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REVIEW

P. Proost · A. Wuyts · J. Van Damme

The role of chemokines in inflammation

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Abstract Chemokines, together with adhesion molecules, cytokines, and proteases, are essential for the directional migration of leukocytes during normal and inflammatory processes. Interleukin-8 and monocyte chemotactic protein-1 are the best-characterized members of the C-X-C and C-C chemokine subfamilies, respectively. However, more than 20 human chemokines have been identified but are only partially characterized at the biological level. Chemokines are involved in chemotaxis of monocytes, lymphocytes, neutrophils, eosinophils, basophils, natural killer cells, dendritic cells, and endothelial cells. This review describes the chemokine subfamilies, the chemokine producer and target cells, their receptors, signal transduction mechanisms, and the role of chemokines during physiological and pathological conditions. More and more evidence points to a role for chemokines in chemotaxis-related phenomena, such as the expression of adhesion molecules, the secretion of proteinases, inhibition of apoptosis, hematopoiesis, and angiogenesis. Chemokines are also involved in diseases such as cancer (tumor regression and tumor metastasis), autoimmune diseases, and bacterial or viral infection.

Key words Chemotaxis · Interleukin-8 · Leukocyte migration · Chemotactic cytokine

Introduction

The inflammatory response is a complex phenomenon in which a number of cells and molecules are involved. Inflammation is the body's reaction against stress conditions, e.g., shear stress, injury, or cellular contact with foreign material such as viral, bacterial, or plant products. These stress conditions induce the expression of proteins in a number of cell types, which include leukocytes, fibroblasts, endothelial and epithelial cells. The inflammatory response involves leukocyte-endothelial cell interaction and cytokine production and evolves into the migration of particular subsets of leukocytes from the blood vessel to the surrounding tissue and organs. Leukocytes can be selectively attracted to the inflammatory site to defend the host against the invading pathogens. Additionally, lymphocytes patrol continuously for foreign antigen. They migrate from the blood circulation through the tissues, into the lymph vessels and nodes, and back to the blood stream.

P. Proost (✉) · A. Wuyts · J. van Damme
Laboratory of Molecular Immunology,
Rega Institute, K.U. Leuven,
Minderbroedersstraat 10, B-3000 Leuven, Belgium

Cytokines, adhesion molecules, chemokines, and proteases in leukocyte transendothelial migration

The recruitment of leukocytes under normal or inflammatory conditions involves a multistep process [1–4]. In an initial step, leukocytes become attached to the endothelial layer but are still allowed to roll along the venular wall (Fig. 1). Attachment and rolling are promoted by vasodilatation and by the expression of a first family of adhesion molecules (*selectins*) on leukocytes (L-selectin) and endothelial cells (E- and P-selectin). L-selectin is expressed constitutively on the majority of circulating lymphocytes, monocytes, neutrophils, and eosinophils. P-selectin is stored in the Weibel-Palade bodies of endothelial cells and in the alpha granules of platelets. Upon induction with inflammatory factors such as cytokines, thrombin, histamine, or complement fragments, P-selectin is mobilized to the cell surface. E-selectin protein production is rapidly induced in endothelial cells by a variety of stimuli including, lipopolysaccharides (LPS) and cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ). All three selectins are composed of similar extracellular domains, including a lectin domain, an epidermal growth factor (EGF)-like domain, and several short consensus repeats. The extending molecular structure allows the interaction with leukocytes above the

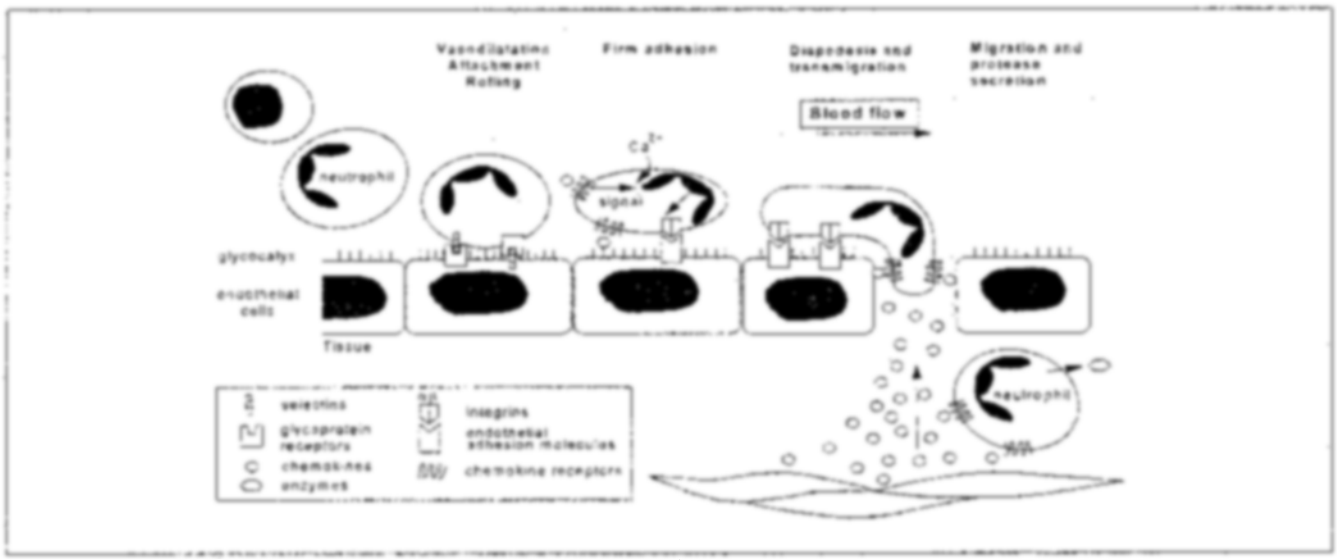

Fig. 1 Schematic representation of the successive steps in leukocyte migration through endothelial layers. Leukocyte migration from the circulation into the peripheral tissue is a stepwise process. The initial leukocyte-endothelial interaction involves weak selectin binding to carbohydrates on glycoprotein receptors. Selectins are constitutively present on the leukocyte (L-selectin) and can be induced on the endothelial cells (E- and P-selectin). When leukocytes are appropriately triggered (e.g., by chemokine-receptor interaction), integrins are activated on the leukocyte and bind to endothelial adhesion molecules which belong to the immunoglobulin superfamily. Finally, leukocytes migrate through the endothelial layer in response to a chemokine gradient and infiltrate the tissues, by degrading the extracellular matrix through the secretion of proteases and glycosidases (Ca^{2+} calcium)

glycocalyx. Leukocyte-endothelial cell adhesion occurs upon interaction of the lectin and EGF-like domains of the selectins with *carbohydrates* on glycoprotein receptors (e.g., glycosylation-dependent cell adhesion molecule-1 and CD34) on the surface of either leukocytes (E- and P-selectin) or endothelial cells (L-selectin). However, if the leukocytes are not further triggered, no strong leukocyte-endothelial cell binding takes place and the leukocyte can still disengage from the vessel wall.

