Annu. Rev. Immunol. 2000. 18:217–242

THE BIOLOGY OF CHEMOKINES AND THEIR RECEPTORS

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Key Words chemokines, inflammation, trafficking, metastasis, angiogenesis

■ **Abstract** During the last five years, the development of bioinformatics and EST databases has been primarily responsible for the identification of many new chemokines and chemokine receptors. The chemokine field has also received considerable attention since chemokine receptors were found to act as co-receptors for HIV infection (1). In addition, chemokines, along with adhesion molecules, are crucial during inflammatory responses for a timely recruitment of specific leukocyte subpopulations to sites of tissue damage. However, chemokines and their receptors are also important in dendritic cell maturation (2), B (3), and T (4) cell development, Th1 and Th2 responses, infections, angiogenesis, and tumor growth as well as metastasis (5). Furthermore, an increase in the number of chemokine/receptor transgenic and knock-out mice has helped to define the functions of chemokines in vivo. In this review we discuss some of the chemokines' biological effects in vivo and in vitro, described in the last few years, and the implications of these findings when considering chemokine receptors as therapeutic targets.

INTRODUCTION

In the last few years, we have witnessed the development of EST (expressed sequence tag) databases and the widespread application of bioinformatics for new gene discovery. As a result, the pace of novel gene discovery has accelerated dramatically. One of the best examples of the impact of these technologies has been in the number of members of the chemokine superfamily identified in this time. The chemokines are ideal molecules to be discovered through bioinformatics because they are small secreted molecules that exhibit very specific cysteine motifs in their amino acid sequence. Most chemokines have four characteristic cysteines, and depending on the motif displayed by the first two cysteines, they have been classified into CXC or alpha, CC or beta, C or gamma, and CX3C or delta chemokine classes. The only exception to the four Cys rule is lymphotactin (6), which has only two Cys residues. Two disulfide bonds are formed between

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the first and third Cys and between the second and fourth. Thus, lymphotactin manages to retain a functional structure with only one disulfide bond. In addition, the CXC or alpha subfamily has been divided into two groups depending on the presence of the ELR motif preceding the first cysteine: the ELR-CXC chemokines and the non-ELR-CXC chemokines.

Chemokine receptors are G-protein coupled, seven-transmembrane receptors. Based on the chemokine class they bind, the receptors have been named CXCR1, 2, 3, 4, and 5 (bind CXC chemokines); CCR1 through CCR9 (bind CC chemokines); XCR1 (binds the C chemokine, Lptn); and CX3CR1 (binds the CX3C chemokine, fractalkine or neurotactin) (Table 1).

Along with the accelerated rate of discovery of chemokines has come the realization that these molecules not only control hemopoietic cell migration, but also are involved in a number of other physiological and pathological processes. Figure 1 summarizes our current understanding of the involvement of chemokine biology in other areas. Also, the characterization of new chemokines has uncovered new roles of these molecules, for example, in lymphoid cell development.

The mouse and human genome/EST projects have generated large sequence databases, which resulted in the identification of most of the members of the chemokine superfamily. When viewed in this light, we can discern certain trends.

TABLE 1 Summary of the known chemokine receptors and some of their known human ligands

Chemokine receptors	Human chemokine ligands
CXCR1	IL-8, GCP-2
CXCR2	IL-8, GCP-2, Gro α, Gro β, Gro γ, ENA-78, PBP
CXCR3	MIG, IP-10, I-TAC
CXCR4	SDF-1/PBSF
CXCR5	BLC/BCA-1
CCR1	MIP-1α, MIP-1β, RANTES, HCC-1, 2, 3, and 4
CCR2	MCP-1, MCP-2, MCP-3, MCP-4
CCR3	eotaxin-1, eotaxin-2, MCP-3
CCR4	TARC, MDC, MIP-1α, RANTES
CCR5	MIP-1α, MIP-1β, RANTES
CCR6	MIP-3α/LARC
CCR7	MIP-3β/ELC, 6Ckine/LC
CCR8	I-309
CCR9	TECK
XCR1	Lymphotactin
CX3CR1	Fractalkine/neurotactin

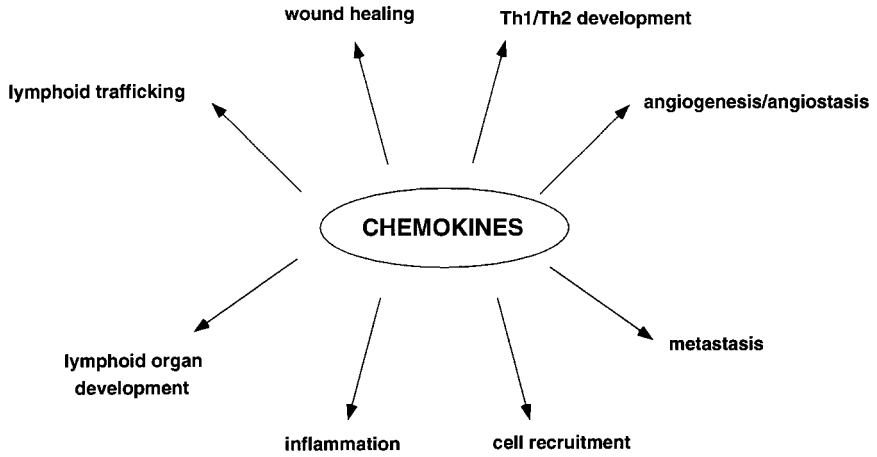

Figure 1 Biological functions of chemokines and chemokine receptors.

For example, among the first ones discovered were those chemokines produced by many cellular sources. Conversely, the last ones found exhibit restricted tissue and cellular specificity. This specificity suggests organ-specific functions, as in the case of TECK described below. This suggests that other chemokines that remain to be discovered will likely exhibit limited tissue distribution and will not be identified until their cellular source is analyzed by EST production.

