MICROSCOPY RESEARCH AND TECHNIQUE 53:298–306 (2001)

III. Chemokines and Other Mediators, 8. Chemokines and Their Receptors in Cell-Mediated Immune Responses in the Lung

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KEY WORDS chemotactic cytokines; delayed hypersensitivity; Th1/Th2; cell-cell communication

ABSTRACT Chemokines constitute a large family of chemotactic cytokines that belong to a super-gene family of 8–10 kDa proteins. The chemokines are considered to be primarily beneficial in host defense against invading pathogens. However, the reactions induced by chemokines can be occasionally excessive, resulting in a harmful response to the host. Recent studies in chemokine biology have elucidated that chemokines are involved in the initiation, development, and maintenance of numbers of diseases including lung diseases. In addition to its chemotactic activity, evidence suggests that chemokines can modify the outcome of the cell-mediated immune responses by altering the Th1/Th2 cytokine profile. Chemokines are also capable of dictating the direction of specific immune responses. Chemokine action is mediated by a large super-family of G-protein coupled receptors, and the receptors are preferentially expressed on Th1/Th2 cells. Certain chemokine receptors are constitutively expressed in immune surveying cells such as dendritic cells and naive T cells. The corresponding chemokines are present in normal lymphoid tissues, suggesting a role of chemokines/receptors in cell homing and cell-cell communication in lymphoid tissue that can be an initial step for immune recognition. Thus, comprehension of the chemokine biology in immune responses appears to be fundamental for understanding the pathogenesis of T cell–mediated immune responses. The following review will highlight the current insight into the role of chemokines and their receptors in the cell-mediated immune response, with a special focus on lung diseases. *Microsc. Res. Tech. 53:298–306, 2001.*

INTRODUCTION

Due to a unique anatomical feature that achieves effective gas exchange, the lung is constantly exposed to the outer environment, which may allow a great variety of infectious microbes and small foreign particles to invade the lung. This can cause infection and inflammation, which may threaten host survival. However, the lung and respiratory tract are protected from invading pathogens by the host defense system (Roitt et al., 1998; Roussos, 1995). The nasal hair functions as a rough "filter." The Waldeyer's ring, a mucosa-associated lymphoid tissue complex at the entrance of the airway, reacts to pathogens that have entered via the surface barriers. The lining cells of the respiratory tract secrete mucus that traps small microbes and foreign particles, enabling the host to eject them from the respiratory tract. In the alveoli of the lung are the alveolar macrophages, which can ingest and destroy pathogens. Certain macrophages and dendritic cells carry processed antigens to adjacent draining lymph nodes, where the cells present antigens to naive T cells. The T cells release cytokines, that enable the phagocytes to destroy the pathogens that they have internalized. T cells also help B cells produce antibody that binds to pathogens and their products. The phagocytes then recognize the complex through Fc receptor binding, allowing them to clear these pathogens. These adoptive immune responses are memorized and provide a more effective and rapid response when the host is re-infected with the same pathogens (Roitt et al., 1998; Roussos, 1995).

However, this normally beneficial immune response can occasionally cause an overwhelming inflammatory response and tissue damage when an adaptive immune response occurs in an exaggerated or inappropriate form. In granulomatous hypersensitivity reactions such as pulmonary tuberculosis, sarcoidosis, and hypersensitivity pneumonia, antigen-sensitized T cells traveling to the site of foci secrete excessive levels of cytokines, following a secondary contact with the same antigen. The cytokines activate macrophages, and activated macrophages amplify the inflammatory responses via releasing inflammatory mediators. These events can cause differentiation of macrophages to epithelioid cells and multinuclear giant cells, resulting in the formation of pulmonary granuloma (Agostini et al., 1998; Ando et al., 1999; Condos et al., 2000; Moller,

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Received 16 June 2000; accepted in revised form 25 June 2000

1999). In allergic airway inflammation such as asthma, T cells secrete cytokines after antigen recognition, which include IL-4, IL-5, IL-10, and IL-13. These cytokines induce the production of antigen (allergen)-specific IgE from B cells. IgE enters the circulation and binds to mast cells throughout the body. Upon encountering the same allergen in the airway, the sensitized mast cells release inflammatory mediators inside the cells, which trigger a series of inflammatory cascades seen in asthma (Kay, 1998; Kon and Kay, 1999; Le Gros et al., 1998; also reviewed by Van Rijt and Lambrecht, pages 256–272, this issue). Recent studies have revealed that chemokines play an essential role in the initiation and maintenance of these types of lung diseases (Lukacs et al., 1999; Rothenberg, 2000; Rothenberg et al., 1999).

