestrated biological responses. The essential roles of many chemokines and receptors are indicated by prominent changes in spontaneous phenotype of gene depleted animals. However, for a large number of chemokines and receptors, depletion of their genes does not yield an obviously abnormal phenotype. Nevertheless, the mice often exhibit markedly altered responses to pathogen or injurious challenge. Compared to other biomedical research fields, chemokine research is relative young but with astonishing achievements during the past few years. The information contained in this review reflects only the tip of an iceburg whose full identity remains to be explored. It is predictable that the importance of chemokines and receptors will be further appreciated with the enthusiastic participation in the research by scientists from multi-disciplinary backgrounds and the development of new therapeutic agents directed against chemokines or receptors with proven effectiveness in circumventing human diseases.

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