This chapter does not aim to be a comprehensive review on chemokines; rather, we highlight those areas of chemokine biology with new developments or therapeutic potential.

ROLE OF CHEMOKINES IN ANGIOGENESIS/ ANGIOSTASIS AND METASTASIS

Angiogenesis is a biological process through which blood vessels are generated. Although it is a strictly controlled and transient event during wound healing, angiogenesis is also associated with several chronic inflammatory diseases, such as psoriasis, rheumatoid arthritis (pannus formation), and idiopathic pulmonary fibrosis (7) as well as with tumor growth and metastasis (8), where neovascularization appears to be aberrantly upregulated. Solid tumor growth requires the presence of neovascularization to guarantee an adequate supply of oxygen and nutrients (9). Strieter (10) and others have proposed that an imbalance between angiogenic and angiostatic factors may be responsible for tumor growth and the development or progress of some chronic inflammatory diseases.

It is well established that ELR-CXC chemokines are potent angiogenic factors, able to stimulate endothelial cell chemotaxis, while most non-ELR-CXC che-

mokines are strong angiostatic factors, which inhibit the endothelial cell chemotaxis induced by ELR-CXC chemokines (10). In fact, CXC chemokines act as angiogenic or angiostatic factors depending solely on the presence of the ELR motif (10). ELR-CXC chemokines bind to CXCR2 and few to CXCR1, while non-ELR-CXC chemokines bind to CXCR3, CXCR4, and CXCR5 (Table 1).

Several examples of diseases in which the balance between angiogenic and angiostatic chemokines is altered appear in the literature. For example, Keane et al (7) demonstrated that lung tissues from IPF (idiopathic pulmonary fibrosis) patients constitutively express more IL-8 and less IP-10 than those from healthy individuals. This suggests that a net angiogenic balance of produced factors may be established in IPF patients, which causes fibroplasia and deposition of extracellular matrix, leading to progressive fibrosis and loss of lung function.

Similar observations (high ELR-CXC chemokines vs. low non-ELR-CXC chemokines) have been described for other inflammatory diseases such as chronic pancreatitis, inflammatory bowel disease (11), and psoriasis (12). In the latter case, high levels of IL-8 and low levels of thrombospondin-1 (an angiogenesis inhibitor) produced by psoriatic keratinocytes directly correlated with their angiogenic capacity, and moreover, correlated with the overexpression of its receptor, CXCR2, but not CXCR1 (13). This suggests a tight relationship between ELR-CXC chemokine expression and its receptor, CXCR2, in angiogenesis.

Interestingly, CXCR2 shares a high degree of homology with a G-protein-coupled receptor (ORF74) encoded by the Kaposi's sarcoma–associated herpesvirus-8 (KSHV/HHV8) (14). Bais et al (14) have shown that conditioned media from cells stably transfected with KSHV-GPCR stimulate the growth of human umbilical vein endothelial cells (HUVEC), and they have also suggested that VEGF (vascular endothelial growth factor) might mediate this response. These results are in accordance with earlier studies done by Arvanitakis and collaborators (15), in which they show that this constitutively activated (agonist-independent) KSHV-GPCR signals through the phosphoinositide-inositoltrisphosphate-protein kinase C pathway. Thus, PKC (protein kinase C) stimulates the transcription of genes with promoters containing AP-1 sites, such as angiogenic factors (e.g. IL-8 and VEGF) (16, 17). In summary, this KSHV-GPCR with high CXCR2 sequence identity is promoting endothelial cell growth and angiogenesis. Therefore, it is possible that CXCR2 mediates angiogenesis in a similar fashion: in a controlled manner during normal wound repair and an abnormal upregulated mode during tumorigenesis.

METASTASIS

Tumor development and progression depend heavily on the presence of angiogenic factors. This group of factors includes chemokines as well as growth factors such as VEGF, FGF (fibroblast growth factor), EGF (epidermal growth factor), PDGF (platelet-derived endothelial growth factor), angiogenin, HGF/SF

(hepatocyte growth factor/scatter factor), and many others not discussed in this review but having equal importance in tumor growth (for a review, see 18).

Some of these angiogenic factors, i.e. the chemokines, display a pattern of expression that appears to be imbalanced during tumor development. Luan et al (19) have described an abnormally increased expression of MGSA/GRO (melanoma growth stimulatory activity/growth-related proteins) and decreased levels of IP-10 in melanoma lesions. Similar results were reported by Arenberg et al (8) in non–small cell lung cancer (NSCLC). Interestingly, two subtypes of NSCLC, adenocarcinoma and squamous cell carcinoma, behave very differently, and this behavior correlates with a different chemokine expression pattern. Squamous cell carcinomas show higher levels of IP-10, have lesser metastatic potential, greater patient survival, and less vascularization than adenocarcinomas, which are associated with a worse prognosis. These data support the model established by Strieter et al (10), in which a shift in the balance of ELR vs. non-ELR-CXC chemokine expression determines whether a tumor grows and metastasizes or regresses.