Historically, chemokines have been viewed as leukocyte chemoattractants that regulate cellular movement from the circulation into inflamed tissue (Baggiolini et al., 1997). However, as investigators continue to examine the function of chemokines in both disease and homeostatic circumstances, the identification of novel functions of chemokines in the regulation of immune responses has begun. Recent evidence suggests that certain chemokines and their receptors appear to be involved in dendritic cell and lymphocyte homing and cell-cell communication in lymphoid tissue (Allavena et al., 1999; Cyster, 1999). The recruitment, regulation, and activation of CD4+ T helper (Th) cells, and cytokine production from the cells may be the most critical issue in immune responses (Moser, 1998). It is now known that chemokine receptors have been found to be differentially associated with Th1/Th2 subsets (Sallusto et al., 1998a, 1999). Certain chemokine members are produced in infectious foci, allowing chemokines to traffic Th1/Th2 cells into inflamed sites (D'Ambrosio et al., 2000; Syrbe et al., 1999). Furthermore, CC chemokine members appear to alter the outcome of the immune responses through altering Th1/Th2 balance (Mantovani et al., 1998). Thus, chemokines and their receptors appear to affect the immune response at multiple levels.

CHEMOKINES AND THEIR RECEPTORS

A decade ago, two functional chemotactic cytokines with different activities were identified, which were designated IL-8 and MCP-1 (Yoshimura et al., 1987; 1989). After these initial discoveries, family members of chemotactic cytokines has been identified at a staggering pace through broad-based searches for sequence homology in EST databases. To date, over 50 members have been reported, and the number of chemokines is still growing (Baggiolini et al., 1997; Zlotnik and Yoshie, 2000). Chemokines belong to a super-gene family of 8–10 kDa basic heparin-binding proteins, and have been divided into 4 sub-families based upon their sequence homology and the position of cysteine residues in the proteins (Table 1). Two of these constitute quite a large number of chemokines, CC and CXC. CC chemokines attract monocytes, dendritic cells, eosinophils, or lymphocytes. CXC chemokines preferentially attract neutrophils, but some of them attract T or B cells. CXC chemokines can be divided into two subsets based on the presence or absence of specific amino acid residues Glu-Leu-Arg (ELR). CXC chemokines that contain the ELR motif are angiogenic factors, while non-ELR CXC chemokines that lack the ELR motif are angiostatic factors (Keane and Strieter, 1999). Recent evidence suggests that ELR-CXC chemokines, but not non-ELR-CXC chemokines, are capable of inducing hepatocyte proliferation (Hogaboam et al., 1999b) as well as wound healing (Richmond et al., 1999). Very recently, lungkine, a novel ELR-CXC chemokine, has been identified, which is selectively expressed in lung epithelial cells, up-regulated in various lung inflammation models, and detected in fetal lung tissue. These activities suggest a role for this chemokine in lung-specific neutrophil trafficking as well as lung development (Rossi et al., 1999).

Chemokine receptors also constitute a subfamily of rhododopsin-like, 7 transmembrane, G protein-coupled receptors. To date, 18 chemokine receptors are known, and classified into 4 subtypes depending on which chemokine subfamily is recognized (Table 1). These chemokine receptors commonly bind multiple chemokines, although some of the chemokine receptors appear to bind a specific chemokine. Different receptors for the same chemokines can be co-expressed on the same cell type, even on the same cell (Murphy, 1997). The expression of a CC chemokine receptor (CCR) was believed to be restricted to cells that can respond to a specific CC chemokine. However, recent studies have shown that neutrophil can express CCR1, 2, and 3 under specific inflammatory conditions (Bonecchi et al., 1999; Johnston et al., 1999). Although CC chemokines were regarded to bind CCRs, a recent study has