In a second step of extravasation, stimulated leukocytes spread and firmly attach to the endothelial layer through interaction of *integrins* on the leukocyte with adhesion molecules on the endothelial cell [2–5]. A family of low molecular mass *chemo*tactic cyto*kines* or *chemokines*, produced by leukocytes as well as endothelial cells and underlying inflammatory cells, is important to enhance integrin adhesiveness. Chemokines can bind to the endothelial layer and can activate leukocytes through receptors belonging to the *G-protein-linked receptors*. Upon chemokine stimulation of leukocytes, integrin expression on the leukocyte membranes is upregulated, the conformation of the integrins is changed, and the integrins are clustered. Integrins are heterodimeric membrane glycoproteins consisting of an α-chain and a β-chain. The two integrin subfamilies involved in leukocyte-endothelial cell adhesion are characterized by common β-chains. The β_1-integrins (or VLA proteins) are composed of the β-chain CD29 and the α-chains α_1-α_6 (CD49a-CD49f). The β_2-integrins (or leukocyte cell-adhesion molecules) LFA-1, Mac-1, and p150,95 combine the common β_2-chain CD18 with the α-chain CD11a, b, or c, respectively. Different integrins bind to extracellular matrix proteins or to different endothelial *adhesion molecules* which belong to the *immunoglobulin superfamily*. ICAM-1 (intercellular adhesion molecule-1) or VCAM-1 (vascular cell adhesion molecule 1) are such examples. Depending on the stimulus (e.g., cytokines such as IL-1, TNF-α, or IL-4) and on the type of endothelium, different integrin ligands are expressed on the endothelial cells. Migration of certain subsets of leukocytes into tissues thus depends on the type of integrin expressed on the leukocyte and on the interaction with a specific endothelial adhesion molecule, of which the expression depends on the type of endothelium and on the stimulating cytokine. This complex mechanism helps to home the correct leukocyte to a specific site.

In the third step, leukocytes migrate through the endothelial layer into the underlying tissue. Classical chemotactic factors such as complement factor 5a (C5a), leukotriene B_4 (LTB_4), platelet-activating factor (PAF), and bacterial formyl-peptides (e.g., fMLP or formyl-methionyl-leucyl-phenylalanine) are not specific for particular subsets of leukocytes. Recently, a number of chemotactic cytokines, or *chemokines*, have been identified, which selectively attract specific types of leukocytes [6–9]. Structurally, the chemokine family can be divided in two branches, namely α- or C-X-C chemokines and β- or C-C chemokines. The C-X-C chemokines (e.g., IL-8) mainly attract neutrophils, while C-C chemokines (e.g., monocyte chemotactic protein-1 or MCP-1) are chemotactic for a variety of leukocytes. Leukocytes can migrate into the underlying tissue by virtue of chemokine gradients. Activation of leukocytes by chemokines stimulates the secretion of *proteases*, which can degrade the subendothelial extracellular matrix and facilitate the migration of leukocytes [10].

The actual mechanism by which leukocytes migrate through the endothelial layer is poorly studied. Certainly,

leukocyte adhesiveness (integrin-ligand interactions) must be modulated to allow the leukocyte to move. Uropod formation and ICAM-3 redistribution on lymphocytes occur upon stimulation with chemokines [11, 12]. Integrins can form the link between intracellular proteins and actin filaments and extracellular matrix proteins [5, 12]. In vivo, actin distribution in the migrating leukocyte has been shown to be strictly regulated. When a leukocyte starts to penetrate the endothelial layer, most actin is located at the anterior portion of the cell. In leukocytes which have nearly passed the endothelial layer, actin is located at the posterior region [13]. Disruption of the cytoskeleton of endothelial cells enhances endothelial permeability and granulocyte diapedesis [14]. In addition to interendothelial migration, diapedesis also occurs through the endothelial cells. Schubert et al. [15] have reported that in inflamed human skin (using $C5a_{desArg}$, LTB_4, IL-8, or IL-1) all junctions between adjacent endothelial cells remain intact. All migrating granulocytes have been found to cross the endothelial layer in a transcellular instead of an intercellular manner. Neutrophils are surrounded by endothelial plasma membranes and finally are completely engulfed by the endothelial cells without mixing of the cytoplasm of both cell types or cell damage [15]. Essentially the same phenomenon has been observed with lymphocyte migration through high endothelial venules of lymph nodes [16]. Upon stimulation with LTB_4, inter- and transendothelial transport of neutrophils could be detected without leakage of macromolecules from the blood [17, 18]. In contrast to LTB_4, fMLP and the two chemokines IL-8 and NAP-2 (neutrophil-activating protein-2) are able to induce marked endothelial barrier dysfunction, permeable interendothelial junctions, and endothelial cell damage [19–22]. In conclusion, leukocytes mainly migrate through transendothelial transport, although interendothelial diapedesis has also been reported.

Chemokines: structure, function, and regulated production

During the last decade, a complex family of proteins, called chemotactic cytokines or chemokines, with leukocyte-attracting and -activating properties has been identified [6–9]. They differ biologically from classical chemoattractant factors, such as fMLP and C5a, in their specificity for particular leukocyte subtypes. Structurally, chemokines are proteins of low molecular mass (5–15 kilodaltons) characterized by four conserved cysteines forming two disulfide bridges. Most secreted human chemokines consist of 70–80 residues and occur as nonglycosylated peptides. The position of the first two cysteines has been used to divide the chemokine family into two branches, the C-X-C (or α-) and C-C (or β-) chemokines (Fig. 2). The first and the second cysteine residues in chemokines form disulfide bridges with, respectively, the third and fourth cysteine. The C-C chemokine I-309 is the only identified human chemokine with an additional pair of cysteines. Whether this third disulfide bridge has functional implications is currently unknown.

The genes for the C-X-C and C-C chemokines are clustered on chromosome 4 (locus q12-21) and 17 (locus q11-21), respectively [6–9]. So far, all identified C-C chemokine genes and the genes for the C-X-C chemokines PF-4 (platelet factor-4) and NAP-2 have been found to appear in a three-exon/two-intron structure. The genes of the other C-X-C chemokines, i.e., IL-8, MGSA/GRO-α (*m*elanoma growth-*s*timulating *a*ctivity), GRO-β, GRO-γ, and γIP-10 (IFN-γ inducible protein-10), consist of four exons and three introns. Recently, a chemokine which includes only the second and fourth cysteine has been discovered. The protein was termed lymphotactin due to its chemotactic activity for lymphocytes and absence of chemotactic activity for monocytes or neutrophils [23, 24]. The discovery of this chemokine suggests the existence of a third chemokine subfamily, the C or γ-chemokines, with the characteristic of only two of the four cysteines. The gene for lymphotactin is located on human chromosome 1.