Besides the role of chemokines and their receptors in angiogenesis, they also seem to be involved in the process of tumor cell migration, invasion, and metastasis. It is known that certain tumors exhibit certain patterns of metastasis (or invasion) to certain organs; in other words, tumor cells do not migrate randomly. One explanation for this phenomenon is that this specific migration of tumor cells may be determined by the chemokine receptors they express and by the chemokines expressed in the target organs. There is some evidence supporting this hypothesis. Youngs et al (20) have reported that different breast carcinoma cell lines respond differentially to distinct chemokines. Indeed, some of them were unresponsive to the chemokines tested, indicating that tumor cells are not uniform in their ability to migrate in response to chemokines. Kleeff et al (21) have shown that MIP-3α and its receptor CCR6 were expressed by all pancreatic cancer cell lines tested. However, it may be too simplistic to envision that chemokines alone determine the site/s where metastasis develop. Other molecules, such as adhesion molecules (integrin, cadherins), proteases, angiogenic factors, etc, may also be involved in the metastatic fate of tumor cells. Although the involvement of these other molecules in metastasis is beyond the scope of this review (for a review, see 22), an example for this process is given. High levels of the β2 integrin CD11b/CD18 have been detected on an adherent T lymphoma cell line that had high metastatic potential in the kidney. This cell line was very responsive to the chemokines RANTES and MCP-1, produced by a normal kidney cell line. In contrast, the nonadherent parental cell line did not migrate in response to these chemokines, even though both cell lines were able to bind to them. Interestingly, the nonadherent cell line expressed lower levels of CD11b/CD18, which explains its inability to migrate and metastasize in response to RANTES and MCP-1 (23). This suggests that while locally produced chemokines (in this case, by normal kidney cells) may guide these metastatic tumor cells preferentially to the kidney, adhesion molecules expressed by these tumor cells also contribute to their final homing site.

In conclusion, these results indicate that not all tumor cells respond equally to chemokines, and they also suggest that chemokines and chemokine receptors work in a coordinated fashion with adhesion molecules to determine the ability of tumor cells to invade and colonize other tissues.

ANGIOSTASIS

Angiostasis is another potential antitumor therapeutic effect of chemokines. The expression of most non-ELR-CXC chemokines (IP-10, MIG, I-TAC, PF4) (24–27) and the receptor they bind (CXCR3) (28) are induced by IFN-γ. The angiostatic activity of these molecules seems to be associated with binding to CXCR3. Mouse 6Ckine/SLC (29, 30), a CC chemokine that can bind mouse CXCR3, is also angiostatic (28). However, the mechanism of the angiostatic phenomenon is not known. Luster et al (31) have shown that only IP-10 and PF-4 binding inhibited endothelial cell proliferation in a calcium flux–independent fashion and required the presence of a specific proteoglycan, HSPG, on the surface of the endothelial cells. Whether the HSPG or the CXCR3 is the receptor responsible for chemokine-induced angiostasis is not clear and will require further study.

How Do Cytokines Regulate the Angiostatic/Angiogenic Balance?

Several cytokines affect chemokine expression (Figure 2). For example, IL-12 and IL-18, cytokines that induce IFN-γ production, synergistically induce tumor regression by inhibiting angiogenesis (32). Moreover, IFN-γ is known to be angiostatic, not only because it induces the expression of non-ELR-CXC chemokines, but also because it suppresses the expression of angiogenic CXC chemokines (33, 34). In addition, IFNs are known to inhibit wound healing (35, 36), probably due to their inhibitory effects on endothelial cells (37).

Another important cytokine that can affect angiogenesis is IL-10. This cytokine downregulates the expression of MHC II on antigen-presenting cells, which results in the inhibition of proinflammatory cytokine production, such as IFN-γ by Th1 cells (38–40). Hence, IL-10 may induce angiogenesis by suppressing IFN-γ production by T cells and, indirectly, the expression of angiostatic CXC chemokines (41). However, there is evidence that IL-10 may suppress tumor growth by inhibiting angiogenesis. Huang et al (42) have shown that IL-10 blocks macrophage-derived angiogenic factors (e.g. VEGF) and, therefore, tumor growth and metastasis.

In summary, an understanding of how the cytokine network regulates this delicate balance of angiostatic and angiogenic chemokines is a promising approach for the control of chronic inflammatory diseases and neoplasias.

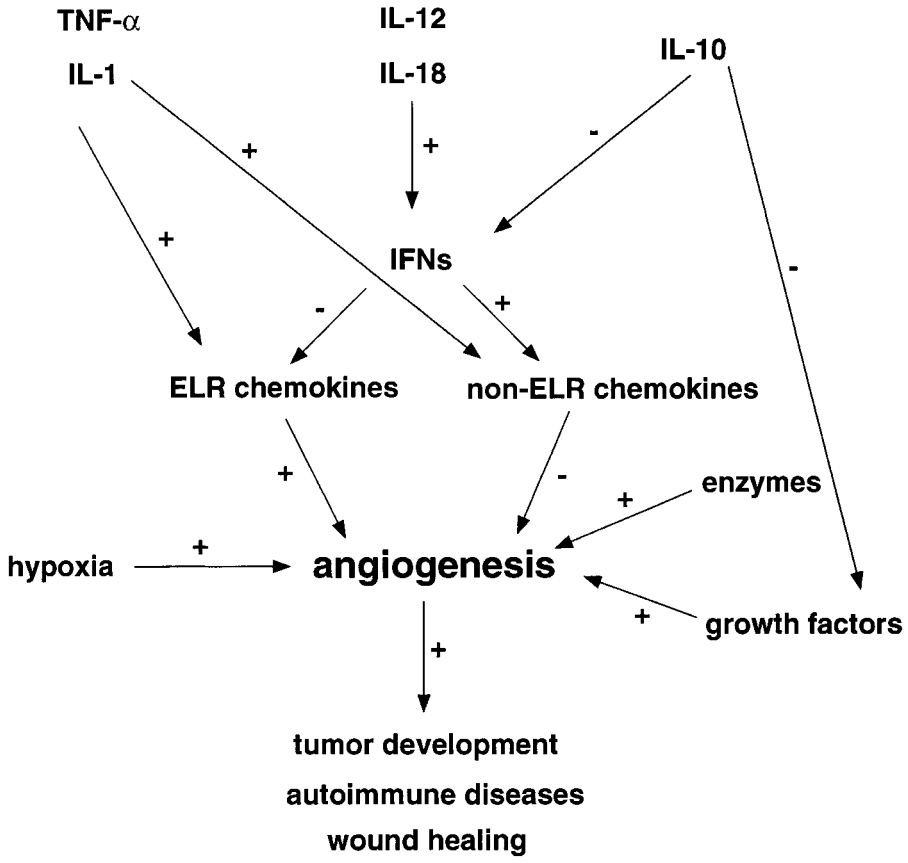

Figure 2 Biological processes and molecules involved in the regulation of angiogenesis.