Abbreviations

Cytokines:	
IFN	interferon
IL	interleukin
TGF	transforming growth factor
CC chemokines:	
CTACK	cutaneous T cell-attracting chemokine
ECF	eosinophil chemotactic cytokine
HCC	human CC chemokine
LCC	liver-specific CC chemokine
MCP	monocyte chemoattractant protein
MDC	macrophage-derived chemokine
MIP	macrophage inflammatory protein
MPIF	myeloid progenitor inhibitory factor
RANTES	regulated on activation, normal T expressed and secreted
TARC	thymus and activation-regulated chemokine
TECK	thymus-expressed chemokine
TCA	thymus-derived chemotactic agent
CXC chemokines:	
BLC	B lymphocyte chemoattractant
ENA	epithelial neutrophil activating protein
GCP	granulocyte chemotactic protein
GRO	growth-related oncogene
IP	interferon-γ-inducible protein
I-TAC	IFN-inducible T cell alpha chemoattractant
MIG	monokine induced by interferon-γ
NAP	neutrophil activating protein
PF	platelet factor
SDF	stromal cell-derived factor

TABLE 1. Chemokines and their sources, target cells and receptors

Chemokines	Proposed nomenclature		Sources	Target cells	Receptors
CC chemokines					
TCA-3/I-309	CCL1		T, MC	T	CCR8
MCP-1/MCAF	CCL2		M, L, F, EC, EP, N, MC, G, ME	M, T, NK, DC, N, SM, BA	CCR2, 10, 11
MIP-1α/LD78α	CCL3		M, L, N, E, F, MC, BA, NK	M, T, NK, E, DC, BA	CCR1, 5
MIP-1β/Act-2/HC21	CCL4		M, L, N, F, MC	M, T, NK, DC	CCR5, 8
RANTES	CCL5		T, M, F, ME	T, E, NK, BA, NK	CCR1, 3, 5, 11
C10/MPR-1 (murine)	CCL6		M, E, microglia	M	?
MCP-3	CCL7		P, M, MC, F	M, T, NK, DC, E, SM, BA	CCR1, 2, 3, 10, 11
MCP-2	CCL8		M, F	M, T, NK, DC, E, SM, BA	CCR2, 3, 11
MIP-1γ/MPR-2/CCF-18 (murine)	CCL9/10		M, DC, liver, thymus, lung, pancreas	DC, T	CCR1
Eotaxin-1	CCL11		EC, EP, E, lung	E, BA	CCR3
MCP-5 (murine)	CCL12		M, lymph node	M, E	CCR2
MCP-4/CKβ10	CCL13		DC, thymus, lung, colon, intestine	M, T, E, BA	CCR2, 3, 11
HCC-1	CCL14		bone marrow, spleen, liver, gut, SM	M, myeloid progenitor	CCR1
HCC-2/MIP-1δ/LKN-1/MIP-5	CCL15		DC, M, T, B	M, T	CCR1
HCC-4/LEC/NCC-4/LMC	CCL16		M	M	?
TARC	CCL17		DC, M, Reed-Sternberg cell	DC, Th2	CCR4, 8
MIP-4/PARC/DC-CK1/AMAC-1	CCL18		DC, M	T	?
MIP-3β/ELC/Exodus-3	CCL19		thymus, lymph node, appendix, spleen, gut	T, B, NK	CCR7
MIP-3α/LARC/Exodus-1	CCL20		M, T, liver, lung, thymus, placenta, appendix	DC, T, NK	CCR6
6Ckin/SLC/TCA-4/Exodus-2/CKβ9			stromal cells in lymph node, EC	T, NK	CCR7
MDC/STCP-1/ABCD-1	CCL22		DC, M, B, T, EP (thymus)	DC, Th2, NK	CCR4
MPIF-1/CKβ8	CCL23		DC, M, lung, liver	M, T	CCR1
Eotaxin-2/MPIF-2/CKβ6	CCL24		M, T, lung, liver, spleen, thymus	E, BA	CCR3
TECK	CCL25		DC, EC, gut	T, thymocyte	CCR9
Eotaxin-3	CCL26		EC, heart, ovary	E, BA	CCR3
CTACK/ILC, ESkine (murine)	CCR27		skin, placenta	T	CCR10
LCC-1			liver	?	?
ECF-L			spleen, bone marrow, lung, heart	E	?
CXC Chemokines	ELR-motif				
GROα/MGSA-α	CXCL1	+	M, N, EC, F, melanoma cell	N, MC	CXCR2>R1
GROβ/MGSA-β	CXCL2	+	M, N, EC, F, melanoma cell	N	CXCR2
GROγ/MGSA-γ	CXCL3	+	M, N, EC, F, melanoma cell	N	CXCR2
PF4	CXCL4	−	P, megakariocyte	M, EC	?
ENA-78	CXCL5	+	EC, P	N, MC	CXCR2
GCP-2	CXCL6	+	EC, osteosarcoma cell	N	CXCR1, 2
NAP-2/CTAP-III	CXCL7	+	P, EC	N, MC	CXCR2
IL-8/NAP-1/MDNCF	CXCL8	+	M, T, F, K, H, EP, EC, N, P, AS, G, ME, BA, NK	N, MC, E, NK	CXCR1, 2
MIG	CXCL9	−	M, N	T, NK, EC	CXCR3
IP-10/CRG-2	CXCL10	−	M, K, N, F, EC, AS, G	T, NK, EC	CXCR3
I-TAC/beta-R1/H174/IP-9	CXCL11		AS, M, N	T, NK	CXCR3
SDF-1/PBSF	CXCL12	−	stromal cell	T, M, DC, NK	CXCR4
BLC/BCA-1	CXCL13	−	spleen, lymph node	B, T, M	CXCR5
BRAK/bolekine	CXCL14	−			?
Lungkine (murine)		+	EC (lung)	N	?
C Chemokine					
Lymphotactin-α/SCM-1α	XCL1		T, NK	T, NK	XCR1
Lymphotactin-β/SCM-1β	XCL2		T, NK	T	XCR1
CX3C Chemokine					
Fractalkine/Neurotactin	CX3CL1		EC, DC, T, brain	M, DC, T, NK	CX3CR1