At present, 21 human chemokines have been described (Fig. 2). In addition, two murine C-C chemokines with two additional cysteines, C10/MRP-1 (macrophage inflammatory protein-related protein-1) and MRP-2 [25], and a murine C-X-C chemokine, stromal cell-derived factor [26], have been cloned. Thus, the existence of more human chemokines is expected.

Human C-X-C chemokines

The amino acid sequences of C-X-C chemokines show between 20% and 90% sequence similarity. The C-X-C chemokines can be subdivided structurally and functionally into two groups (Fig. 2). A conserved Glu-Leu-Arg- (ELR-) motif just before the first cysteine is found in most C-X-C chemokines, including IL-8, NAP-2, MGSA(GRO-α), GRO-β, GRO-γ, ENA-78 (epithelial neutrophil-activating peptide-78), and GCP-2 (granulocyte chemotactic protein-2). This motif has been proven to be essential for the biological activity of these chemokines [6, 7]. All the ELR-containing chemokines are chemotactic and have activating properties (e.g., degranulation and enhancement of the intracellular calcium concentration $[Ca^{2+}]_i$) for neutrophils if appropriately processed (Table 1). PBP (platelet basic protein) or truncation products thereof, namely CTAPIII (connective tissue activating peptide III) and β-thromboglobulin, have to be cleaved proteolytically at the amino-terminus (NH_2-terminus) into NAP-2 (AELR...) before these proteins become chemotactic for neutrophils. NH_2-terminal truncation of 77-residue IL-8 into the 72-amino acid form enhances the chemotactic activity. For other C-X-C chemokines, the length of the NH_2-terminus seems to be less critical. We could not detect differences in the biological activity of the different NH_2-terminal forms of human CGP-2 [27]. When the glutamic acid (E) of the ELR-motif is removed from these chemokines, they lose their chemotactic and activating properties for neutrophilic granulocytes [6, 7]. Three other C-X-C chem-

Fig. 2 Sequence alignment of human chemokines. Amino acid sequences of human C-X-C, C-C and C chemokines [6, 23, 36–39, 43] are aligned. The four characteristic cysteines and the conserved ELR-motif in most C-X-C chemokines are *underlined*. SCM-1 is an alternative name for lymphotactin [23] (*IL-8* interleukin-8, *NAP-2* neutrophil-activating protein-2, *GRO* melanoma growth-stimulating activity, *ENA-78* epithelial neutrophil-activating peptide-78, *GCP-2* granulocyte chemotactic protein-2, *PF-4* platelet factor-4, *γIP-10* interferon-γ-inducible protein-10, *MIG* monokine induced by interferon-γ, *MCP* monocyte chemotactic protein, *MIP* macrophage inflammatory protein, *HCC-1* hemofiltrate-derived C-C chemokine-1)

okines, PF-4, γIP-10, and MIG (*m*onokine induced by *i*nterferon *g*amma), lack the ELR-sequence and are not chemotactic for neutrophils [6, 7, 28].

The most extensively studied activity of C-X-C chemokines is their chemotactic activity for neutrophils using the Boyden microchamber migration test (Table 1). Although all C-X-C chemokines with the ELR-motif are chemotactic for neutrophils, they differ significantly in specific biological activity. When natural chemokines were compared for activation of neutrophils, IL-8 was the most potent chemokine in terms of chemotaxis and enzyme release [29]. The minimal effective concentrations for IL-8 are 0.1 nM or lower. GCP-2, GRO-α, GRO-γ, ENA-78, and NAP-2 are only active at 10 to 100 times higher concentrations, while the C-X-C chemokines without the ELR-motif are inactive. In addition to chemotaxis and enzyme release, in vitro activities of IL-8 on neutrophils include shape change, respiratory burst, and increase in $[Ca^{2+}]_i$, enhanced expression of adhesion molecules, and increased adherence to endothelial cells, to fibrinogen, and extracellular matrix proteins [6–8]. So far neutrophils seem to be the major target cells for C-X-C chemokines, although IL-8, γIP-10, and MIG are also chemotactic for (subsets of) activated T lymphocytes. IL-8 and γIP-10 were, however, inactive in experiments of T cell chemotaxis through endothelial cell-coated membranes [30]. IL-8 is a weak chemotactic agent for basophils and an inhibitor of the release of leukotrienes and histamine from basophils. In addition, IL-8 has been reported to inhibit IL-4-induced IgE production by B cells without effect on the production of other immunoglobulins [6–8]. PF-4 is characterized by its high affinity for heparin and this explains its ability to promote blood coagulation. In vivo, the chemotactic activity for neutrophils of most ELR C-X-C chemokines has been confirmed in rabbits and/or mice [6, 8]. Finally, ELR C-X-C chemokines are stimulators of angiogenesis, while the three chemokines without ELR-motif are inhibitors of angiogenesis [31].

C-X-C chemokines differ considerably with respect to their inducibility and cellular sources [6, 29]. NAP-2 and PF-4 are only secreted by platelets. IL-8 can be induced on virtually all cells (e.g., leukocytes, fibroblasts, endothelial and epithelial cells, and tumor cells) upon stimulation with a variety of products, including cytokines (e.g., IL-1β, TNF-α), other chemoattractants (e.g., LTB_4, C5a), bacterial (e.g., LPS, fMLP, *Mycobacterium tuberculosis*), viral [e.g., measles virus, double stranded (ds) RNA], and plant [e.g., concanavalin A, phytohemagglutinin (PHA), and phorbol esters] products or other stress factors (e.g., asbestos, elastase, and silica) and upon leukocyte-endothelial adhesion [6]. Although the induction of the three GRO chemokines and γIP-10 is studied less extensively than induction of IL-8, many cell types are able to produce these chemokines after proper stimulation (e.g., IFN-γ for γIP-10). For the recently identified chemokines ENA-78, GCP-2, and MIG, there is little information available.