CHEMOKINES AS THERAPEUTIC AGENTS

Chemokines are likely to be primarily responsible for the cell infiltration observed in many disease states. The presence of proinflammatory chemokines may not be beneficial in a chronic inflammatory disease, but it is desirable in diseases where the immune response needs to be promoted, (e.g. cancer). In theory, any chemokine capable of inducing the migration of T, NK cells, dendritic cells, and/or macrophages could promote the regression or even eradication of a tumor mass by boosting the immune response against the tumor. Therefore, several chemokines are now being studied for their potential use as adjuvants in antitumor immune responses. Recent findings have demonstrated that IP-10, MIG, and Lptn have antitumor activity, as well as MCP-1, MCP-3, TCA-3 and others (see below, Antitumor Activity).

Conversely, a chronic deleterious immune response can be reduced by interfering with the proinflammatory actions of chemokines. Based on this idea, three types of antagonists have received attention: (*a*) small molecule inhibitors of chemokine receptors, (*b*) modified chemokines or N-terminal peptides, and (*c*) neutralizing monoclonal antibodies against chemokines or their receptors (see below, Chemokines in Infectious and Inflammatory Diseases).

AntiTumor Activity: Chemokines as Agonists

In a mouse syngeneic tumor model, Lptn (lymphotactin) has shown antitumor activity only when combined with IL-2 (43). The most likely explanation for this effect is that Lptn induces T and NK cell infiltration (44) to the tumor site, while IL-2 expands the T cell clones upon TCR activation, enhancing a specific immune response. Similar results were obtained by Emtage and collaborators combining Lptn with IL-2 or IL-12 delivered using adenoviral vectors (45). These methods attempt to increase the probability of encounter between T lymphocytes and malignant cells to induce a specific antitumor response.

Another approach using chemokines in cancer immunotherapy is DC (dendritic cell)–based vaccines, which favor DC antigen presentation and induce Ag-specific CTL responses. For example, Cao et al (46) transduced DC with an adenovirus expressing Lptn and then pulsed the cells with tumor peptides. The modified DC were more effective than uninfected pulsed peptide-DC in reducing metastasis in the 3LL tumor model. These results illustrate the potential use of chemokines as antitumor agents.

In addition to Lptn, other chemokines display antitumor activities. IP-10 and MIG are potent chemoattractants for Th1 cells and induce tumor infiltration with $CD8^+$ lymphocytes. Several laboratories have demonstrated that IP-10 and MIG are responsible, at least in part, for the antitumor effect of IL-12, mediated through IFN-γ (47, 48). Either expression or inoculation of these chemokines or cytokines intratumorally results in tumor regression, associated with extensive vascular damage and necrosis (49–51). Evidently, both the inhibition of angiogenesis and the increased T cell recruitment (52, 31) are a result of the concerted actions of IP-10 and MIG through IL-12, IFN-γ, IL-18 (32), and possibly other factors yet to be determined.

Other examples of antitumor activity by chemokine gene transfer are MCP-3 (53), MIP-1α (54), MCP-1 (55), and TCA-3 (56). In most cases, augmented leukocyte infiltration occurred in the perivascular areas, peritumoral tissue, or within the tumor that led to tumor necrosis.

Various approaches have been used to deliver chemokines in vivo. Some examples, chemokine-transfected tumors (54) or dendritic cells (46), protein injection, and adenoviral vectors, have been mentioned here. Although gene transfer technology is still in its early stages, it has large therapeutic potential, particularly for chemokine delivery. We conclude that inducing chemokine expression in tumors

and inhibiting it in chronic inflammatory diseases may restore the normal cytokine and chemokine balance and reverse the disease process.

Chemokines in Infectious and Inflammatory Diseases

Chronic inflammatory diseases are characterized by the presence of cell infiltrates, and chemokines are likely to be involved in this phenomenon. The most common way to resolve, or at least ameliorate, this type of disease is to decrease the inflammatory response. Traditionally, this has been accomplished by administering corticosteroids, cyclosporin A, and similar drugs. But due to the success of small molecule inhibitors of GPCRs (G protein–coupled receptors) in the treatment of various diseases, and the fact that chemokine receptors are GPCRs expressed on hematopoietic cells, the pharmaceutical and biotechnology industries have demonstrated particular interest in the production of small-molecule inhibitors of chemokine receptors.

In view of the critical role of CCR5 and CXCR4 in HIV infection (1), the search for and development of antagonists against these two chemokine receptors have been the focus of interest of many laboratories. A successful example of antagonists is NSC 651016, a distamycin analog that inhibits HIV-1 replication by downregulating CCR5 and CXCR4 expression (57). Unfortunately, some HIV strains (HIV-2) appear to also use other chemokine receptors as co-receptors for cell entry, such as CCR2b, CCR3, GPR15/BOB (58), US28 (59), and others. Still, the most relevant co-receptor in HIV infection seems to be CCR5, since individuals with defective CCR5 alleles exhibit resistance to HIV-1 infection (60–62).

However, the discovery and development of pharmacological antagonists is a long and expensive process. For this reason, other avenues are being explored. For example, modified chemokines and N-terminal peptides can be engineered to allow them to retain binding specificity and affinity to a receptor while blocking it. Several examples have been described in the literature. Plater-Zyberk et al (63) have shown reduced incidence of arthritis in DBA/1 mice treated with the modified chemokine MetRANTES. A similar antagonist, (AOP)-RANTES (amino oxypentane), inhibits HIV-1 infectivity in macrophages and lymphocytes (64). However, the success of modified chemokines or N-terminal peptides as antagonists depends mostly on their capacity to fully occupy the chemokine receptor/s at nanomolar concentrations, competing with the natural ligand/s binding and thus blocking signaling. One of the advantages of using a modified ligand is that most of the receptors used by that ligand can be blocked or partially blocked by a single antagonist (65).