Cell abbreviations: AS, astrocyte; B, B cell; BA, basophil; DC, dendritic cell; EC, endothelial cell; EP, epithelial cell; E, eosinophil; F, fibroblast; G, glioblastoma; H, hepatocyte; K, keratinocyte; L, lymphocyte; M, monocyte/macrophage; MC, mast cell; ME, mesangial cell; N, neutrophil; P, platelet; SM, smooth muscle cell; T, T cell. The nomenclature was proposed by Drs. O. Yoshie and A. Zlotnik (Immunity, 12, 121–127, 2000).

revealed that CC chemokine 6Ckine binds the CXC chemokine receptor CXCR3 (Soto et al., 1998). Thus, receptor expression and its recognition by chemokines appear to be more complicated than anticipated. It is possible that the overlapping receptor recognition by chemokines may be important for inducing an efficient signal transduction or may function as a back-up system.

CHEMOKINES AS CENTRAL MEDIATORS OF CELL-CELL COMMUNICATION IN LYMPHOID TISSUE

The antigen presentation to T cells is the initial step for the immune response. In this regard, dendritic cells (DC) play a crucial role as a sentinel of the adoptive

TABLE 2. Preferential expression of chemokine receptors on Th1/Th2 cells

Th1/Th2 cells	Receptors	Chemokines
Th1 cells	CCR5	MIP-1α, -β, RANTES
	CXCR3	MIG, IP-10, I-TAC
Th2 cells	CCR3	RANTES, MCP-2, -3, -4, Eotaxin-1, -2, -3
	CCR4	TARC, MDC
	CCR8	TCA-3, MIP-1β, TARC