Table 1 Chemotactic activity of C-C and C-X-C chemokines on different leukocyte subclasses [6–9, 27, 29, 32, 33, 35–38, 43, 80, 81, 102–116] (*NK* natural killer, *IL-8* interleukin-8, *NAP-2* neutrophil-activating protein-2, *GRO* melanoma growth-stimulating activity, *ENA-78* epithelial neutrophil-activating peptide-78, *GCP-2* granulocyte chemotactic protein-2, *PF-4* platelet factor-4, *γIP-10* interferon-γ-inducible protein-10, *MIG* monokine induced by interferon-γ, *MCP* monocyte chemotactic protein, *MIP* macrophage inflammatory protein, *HCC-1* hemofiltrate-derived C-C chemokine-1, *ND* not determined, 2+ strong, + moderate, ± low or questionable, – absent)

C-X-C Chemokines	IL-8	NPA-2	GRO	ENA-78	GCP-2	PF-4	γIP-10	MIG		
Monocytes	–	–	–	–	–	±	+	–		
T lymphocytes	+	ND	ND	ND	ND	ND	+	+		
B lymphocytes	–	ND	ND	ND	ND	ND	ND	ND		
NK cells	–	ND	ND	ND	ND	ND	±	ND		
Dendritic cells	–	ND	ND	ND	ND	ND	–	ND		
Neutrophils	2+	+	+	+	+	±	–	–		
Eosinophils	–	–	–	ND	ND	–	–	ND		
Basophils	+	ND	ND	ND	ND	ND	ND	ND		
C-C Chemokines	**MCP-1**	**MCP-2**	**MCP-3**	**MCP-4**	**Eotaxin**	**RANTES**	**MIP-1α**	**MIP-1β**	**I-309**	**HCC-1**
Monocytes	2+	2+	2+	+	–	+	+	+	+	–
T lymphocytes	2+	2+	2+	+	–	+	+	+	ND	–
B lymphocytes	ND	ND	ND	ND	ND	–	+	–	ND	ND
NK cells	+	+	+	ND	ND	+	+	±	–	ND
Dendritic cells	±	–	2+	ND	ND	ND	ND	ND	ND	ND
Neutrophils	–	–	–	–	–	–	–	–	–	–
Eosinophils	–	+	2+	2+	2+	2+	+	±	ND	–
Basophils	+	+	2+	ND	ND	2+	+	–	ND	ND

ENA-78 was first isolated from epithelial cells but can also be produced by fibroblasts, monocytes, neutrophils, and endothelial cells. MIG [32] and GCP-2 [29] were initially identified from stimulated monocytes and osteosarcoma cells, respectively. IL-8, GRO, and ENA-78 are strongly induced by cytokines such as IL-1β and TNF-α, but their production is inhibited by IFN-γ [33]. In contrast, the non-ELR cytokines γIP-10 and MIG have been identified as IFN-γ-inducible genes [6]. There exists significant variance in the production levels of the individual C-X-C chemokines. We succeeded in purifying relatively high levels of IL-8 and GRO-α (>10 μg/l) from in vitro stimulated cell lines and buffy coats. Other chemokines such as GRO-β, GRO-γ, GCP-2, ENA-78, and γIP-10 are produced in 10 to 100 times lower amounts [29].

Human C-C chemokines

To date, no sequence motif with such pronounced biological implications as the ELR-motif in the C-X-C chemokine family has been identified in the C-C chemokine family. In general, almost all C-C chemokines are chemotactic for monocytes [8] and memory T lymphocytes [30]. Structurally, eotaxin and the monocyte chemotactic proteins MCP-1, MCP-2, MCP-3, and MCP-4 are the most related (Fig. 2) [34–39]. However, the spectrum of target cells, the specific activities, the production levels, and the inducers of these five C-C chemokines are quite different (Table 1). MCP-1, -2, and -3 are the most potent chemokines on mononuclear cells, both monocytes and lymphocytes. MCP-3, MCP-4, and eotaxin, in contrast to MCP-1, are strong chemotactic agents for eosinophils, and MCP-3 is the most potent C-C chemokine on dendritic cells. In general, MCP-3 seems to be the most pluripotent chemokine, acting on multiple cell types, including monocytes, lymphocytes, eosinophils, basophils, natural killer (NK) cells, and dendritic cells. The results from chemotaxis experiments in Boyden microchambers have been confirmed by measuring enhanced $[Ca^{2+}]_i$ in the target cells. MCP-2 is so far the only exception to this rule. We could only detect enhanced $[Ca^{2+}]_i$ if the target cells were treated with about 100 times more natural or synthetic MCP-2 than necessary for a chemotactic response [34, 40, 41].

Two other C-C chemokines, the macrophage inflammatory proteins (MIP), were originally purified as one factor with chemokinetic properties on neutrophils. MIP also induces footpad inflammation in mice [6, 9]. This factor actually consists of two murine proteins, MIP-1α and MIP-1β. Human MIP-1α and MIP-1β are encoded by several non-allelic genes. MIP-1α and MIP-1β consist of about 70% identical amino acids and are the first isolated human C-C chemokines. Their production seems to be regulated more strictly than that of MCP-1. They have been detected in lymphocytes, monocytes, and fibroblasts. Considerable differences in the biological functions of MIP-1α and MIP-1β have been reported (Table 1). MIP-1α is chemotactic for NK cells, suppressor and cytotoxic T cells ($CD8^+$), while MIP-1β mainly attracts helper T cells ($CD4^+$). To date, MIP-1α is the only chemokine for which chemotactic activity on B cells has been reported. MIP-1α has also been described as a stem cell inhibitor, due to the suppression of the proliferation of IL-3-dependent progenitor cells. This effect is prevented by MIP-1β.

RANTES is the only C-C chemokine which has been isolated from platelets and which is constitutively expressed in unstimulated T cells [7–9]. Rheumatoid synovial fibroblasts and tumor cell lines also release this chem-

okine. RANTES is chemotactic for memory T lymphocytes, monocytes, NK cells, basophils, and eosinophils. I-309, a C-C chemokine cloned from a T cell line, contains an extra pair of cysteines forming a third disulfide bridge. I-309 is – in analogy with most other C-C chemokines – chemotactic for monocytes and not for neutrophils. I-309 has also been identified as an anti-apoptotic factor for thymic lymphoma cells [42]. Recently, a C-C chemokine has been isolated from hemofiltrate of patients with chronic renal failure [43]. This hemofiltrate-derived C-C chemokine, HCC-1, has been detected in significantly higher levels in human plasma than any other human chemokine identified to date. The protein is, however, inactive in chemotaxis assays on all tested cells, including monocytes, T cells, neutrophils, and eosinophils.

Chemokine receptors and signal transduction

Chemokines, like many other chemotactic factors, e.g., fMLP, PAF, and C5a, bind to their target cells through seven transmembrane spanning G-protein-linked receptors [44–47]. Recently, two C-X-C and six C-C chemokine receptors (CCR and CXCR) have been cloned and partially characterized. Most receptors are not specific for one chemokine but can be activated by different chemokines, which bind with varying affinities. Chemokine receptors expressed on leukocytes can bind either C-C or C-X-C chemokines. In addition, a seven transmembrane spanning receptor expressed on erythrocytes has been cloned, which can bind chemokines belonging to both subfamilies. This Duffy antigen receptor for chemokines (DARC) does not signal through G-proteins. DARC is the receptor used by the malaria parasite *Plasmodium vivax* for the invasion of human erythrocytes.