Finally, a third type of antagonist is monoclonal antibodies against chemokines or their receptors. Eosinophils and Th2 lymphocytes are main players in allergic responses. Both cell types express CCR3 (66, 67) and respond through this receptor to several chemokines (RANTES, eotaxin, MCP-4, MCP-3, etc), which makes it a good target for development of antagonists. Heath et al (68) have made a

monoclonal antibody against CCR3 that blocked chemotaxis and calcium flux induced by all CCR3 ligands. Furthermore, monoclonal antibodies have been proven to work successfully as antagonists in vivo, for example, the anti-TNF-α antibody for the treatment of rheumatoid arthritis (69, 70). This effect may be due, at least in part, to the inhibition of chemokine production brought about by the neutralization of excess TNF-α in the joints of these patients. In sum, all these types of antagonists are promising candidates to block inflammation and/or HIV infection.

CHEMOKINES IN ORGANOGENESIS AND LYMPHOCYTE TRAFFICKING

The proinflammatory activities of chemokines during immune responses have been extensively described in the literature (71). However, in recent years we have learned that chemokines are also involved in noninflammatory functions such as the regulation of lymphocyte trafficking, T and B cell development, and particularly cell compartmentalization within lymphoid tissues (T cell vs. B cell areas).

The redundancy of chemokine expression plus the promiscuity of ligand-receptor binding have made it very difficult to understand how the cell migration process works in vivo. Nevertheless, recent findings suggest that chemokine/receptor expression changes in cells during development and between organs (Figure 3), as do the chemotactic responses.

THYMUS

Various chemokines are expressed in the thymus at significant levels: MDC, TARC, 6Ckine/SLC/TCA-4, TECK, SDF-1, and MIP-3β/ELC. Some thymus-expressed chemokines attract mature lymphocytes. For example, MDC (72) attracts activated T cells among other cells (73); TARC attracts peripheral blood T cells (74); TCA-4/6Ckine attracts mature T cells (75). Therefore, this group of chemokines may coordinate the trafficking of mature T cells into the thymus. However, chemokines such as TECK, MIP-3β, and SDF-1 are also able to attract immature T cells and thymocyte subsets with varying efficacy (76). Thus, the specific localization of thymocyte subsets within the thymus (cortex or medulla) may possibly be explained by the differential chemotactic response of these subsets.

Mouse TECK is expressed by thymic dendritic cells and induces the migration of thymocytes, but not mature peripheral T cells (4). Recently, GPR9–6/CCR9, a thymus-expressed GPCR, has been reported to be the receptor for TECK (77) and was specifically detected in immature and mature thymocytes. Based on these

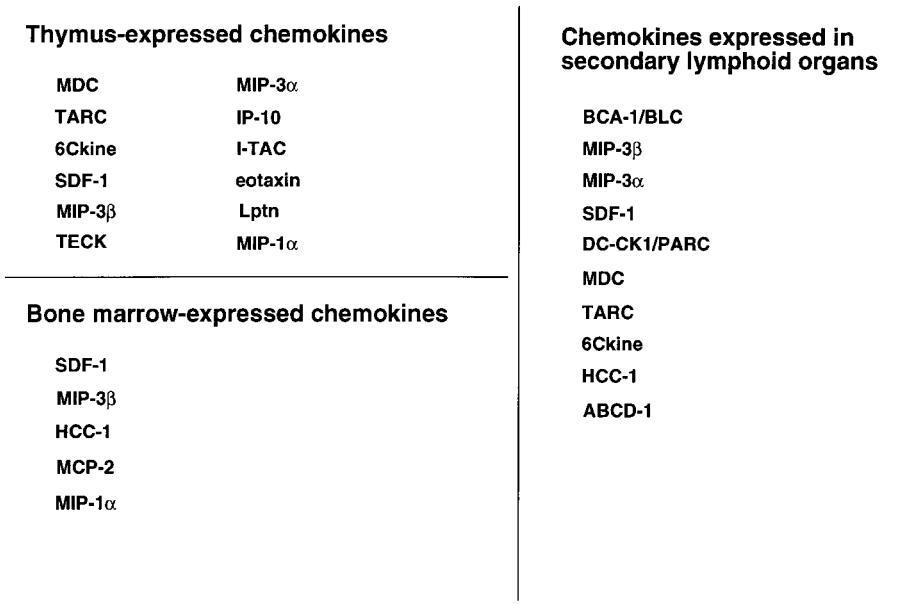

Figure 3 Chemokine expression in lymphoid organs.

data, TECK could attract T cell progenitors from bone marrow to fetal thymus and retain them until T cell development is completed. Probably, once T cells are ready to move to the periphery, they may lose GPR9–6 expression and be able to leave the thymus microenvironment. It is possible that this receptor may be downregulated in peripheral T lymphocytes, since Vicari et al (4) did not detect any chemotactic response with these cells, nor did Wilkinson et al (78). In contrast, there is evidence that TECK may not be responsible for the migration of T cell progenitors to the thymus, since Wilkinson et al (78) have shown that antibodies to TECK did not prevent thymus recolonization by T cell precursors. GPR9–6-deficient mice may help resolve this paradox.

SDF-1 and MIP-3β are also chemoattractants for thymocytes. Kim et al (76) have done an extensive characterization of the chemotactic responses of thymocyte subsets to these two chemokines. Thymocytes can be divided into four subpopulations based on their expression of CD4 and CD8 that comprise the immature double negative (DN) $CD4^-$ $CD8^-$, and double positive (DP) $CD4^+$ $CD8^+$ subsets and the mature $CD4^+$ and $CD8^+$ single positive cells (SP). Interestingly, immature DN and DP thymocytes are more responsive to SDF-1 and are located in the thymic cortex, while mature $CD4^+$ SP and $CD8^+$ SP are more responsive to MIP-3β and are located in the medulla, from where mature T cells migrate to the peripheral blood. These results suggest that chemokines may control the compartmentalization seen within lymphoid organs and coordinate, along with other molecules, T cell development.

It is very likely that chemokines will be found to regulate intrathymic T cell migration in a very precise manner. As developing T cells achieve specific stages of development (79), they may change their chemokine receptor expression and become responsive to other chemokines that will induce their migration to new intrathymic locations where their subsequent development may proceed. These observations, however, raise the question of whether chemokines merely control intrathymic cell migration or also have direct differentiation effects on the developing thymocytes.

BONE MARROW

SDF-1 is a chemoattractant for T cells, B cells, and megakaryocytes (80) that selectively binds to CXCR4. SDF-1 is a growth factor for progenitor B cells, and chemotactic for human pre- and pro-B cell lines, as well as mature B cells (81, 82). Bone marrow (BM) stromal cells produce SDF-1, which attracts B cell progenitors and places them in contact with the stromal cells. These cells release growth and differentiation factors that are necessary for B cell maturation (81). Also, SDF-1 induces bone marrow colonization by hematopoietic precursor cells ($CD34^+$ cells) during embryogenesis (83). These data suggest that SDF-1 and CXCR4 expression are essential for B cell development and maturation in the BM. This has been confirmed by analysis of SDF-1- and CXCR4-deficient mice, which show defects in the hematopoietic, nervous, and vascular systems (84–86). Ma et al (87) and Kawabata et al (88) have reported the phenotype of the CXCR4-deficient mouse. In these mice, B cell precursors are decreased in fetal liver and BM and abnormally increased in blood. Granulocytes are also decreased in BM and elevated, but immature, in blood. Evidently, B cell and granulocytic precursors are released prematurely into the periphery. Although T cells express CXCR4, their development does not seem to be impaired in the CXCR4-deficient mice. Interestingly, these mice show normal T and B cell localization in secondary lymphoid organs. In summary, CXCR4 may regulate B lymphopoiesis and myelopoiesis by retaining the precursors within the fetal liver and BM microenvironment.

MIP-3β is also expressed by bone marrow stromal cells, but only upon LPS (lipopolysaccharide) stimulation. It specifically attracts macrophage progenitors (76) and may increase the number of macrophage progenitors in the BM during inflammatory responses. In this way, more macrophages are generated and exported to the blood during inflammation.

Other chemokines expressed in the BM are HCC-1 (89), MCP-2 (90), and MIP-1α (91). However, the B cell–specific chemoattractant BCA-1/BLC is not expressed in BM (92). The role that each chemokine plays in the BM microenvironment is still under investigation. Nevertheless, some chemokines have shown inhibitory effects on the proliferation of hematopoietic progenitors. Some

examples are MPIF-1, MPIF-2 (93), MIP-1α (94), PF4, and IL-8 (95). Some of these antiproliferative chemokines may be useful therapeutically by preventing cellular damage during anticancer therapies such as chemotherapy or radiation.

SECONDARY LYMPHOID ORGANS

B Cells

The B cell homing chemokine BLC/BCA-1 (96, 92) is expressed in follicles in the spleen, Peyer's patches, and lymph nodes, specifically in FDC (follicular dendritic cells). Its receptor, BLR-1/CXCR5 (97) is mainly expressed on B cells, Burkitt's lymphoma cells, and to a lesser extent, in T cells (3) and monocytes (98). Forster et al (97) demonstrated that BLR-1/CXCR5 is required for B cell migration into splenic and Peyer's patch follicles and for germinal center formation, but not for migration into lymph node follicles. This correlates with a report by Gunn et al (96) who did not detect BLC expression in lymph node follicles. Evidently, other B cell chemoattractants may be responsible for B cell migration into lymph node follicles. One candidate is MIP-3β, which is expressed in lymph nodes and induces B, T, and dendritic cell chemotaxis (76, 99, 100). Interestingly, MIP-3β attracts these cell populations to lymph nodes that are involved in the antigen presentation process, assisting in the initiation of the immune response. Another probable candidate responsible for the B cell migration into lymph node follicles is MIP-3α, which also attracts B cells (101).

Another B cell chemoattractant expressed in secondary lymphoid organs is SDF-1. Bleul et al (82) showed that naive and memory B cells are responsive to SDF-1; however, germinal center B cells are not. These cells are responsive to BCA-1, which retains them within the germinal center to undergo somatic hypermutation and affinity maturation. These data correlate very well with chemokine receptor expression, since only naive and resting B cells express CXCR5 (BCA-1/BLC binds to CXCR5). Once B cells have been activated, the cells surrounding GC (germinal center/s) express SDF-1 (SDF-1 binds to CXCR4), which probably attracts them out of the GC. Although B cells express CXCR4 at all stages, GC B cells are not responsive to SDF-1α. This could be due to the downregulated surface expression of CXCR4 on GC B cells being much slower than on naive or memory B cells, when incubated with SDF-1. In addition, when GC cells are differentiated in vitro into memory B cells, they increase L-selectin, ICAM-1, LFA-3, and B7.1/CD80 expression as well as responsiveness to SDF-1α (82). This indicates that other molecules, such as adhesion molecules, can also be responsible for changes in chemokine responsiveness of cells.

T Cells

SLC/6Ckine/Exodus-2 (30, 29, 102) is expressed in HEV (high endothelial venules) and in T cell areas in the spleen, Peyer's patches, and lymph nodes, and the

marginal zone of follicles. Indeed, Willimann et al (103) demonstrated that the cells expressing SLC/6Ckine in human lymph nodes were interdigitating dendritic cells. Although SLC/6Ckine is expressed in other nonlymphoid organs, Gunn et al showed that this is due to its expression on lymphatic endothelium (104). Probably, the role of SLC/6Ckine on lymphatic endothelium is to recruit lymphocytes from tissues to draining lymphatics.