Chemokine receptors have an extracellular NH_2-terminus and an intracellular COOH- (carboxy-) terminus. Ligand-associated receptors on leukocytes can be internalized within minutes. The ligands are degraded through the lysosomal pathway and the receptors are re-expressed on the cell surface. The second intracellular receptor loop, together with the COOH-terminus and the third transmembrane domain, are involved in G-protein binding. The COOH-terminal region contains many Ser and Thr residues, which are targets for phosphorylation and desensitization of the receptors [44–46, 48].

C-X-C chemokine receptors

Two related G-protein-coupled C-X-C chemokine receptors, CXCR1 (IL-8-R1 or IL-8-RA) and CXCR2 (IL-2-R2 or IL-8-RB), have been identified. Both receptors are high-affinity receptors for IL-8, but CXCR1 has a somewhat lower affinity (two- to five-fold) for IL-8 than CXCR2. CXCR1 can be recycled quickly (minutes), while CXCR2 is only partially and slowly (hours) recycled [49]. CXCR2 also interacts with other C-X-C chemokines. All tested C-X-C chemokines which contain the ELR-motif in their NH_2-terminal sequence (necessary for chemotactic activity on neutrophils), namely IL-8, GRO-α, ENA-78, and NAP-2, bind to CXCR2 with high affinity. CXCR2 shares 77% of its amino acids with CXCR1. The extracellular NH_2-terminal domains of both receptors, however, show low amino acid homology (24%). This considerable variance in the NH_2-terminal structures of both receptors explains their different binding characteristics to distinct C-X-C chemokines. The NH_2-terminus together with the extracellular loops and the fourth transmembrane domain are important for chemokine interaction with the receptors [45, 47, 50], while the COOH-terminus (residues 317–324) is important for further signalling [51].

Both IL-8 receptors are co-ordinately expressed, predominantly on neutrophils, but also on monocytes and on a subset of NK and T cells, but not on eosinophils or endothelial cells [52, 53]. In addition, low expression of CXCR1, but not of CXCR2, has been detected in platelets [54]. The expression of IL-8 receptors on neutrophils is upregulated by fMLP and LPS. fMLP induces degranulation of neutrophils resulting in receptor expression on the cell membrane, while LPS induces de novo receptor synthesis [55]. LPS-enhanced IL-8 receptor expression is almost completely downregulated by aminopeptidases [56]. Recently, CXCR2 expression has been detected on astrocytes and on microglia [57]. Therefore, IL-8 and other CXCR2-binding C-X-C chemokines may be important for the recruitment of phagocytosing microglia and antigen-presenting astrocytes to the inflammatory site in the central nervous system.

In mice, IL-8 probably does not exist and only one murine IL-8 receptor homologue (CXCRh or IL-8-Rh) has been cloned. CXCRh knock-out mice looked outwardly healthy but had enlarged spleens and lymph nodes due to increased numbers of B cells and immature and mature neutrophils. No neutrophil migration could be detected in vitro or in vivo with two ligands for the murine CXCRh, the murine chemokine MIP-2, and human IL-8 [58].

C-C chemokine receptors

In general, the related protein sequences of C-C chemokine receptors (CCR) differ mainly in their NH_2-terminal part, which might explain the different specificity of the C-C chemokines for particular receptor interactions. An additional factor which may enhance the specificity of C-C chemokines for target cells may be the cellular distribution of the receptors (Table 2). Moreover, most CCR are shared for binding by several C-C chemokines with different affinities [34, 47].

CCR1, also designated the RANTES/MIP-1α receptor or C-C chemokine receptor-1 (C-C CKR-1), was originally isolated from HL60 cells. Similar to that of IL-8, this receptor has properties of the G-protein-linked receptors of the seven transmembrane spanning receptor superfamily. The amino acid sequence is about 30% identical to that of the two IL-8 receptors. CCR1 binds MIP-1α, RANTES and

Table 2 Interaction of C-C chemokines with their receptors on leukocytes

Leukocyte	Receptor	Ligand
Mononuclear	CCR-1	MIP-1α, RANTES, and MCP-3
	CCR-2	MCP-1 and MCP-3
	CCR-4	MIP-1α, RANTES, and MCP-1
	CCR-5	MIP-1α, MIP-1β, and RANTES
Eosinophil	CCR-1	MIP-1α, RANTES, and MCP-3
	CCR-3	Eotaxin, RANTES, and MCP-3
Basophil	CCR-4	MIP-1α, RANTES, and MCP-1

MCP-3, and to a lower extent also MIP-1β and MCP-1, but not the C-X-C chemokines IL-8, GRO-α, and NAP-2 [59–62]. RANTES, MCP-3, and MIP-1α are also most efficient in the induction of enhanced $[Ca^{2+}]_i$ through this receptor. CCR1 is expressed on monocytes, B cells, eosinophils, and neutrophils. No CCR1 could be detected on PHA-activated T cells, although RANTES was identified as a T cell chemotactic factor.

Two other MCP receptors, CCR2A and CCR2B (C-C CKR-2A and C-C CKR-2B or MCP-1RA and MCP-1RB), only differ in their alternatively spliced COOH-terminal tails [63]. They are probably splicing variants of a single gene. CCR2A and CCR2B respond to MCP-1 and MCP-3 in terms of enhanced $[Ca^{2+}]_i$ and inhibition of adenylyl cyclase. MCP-2 showed minor effects at 100 times higher concentrations, and no response was detectable with MIP-1α, MIP-1β, RANTES, and IL-8. CCR2A and CCR2B mRNA are both expressed in monocytes. In contrast to CCR1, no CCR2B mRNA is expressed in neutrophils and eosinophils [59, 64].

A fourth C-C chemokine receptor, CCR3 or C-C CKR-3, most closely related to CCR1, has been detected on human eosinophils and is the receptor for eotaxin, MCP-3, and RANTES. CCR3 does not bind MIP-1α or MIP-1β [59, 65, 66]. CCR4 (C-C CKR-4 or K5-5), which can be stimulated with MIP-1α, RANTES, and MCP-1 but not with IL-8 or MIP-1β, was identified by molecular cloning from a human basophilic cell line (Table 2). Expression of mRNA for CCR4 was detected in basophils, T cells, B cells, monocytes, and platelets. Upon stimulation with IL-5, there was a significant upregulation of CCR4 expression in basophils [54, 67]. In contrast to CCR3, another receptor, CCR5 or C-C CKR-5, is selectively expressed on peripheral blood monocytes. CCR5 is selective for MIP-1α, MIP-1β, and RANTES, but not for MCP-1, MCP-2, or MCP-3 [59, 68].