SLC/6Ckine attracts naive T cells (104), dendritic cells (100), and less efficiently, B cells (104). In addition, it induces firm adhesion of naive T cells via β2 integrin binding to ICAM-1 (104). Moreover, Nakano et al (105) have described a T cell–homing defect in plt mice (*p*aucity of *l*ymph node *T* cell) that is related to a gene localized on mouse chromosome 4, where SLC/6Ckine gene maps. Recently, Gunn et al (106) have reported that these mice do not express SLC/6Ckine mRNA, though the sequence of SLC/6Ckine introns and exons is normal. In addition, DCs do not accumulate in the T cell zones of lymph nodes and spleen in the plt mice, which correlates with the DC-chemoattractant ability of SLC/6Ckine described by Kellerman et al (100). These data indicate that SLC/6Ckine mediates the homing of naive T lymphocytes and dendritic cells to secondary lymphoid organs. Interestingly, DC-CK1/PARC also attracts naive T lymphocytes. It is expressed by dendritic cells of lymph node–germinal centers and in T cell areas of secondary lymphoid organs (107, 108). One possibility is that SLC/6Ckine directs the migration of naive T cells to lymph nodes through HEV, and then DC-CK1/PARC guides them to the germinal centers. DC-CK-1/PARC is expressed by a specific subpopulation of human DCs (107) located in close contact with T cells in germinal centers (in human tonsils, spleen, and lymph nodes). However, this human DC subset appears to be involved in maintaining the activation state of GC memory T cells and promoting T-B cell interaction (109) rather than activating naive T cells, since no naive T cells could be detected in the GCs (109). In fact, it is more likely that MDC, TARC, or MIP-3α perform this function. MDC is expressed by monocyte-derived-DC and lymph node-DCs (Langerhans cells) (72, 110) and attracts activated T lymphocytes. TARC is also produced by monocyte-derived DCs and attracts activated T cells (111). In fact, it may be the most DC-specific chemokine. MIP-3α/LARC is expressed in lymph nodes (112, 113) and attracts B cells, activated T cells (114), and $CD34^+$-derived DCs (115).

In summary, most of the chemokines previously mentioned attract T, B, and dendritic cells, cells that are involved in the antigen presentation process. This suggests that the seeming redundancy of chemokine expression in lymphoid organs may serve the purpose of attracting different cell subsets into different microenvironments and, consequently, may regulate the antigen presentation process. In addition, this redundancy can also be explained by the fact that chemokines can work sequentially, guiding each cell subpopulation to a specific site (116). Further investigation will be needed to clarify the individual role of each of these chemokines in lymphocyte trafficking and antigen presentation.

HOMEOSTATIC VERSUS INFLAMMATORY CHEMOKINES

When discussing the function of chemokines, it is possible to make a distinction between those whose expression suggests more of a homeostatic function than a regulatory function in inflammation. Many chemokines show an expression pattern that strongly suggests a role in inflammation. They are typically induced in either monocytes or macrophages or in epithelial, endothelial, or fibroblastic cells by proinflammatory cytokines (IL-1, TNF-α, or IFN-γ) or stimuli (LPS). This is in fact the most common perceived role for chemokines, a proinflammatory function, frequently associated with a Th1 cytokine expression profile *(*IFN-γ, IL-2, IL-12) and thus with a Th1 cell infiltrate at the inflammation site. However, not all chemokines fit this pattern. For example, other chemokines [e.g. C10 (117), DC-CK1/AMAC-1/PARC (118)] are specifically induced by Th2 cytokines (IL-4, IL-10, IL-13) in monocytes or other cells. We recently reported that a new member of the HCC subfamily of chemokines, HCC-4 (119), is induced by IL-10 in monocytes (IL-10 is generally considered an anti-inflammatory cytokine). The latter observations raise the possibility that the production of certain chemokines will be associated with Th1 responses (proinflammatory) while others will be associated with Th2 responses. Recently, it has been reported that Th1 cells produce more chemokines than Th2 (120). It is therefore very likely that there will be a segregation of Th1 vs Th2 chemokines depending on the nature of the developing immune responses. This is an area that deserves further investigation.

While the identification of chemokines associated with Th1 or Th2 responses is a developing story, the association of chemokine receptor expression with the Th1 or the Th2 phenotypes is well established (reviewed by Lanzavecchia et al in this volume). Several chemokine receptors are associated with the Th1 phenotype (including CXCR3 and CCR5), while others are associated with the Th2 phenotype (CCR3, CCR4, and CCR8) (for a review, see 121). However, some receptors are associated more than others. For example, CCR8 expression is far more abundant at the mRNA level in activated Th2 cells than CCR3. It is likely that CCR3 may actually define a subset within the Th2 population of cells. The expression of chemokine receptors in T helper cells depends on the state of activation of these cells. For example, CXCR3 is present in resting Th1, while CCR8 is only present in activated Th2. Finally, the issue arises of whether the expression of these receptors is only for the purposes of directing the migration of developing Th1 or Th2 cells to the appropriate sites where these responses are occurring, or whether the corresponding ligands may actually have effects on the differentiation of Th1 or Th2 cells. In support of the latter possibility, it has been reported that MIP-1α (a CCR5 ligand) promotes differentiation toward a Th1 phenotype (122).

In contrast, there are several chemokines whose expression strongly suggests a homeostatic role. Typically, this is due to the fact that they are expressed in

normal organs or tissues in the apparent absence of inflammatory stimuli, and/or they may be produced by cells that do not typically participate as active inducers of inflammation. For example, the chemokine HCC-1 is present in large concentrations in serum and is constitutively expressed in several organs (89). Several members of this family (HCC-2 and HCC-4—also called LEC) show strong constitutive expression in various organs, suggesting a homeostatic role. In this category, we could also include many other chemokines that tend to be tissue specific, including some described earlier, such as TECK (abundantly expressed in the thymus), which is likely to have an organ-specific function (for example, involvement in T cell development). Still, other chemokines may represent a ''mixed'' category, with both homeostatic and inflammatory functions. An example of the latter is fractalkine (123), which is highly expressed in the brain and may have a homeostatic function there but is also induced by TNF-α in endothelial cells and may thus participate in inflammatory reactions.

CONCLUSION

The chemokines and their receptors have received increasing attention in the last few years. Besides their role in HIV pathogenesis, it is now clear that chemokines participate intimately in many pathological conditions like inflammation and autoimmunity. They also play a very important role in normal homeostasis, including lymphoid development and migration. Some chemokines have potential therapeutic applications, mainly in cancer through their ability to attract subpopulations of lymphoid cells and also through their angiostatic effects. The nature of their receptors (seven-transmembrane G-protein-coupled receptors) also makes them compelling candidates as therapeutic targets in many areas where chemokines are involved.

In addition, chemokines are likely key regulators of immune responses. In particular, the emerging picture is that of a discrete network of cells interacting through their specific production of chemokines or expressing a highly specific pattern of chemokine receptors. The emerging view of this specificity has replaced the older view of a redundant system and in turn suggests that chemokine receptors, in particular, have the potential of evolving into specific markers to identify subsets of cells involved in a given immune response. Little effort has so far been directed toward the functional characterization of subsets of immune cells defined by chemokine receptor expression. This situation will probably change when reagents become available. There is an important need for reagents for flow cytometry as well as a need for neutralizing monoclonal antibodies in order to advance this field.

We should expect advances (and surprises) to come from the chemokine field. It is one of the first molecular families on which we have witnessed the impact of bioinformatics and genomics. It is therefore also valuable to learn from these

TABLE 2 Proposed new nomenclature for human chemokines

Systemic name	Human ligand	Mouse ligand (if only the mouse ligand is known)
CXCL		
CXCL1	Groα/MGSA-α	
CXCL2	Groβ/MGSA-β	
CXCL3	Groγ	
CXCL4	PF4	
CXCL5	ENA-78	
CXCL6	GCP-2	
CXCL7	NAP-2	
CXCL8	IL-8	
CXCL9	Mig	
CXCL10	IP-10	
CXCL11	I-TAC	
CXCL12	SDF-1/PBSF	
CXCL13	BLC/BCA-1	
CXCL14	BRAK/Bolekine	
CXCL15	Lungkine	
XCL		
XCL1	lymphotactin/SCM-1α/ATAC	
XCL2	SCM-1β	
CX3CL		
CX3CL1	Fractalkine/neurotactin	
CCL		
CCL1	I-309	
CCL2	MCP-1	
CCL3	MIP-1α	
CCL4	MIP-1β	
CCL5	RANTES	
(CCL6)		C10/MRP-1
CCL7	MCP-3	
CCL8	MCP-2	

TABLE 2 (*continued*) Proposed new nomenclature for human chemokines

Systemic name	Human ligand	Mouse ligand (if only the mouse ligand is known)
(CCL9/10)		MRP-2/CCF18/MIP-1γ
CCL11	Eotaxin	
(CCL12)		MCP-5
CCL13	MCP-4	
CCL14	HCC-1/HCC-3	
CCL15	HCC-2/leukotactin	
CCL16	HCC-4/LEC	
CCL17	TARC	
CCL18	DC-CK1/PARC/AMAC-1	
CCL19	MIP-3β/ELC/exodus-3	
CCL20	MIP-3α/LARC/exodus-1	
CCL21	6Ckine/SLC/exodus-2	
CCL22	MDC/STCP-1/ABCD-1	
CCL23	MPIF-1	
CCL24	MPIF-2/Eotaxin-2	
CCL25	TECK	
CCL26	SCYA26/Eotaxin-3	
CCL27	(MCC)/ALP/CTACK/ESkine	

developments so that in the future we will be able to apply some of the lessons learned from the chemokines to other molecular families.

ACKNOWLEDGMENTS

We thank Elizabeth Oldham and Lewis Lanier for their comments and suggestions, and Dovie Wyler for reviewing the manuscript.

DNAX Research Institute is supported by Schering-Plough Corporation.

Note Added in Proof: Proposed Nomenclature

At the 1998 Gordon Conference on Chemokines, a Committee headed by Dr. Osamu Yoshie (Kinki University, Japan) was formed to study options for a standardized new chemokine ligand nomenclature. It became clear that with the proliferation of new chemokines, there was a problem with their nomenclature. Often, various groups published the same molecule with different names, leading to confusion in the literature. Dr. Yoshie presented his recommendation at the 1999 Keystone Symposium on Chemokines; it was approved by the audience

composed of chemokine researchers from most leading laboratories worldwide. Table 2 here shows the recommendation for a new systematic nomenclature for human chemokines. It is based on the fact that the genes for chemokines have already received a standardized designation. For example, the CC gene family is called SCYA (small cytokine-A family) followed by a number. The proposal uses the same numbering system already in use for chemokine genes, but replaces the SCY abbreviation with CXCL for the CXC family, CCL for the CC family, XC for the lymphotactin, and CX3CL for fractalkine. In the case of the CC chemokines, there are some spaces for ligands that have been described in the mouse, but not yet in the human. However, it offers the advantage that the number representing a particular gene will be the same as its ligand, which is represented by the letter ''L'' after the family (CXC, CC, XC, CX3C). Thus, this nomenclature proposal is analogous to the current one in use for receptors and offers the added advantage that each ligand will be immediately recognizable as belonging to a particular subclass. But the main advantage is that it eliminates nomenclature ambiguities when referring to each chemokine. It is recommended that future articles use this nomenclature.

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