Duffy antigen receptor for chemokines

DARC is the only identified human receptor which interacts with both C-C and C-X-C chemokines, but not with the recently identified C chemokine lymphotactin. This receptor does not signal through G-proteins or through changes in the $[Ca^{2+}]_i$. DARC binds with high affinity the ELR-C-X-C chemokines IL-8, NAP-2, ENA-78, and GRO-α, and the C-C chemokines RANTES, MCP-1, and MCP-3. Non-ELR-C-X-C chemokines (γIP-10 and PF-4) bind with low affinity, and MIP-1α and MIP-1β do not interact with this receptor. C-C and C-X-C chemokines compete for binding to a shared site. Binding of GRO-α or IL-8 to erythrocytes blocks the binding to and invasion of erythrocytes with the malaria parasite [45, 47, 69]. In addition to erythrocytes, postcapillary venule endothelial cells, but not endothelial cells of arteries, capillaries, or large veins (including umbilical vein), also express DARC [70].

The function of this chemokine receptor is currently not clear. DARC on erythrocytes might act as a sink for circulating chemokines in the blood stream. IL-8 and GRO-α bind to DARC-positive erythrocytes and to a much lesser extent to DARC-negative cells [71]. On endothelial cells, DARC might serve as an active receptor facilitating leukocyte-endothelial cell interaction, or DARC could concentrate chemokines on endothelial cells [72]. In this respect, IL-8 binding to postcapillary venules has been observed in rats, although no IL-8-specific receptors could be detected on endothelial cells and no IL-8 was internalized [52, 72]. DARC on endothelial cells might present the chemokines to their receptors on leukocytes. Also proteoglycans on endothelium could serve as a scaffold to bind chemokines to the endothelium. MIP-1β, which is a $CD8^+$ T cell chemoattractant and which does not interact with DARC, binds to cellular proteoglycans [73]. Both binding to DARC or proteoglycans could prevent the dilution of the chemokines in the blood stream.

Signal transduction through chemokine receptors

Ligand binding to chemokine receptors on the leukocyte membrane results in signal transduction through activation of G-proteins. G-proteins consist of a heterotrimeric complex of the G_α-, G_β-, and G_γ-subunits. Ligand-receptor interaction results in the exchange of bound GDP for GTP on the G_α-subunit. The G_α-subunit dissociates from the $G_{\beta\gamma}$-subunit complex, and GTP-bound G_α-subunits and $G_{\beta\gamma}$-subunits can subsequently activate different enzymes. This can result in enhanced $[Ca^{2+}]_i$, activation of phospholipases, enhanced arachidonic acid concentrations, activation of kinases, cyclic AMP generation, integrin redistribution, and eventually in uropod formation, cytoskeletal rearrangements, and/or chemotaxis. When GTP is hydrolyzed to GDP, G_α-subunits can be recycled and bind to the receptor in a $G_{\alpha\beta\gamma}$-complex.

Most chemokines use *Bordetella pertussis* toxin-sensitive G-proteins in their signal transduction pathway. The signal transduction of C-X-C chemokines through CXCR1 and CXCR2 involves G-proteins which activate phospholipase C (PLC) (Fig. 3). PLC generates two second messengers, inositol triphosphate (IP_3) and diacylglycerol (DAG), from membrane-bound phosphatidylinositol 4,5-bisphosphate. IP_3 diffuses in the cytosol and induces the release of Ca^{2+} from intracellular stores. DAG activates protein kinase C (PKC) [74, 75]. In addition, both IL-8 receptors,

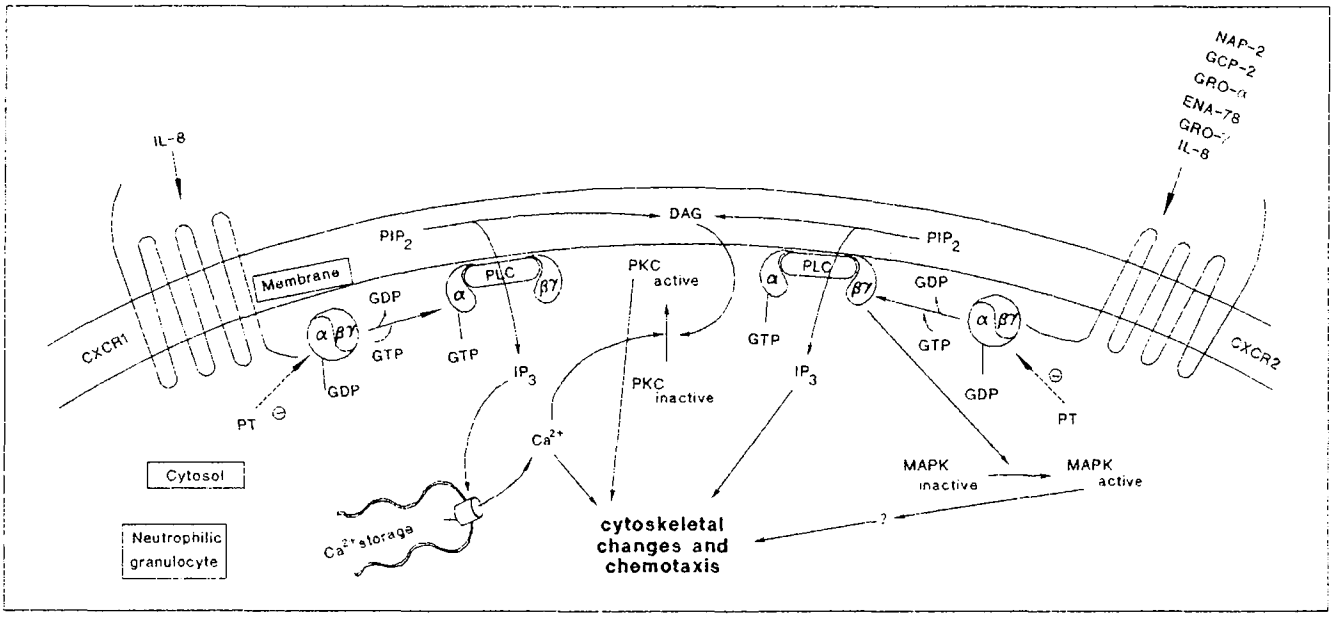

Fig. 3 Signal transduction on neutrophil granulocytes through C-X-C chemokine receptors (CXCR). Schematic presentation of ELR-C-X-C chemokine signal transduction pathways in neutrophils. IL-8 binds with high affinity to both C-X-C chemokine receptors (CXCR1 and CXCR2) while the other ELR-C-X-C chemokines bind only CXCR2 with high affinity. Signal transduction through both seven transmembrane spanning receptors, CXCR1 and CXCR2, involves pertussis toxin (*PT*)-sensitive G-proteins which active *MAPK* (mitogen-activated protein kinase) and phospholipase C (*PLC*). PLC cleaves PIP_2 (phosphatidylinositol 4,5-biphosphate) into two second messengers DAG (*diacylglycerol*) and IP_3 (inositol trisphosphate), resulting in activated *PKC* (protein kinase C) and enhanced intracellular Ca^{2+}. A combination of these phenomena leads to cytoskeletal changes and chemotaxis

in a pertussis toxin-sensitive way, can activate p42/p44 mitogen-activated protein kinases or extracellular signal-regulated kinases [75, 76]. These kinases may activate transcription factors, phospholipase A_2 (PLA_2), and other kinases and reorganize cytoskeletal elements.

IL-8-induced signal transduction pathways in T lymphocytes seem to be partially different from the signalling events in neutrophils [77]. IL-8 seems to work on T lymphocytes mainly through CXCR2, or the shared receptor among all C-X-C chemokines containing the ELR-motif. In T lymphocytes, no rapid rise in $[Ca^{2+}]_i$ is detected. In contrast, Ca^{2+} mobilization is slowly elevated but is long-lasting. In addition to PLC and PKC activity, activation of PLD in a Ca^{2+}- and PKC-dependent way has also been detected. Although stimulation of neutrophils with fMLP resulted in marked PLD activity, no such activity could be detected on IL-8-stimulated neutrophils [77]. Finally, integrin redistribution (ICAM-3) and uropod formation upon chemokine stimulation of lymphocytes are dependent on G-protein signalling through chemokines and on cyclic AMP activation [11].

The signal transduction mechanisms of C-C chemokines on monocytes are partially different from those of the C-X-C chemokines receptors. MCP-1 and MCP-3 stimulation of monocytes results in an enhanced $[Ca^{2+}]_i$ and in activated (phosphorylated) cytosolic PLA_2. The $[Ca^{2+}]_i$ is increased, mainly due to the influx of Ca^{2+} into the cell [40]. This is in contrast to the release of Ca^{2+} from intracellular stores in neutrophils in response to ELR-C-X-C chemokines. Activated cytosolic PLA_2 results in the release of arachidonic acid from phosphatidylcholine and is necessary for monocyte chemotaxis [78]. MCP-2 is to date the only chemokine for which signalling through cholera toxin-sensitive G-proteins has been described on monocytes [40].

It can be concluded that cell-specific expression of chemokine receptors (qualitatively and quantitatively) determines the response of target cells to the respective chemokines. Moreover, one chemokine can activate several receptors (e.g., IL-8) and one receptor can interact with different chemokines (e.g., CXCR2). In addition, signal transduction through one chemokine receptor may differ depending on the cell type (e.g., CXCR2 on neutrophils or lymphocytes) and activation of one receptor may desensitize the signalling of other receptors. The chemokine-receptor interactions are only partially elucidated. Most receptors have only recently been identified and for some chemokines (e.g., MIP-1β) the existence of other specific receptors is expected. In addition, chemokines can bind to extracellular matrix proteins and to a receptor on erythrocytes and endothelial cells. This network of responses, together with the differences in chemokine induction and production, suggests a complex in vivo situation.

Role of chemokines in normal and pathological processes

Not only are chemokines important in acute and chronic inflammation, but they have also been implicated in lym-

phocyte trafficking during T cell development and maturation in germinal centers, coagulation, hematopoiesis, angiogenesis, wound healing, autoimmune disease, allergy, and malignancy. Here, examples are given of normal and pathological conditions in which chemokines have been proven to play a crucial role.

Hematopoiesis

Several chemokines may have a function in blood cell development. The most extensively studied chemokine in this respect is MIP-1α. Stem cell inhibitor appeared to be identical to the C-C chemokine MIP-1α, which inhibits in a reversible manner the cell cycle of hematopoietic progenitor cells. The inhibitory effect of MIP-1α is blocked with MIP-1β [8]. MIP-1α protects multipotent hematopoietic progenitor cells in a chemotherapy model using repeated cycles of cytotoxic hydroxyurea. In addition, MIP-1α mobilizes hematopoietic stem cells from the bone marrow to the blood. A MIP-1α mutant, which, in contrast to natural MIP-1α, does not form multimers in solution, is now being tested in clinical trials to assess its value in chemotherapy and as a mobilizer of hematopoietic stem and progenitor cells [79].

IL-8, PF-4, GRO-β, γIP-10, and MCP-1 (but not GRO-α, GRO-γ, NAP-2, MIP-1β, and RANTES) also suppress the colony formation of myeloid progenitor cells stimulated with granulocyte-macrophage colony-stimulating factor and stem cell factor [8, 80]. A combination of the suppressive chemokines was active at ±1,000-fold lower concentrations than at individual chemokine dosages. A single intravenous or intraperitoneal injection of IL-8 induces a rapid mobilization of neutrophils and hematopoietic stem cells in mice and rabbits [6, 81, 82]. This observation might be useful in peripheral blood-derived stem cell transplantation. Indeed, in in vivo experiments, transplantation of mononuclear cells from IL-8-treated mice into lethally irradiated mice resulted in a threefold higher survival rate than with transplanted mononuclear cells from untreated mice [82].

Angiogenesis

The formation of novel blood vessels is an essential process in several normal and pathological processes, including embryonic development, wound healing, chronic inflammation, and tumor cell growth [83]. During wound repair, angiogenesis is normally rapidly initiated, tightly controlled, and abruptly terminated. Thus, it is interesting that members of the C-X-C chemokine family can be stimulators (IL-8) or inhibitors (PF-4) of angiogenesis [84, 85].

Recently, the presence or absence of the ELR-sequence in the NH_2-terminal region of C-X-C chemokines has been shown to be crucial for the angiogenic or angiostatic activity, respectively [31]. IL-8, GCP-2, GRO-α, and ENA-78, all ELR-C-X-C chemokines, are potent chemotactic cytokines for endothelial cells and are angiogenic proteins in the corneal micropocket model in rabbits. PF-4, γIP-10, and MIG, C-X-C chemokines without the ELR-motif, can inhibit endothelial cell (but not neutrophilic) chemotaxis and rat cornea neovascularization in response to ELR-C-X-C chemokines or basic fibroblast growth factor. Moreover, a mutation of three amino acids in IL-8 (ELR into TVR or DLQ) changes IL-8 into an inhibitor of angiogenesis and a mutation of MIG (KGR into ELR) transforms MIG into an angiogenic factor. The difference between the two C-X-C chemokine subfamilies with respect to angiogenic activity may explain the inhibitory action and important role of interferons in angiogenesis. Production of ELR C-X-C chemokines (IL-8 and ENA-78) is inhibited by IFN-γ, while γIP-10 and MIG are both upregulated by IFN-γ [33].

Tumorigenesis

In tumor biology, chemokines may have a tumor-promoting and/or tumor-regressing effect. Chemokines are constitutively expressed in a variety of tumor cells. Upon induction of tumor cells, levels of chemokine production can be enhanced significantly. We have been able to isolate most of the currently known human chemokines from MG-63 osteosarcoma cells or THP-1 monocytic cells. In fact, many chemokines (e.g., MCP-2, MCP-3, and GCP-2) have originally been isolated from these tumor cell lines [29, 35]. Moreover, in many solid tumors, tumor-associated leukocytes are found, which were probably attracted through tumor cell-derived chemotactic factors [86].

When tumor cells transfected with MCP-1 or RANTES are transplanted into animals, no tumor growth is detected, while the parent cells formed large tumors. T cell function and macrophage migration have been found necessary for the tumor-inhibitory effect of these chemokines [9, 86]. Tumor growth and metastases largely depend on the generation of novel blood vessels. PF-4, γIP-10, and MIG inhibit angiogenesis and may thus inhibit tumor growth. Thus certain C-C and C-X-C chemokines may have inhibitory effects on tumor growth and may be useful in therapy in combination with other inhibitors of angiogenesis such as angiostatin [83].

For metastasis, tumor cells have to find their way to the blood circulation. Leukocytes can be attracted by the chemokines which are constitutively produced by tumor cells. During their migration, activation of leukocytes by chemokines results in the release of proteases, resulting in the degradation of extracellular matrix proteins. In addition, the tumor-associated leukocytes may provide the tumor with additional stimuli (cytokines) for an upregulated chemokine production. Since tumor-associated leukocytes have been found to produce several growth and angiogenic factors (e.g., platelet-derived growth factor, EGF, and angiogenic ELR-C-X-C chemokines), these cells may promote tumor growth and metastasis [86]. Thus, the immune system may provide the tumor cells with the necessary tools to find their way to the circulation through a countercurrent principle, in which the leukocytes actively mi-

grate and generate "channels" for the metastasizing tumor cells [87].

In conclusion, chemokines may provide tumor-promoting and/or tumor-regressing signals, depending on the type and amount of chemokines produced. Chemokines may be important factors for the balance or imbalance between the tumor-promoting and -regressing activities.

Inflammation

Inflammation implies the recruitment of leukocytes. Thus, it is obvious that leukocyte chemotactic and activating proteins play an important role in inflammatory diseases. Since their discovery, chemokines (also designated pro-inflammatory cytokines) have been associated with inflammation. They can be detected in body fluids and on histological sections (both at the protein and mRNA level) in a variety of inflammatory diseases [6, 7, 9]. In addition to the detection of chemokines, more evidence for the role of chemokines in inflammation is derived from two types of neutralization experiments [8]. In experimental collagen-induced arthritis, administration of anti-IL-8 antibodies to the inflammatory joint reduces the inflammation. When anti-IL-8 antibodies are combined with the re-establishment of the blood flow in ischemic lungs, these antibodies are able to lower significantly the reperfusion-induced injury.

Autoimmune diseases

In autoimmune diseases such as multiple sclerosis (MS), arthritis, and psoriasis, different leukocyte subtypes are recruited to the inflammatory site. In psoriatic scales and in the arthritic synovium a variety of chemokines, including MCP-1, IL-8, and GRO, have been identified [6–8]. Chemokines might be responsible for the migration of leukocytes to these inflammatory sites and could locally stimulate leukocytes to release proteases. The latter are able to cleave proteins into autoreactive peptides [88]. In this respect, gelatinase B, an enzyme which can be released from neutrophils and mononuclear cells upon stimulation with chemokines [29, 89, 90], is able to cleave myelin basic protein and to generate encephalitogenic autoantigens [91]. In MS, these autoantigens stimulate the autoreactive T cells, which in turn can produce cytokines such as IFN-γ. IFN-γ can upregulate the production of chemokines, particularly C-C chemokines, which again attract mononuclear cells. Since mainly mononuclear cells are detected in MS lesions, it is not surprising that IFN-γ is a damaging cytokine in this disease. In contrast, in hyperacute experimental allergic encephalomyelitis mainly neutrophils are involved [88]. Here, IFN-γ is beneficial, corresponding to the inhibitory effect of IFN-γ on the production of C-X-C chemokines with chemotactic activity on neutrophils like IL-8.

More direct evidence for the role of chemokines in autoimmune diseases has been found in MIP-1α knock-out mice [92]. In myocarditis, cardiac lesions are primarily induced through an autoimmune mechanism, mediated by cytotoxic T cells. In MIP-1α knock-out mice, 10 days after infection with Coxsackie virus B3, the viral titers are similar to those of control mice. However, knock-out mice do not develop myocarditis. This indicates that the virus is not directly responsible for the disease. MIP-1α probably recruits the early (after 5 days) detectable macrophages and neutrophils, which in turn can process (cleave) self-proteins. The generated peptides are recognized as foreign material by attracted cytotoxic T lymphocytes.

Infectious diseases

Chemokines may play an important role in the recruitment of leukocytes to virally infected sites. Chemokines are produced by a variety of cell types (mononuclear cells, fibroblasts, ...) upon stimulation with virus or dsRNA [6, 34, 93, 94]. When MIP-1α knock-out mice are infected with influenza virus, much higher virus titers and less inflammation (lower mononuclear cell counts) are detectable after a few days than in control mice [92]. Viral clearance in control mice is faster than in MIP-1α knock-outs. Thus, MIP-1α plays an important role in influenza virus-induced pneumonitis, due to its chemotactic effect on mononuclear cells. Recently, C-C chemokines and their receptors have been linked to the infection of $CD4^+$ cells with human immunodeficiency virus (HIV). Three $CD8^+$ T cell products, the C-C chemokines MIP-1α, MIP-1β, and RANTES, but not MCP-1, have been identified as HIV-suppressive factors [95]. A combination of neutralizing monoclonal antibodies against these three chemokines inhibited the HIV-suppressive activity of $CD8^+$ T cells. Seven transmembrane G-protein-coupled receptors, including fusin and the C-C chemokine receptor CCR-5, have been identified as co-receptor (together with CD4) for virus binding and virus-target cell membrane fusion [96–99].

LPS and bacteria have been reported as powerful inducers of chemokines. IL-8 was originally discovered in monocytes induced by LPS. The most extensively studied chemokines, IL-8 and MCP-1, are induced by LPS in leukocytes, chondrocytes, endothelial and smooth muscle cells [6, 7, 34]. Epithelial cells, which are primary targets for bacterial infection, can secrete IL-8 upon infection with a variety of bacteria, but not upon LPS challenge [100]. The production levels of chemokines with bacterial infections may vary depending on the type of infected cells. Moreover, depending on the kind of infection, different chemokines may be produced. In addition, circulating MCP-1, MCP-2, and IL-8 levels are elevated in sepsis patients [101]. MCP-1 and IL-8 levels are increased both during Gram-positive and Gram-negative infection.

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