immune system (Ludewig et al., 1999). Immature DCs, which localize in non-lymphoid tissue, capture and process antigens. Upon stimulation, DCs travel to adjacent lymphoid tissue and present the processed antigen to naive T cells. Chemokines and their receptors appear to be involved in this cell movement and trafficking (Cyster, 1999). Immature DCs respond to an array of CC and CXC chemokines including MIP-1α, MIP-1β, MIP-1γ, MIP-3α, MCP-1, MCP-2, MCP-3, MCP-4, TARC, MDC, SDF-1, and Fractalkine (Table 1). The most potent chemoattractant of DCs is MIP-3α, and the receptor CCR6 is expressed on immature DCs. Upon stimulation, the CCR6 expression is shown to be downregulated, whereas CCR7 expression is upregulated (Dieu et al., 1998). MIP-3α is present only in inflamed site, while CCR7 ligand 6Ckine is expressed by high endothelial venules (HEVs) in lymphoid tissue. 6Ckine and another CCR7 ligand MIP-3β are also expressed in the T cell area of lymphoid tissue (Dieu et al., 1998), suggesting a role of CCR7 and its ligands in DC trafficking into lymphoid tissue (Saeki et al., 1999). Correspondingly, CCR7 knockout mice showed decreased migration of DCs into the T cell area (Forster et al., 1999; Gunn et al., 1999). Mature DCs secrete T cell chemoattractants, such as MIP-3β (Dieu et al., 1998; Ngo et al., 1998) and MIP-4 (Adema et al., 1997; Guan et al., 1999), probably enabling naive T cells to scan efficiently for antigen that is presented by DCs. When naive T cells are activated, the T cells undergo a transient switch in receptor expression, depending on the Th1/Th2 polarization (Sallusto et al., 1999). The activated T cells may decrease CCR7 expression and upregulate CXCR5 expression, and become responsive to BLC, while at the same time losing response to 6Ckine and MIP-3β (Ansel et al., 1999; Walker et al., 1999), probably allowing T cells to encounter B cells. CXCR5 is also expressed on B cells, and BLC-CXCR5 interaction is essential for follicle formation, as migration of lymphocytes into the follicles is impaired in CXCR5 deficient mice (Forster et al., 1996). These findings suggest that chemokines and their receptors are essential for the immune recognition that is an initial step for immune responses.

DIFFERENTIAL EXPRESSION OF CHEMOKINES RECEPTORS ON Th1/Th2 CELLS

It is well known that CD4+ T helper (Th) cells have two subsets based on the profile of cytokine production. Th1 cells are characterized by the production of IFNγ, IL-2, and IL-12, whereas Th2 cells are typified by the production of IL-4, IL-5, IL-10, and IL-13. Cytokines produced from Th1 cells inhibit the actions of Th2 cells, and vice versa (Romagnani, 1997). The selective differentiation of either subset is established during priming, depending on their antigenic experience and a variety of surrounding factors (Constant and Bottomly, 1997). Recent in vitro data using polarized human T-cell lines suggest that chemokine receptors are preferentially expressed on Th1/Th2 cells, as part of the cell differentiation (Table 2). CCR5 and CXCR3 are preferentially found on Th1 cells, whereas CCR3, CCR4, and CCR8 are on Th2 cells (Bonecchi et al., 1998; D'Ambrosio et al., 1998; Sallusto et al., 1998b; Imai et al., 1999). It is thus conceivable that Th1/Th2 cells selectively migrate in response to the corresponding chemokines, which can be produced at the sites (Baggiolini, 1998; Sallusto et al., 1999; Zlotnik et al., 1999). Th1/Th2 cells produce sets of chemokines, including MIP-1α, MIP-1β, RANTES, MDC, TARC, and TCA-3, which may amplify the recruitment of Th1/Th2 cells at sites of antigenic recognition. Recent clinical studies have shown the existence of flexible programs of chemokine receptor expression during the development of diseases. CCR5 was found on memory T cells from Crohn's disease, a Th1-dominated disorder, whereas CCR3 was found on the cells from systemic sclerosis, a Th2-dominant disorder (Annunziato et al., 1999). Likewise, an elevated serum level of MDC was detected in patients with mycosis fungoides/Sezary syndrome or atopic dermatitis, a Th2-dominant disorder (Galli et al., 2000). Animal studies have shown that chemokines play an essential role in attracting Th1/Th2 cells to inflammatory sites, depending on the Th1/Th2 polarization (Yoneyama et al., 1998; Vestergaard et al., 1999; Lloyd et al., 2000). Evidence from recent studies also suggest that CCR1 and CCR2 may play an important role in tissue-specific localization of Th1 and Th2 cells, respectively, as Th1-type cytokine up-regulated the expression of CCR1 while inhibiting CCR2 (Penton-Rol et al., 1998; Bonecchi et al., 1999; Colantonio et al., 1999).

CHEMOKINES IN Th1/Th2-CELL MEDIATED PULMONARY GRANULOMA

As discussed above, the Th1/Th2 paradigm appears to direct the feature of immune responses, and the recruitment of Th1/Th2 cells is likely to be regulated by chemokines. In the context of T cell–mediated pulmonary disease, models have been established that predominantly exhibit either a Th1- or Th2-type cytokine profile (Kunkel et al., 1996, 1998). Mice sensitized with purified protein derivative (PPD) from *Mycobacteria bovis* or *Schistosoma mansoni* eggs challenged with beads coated with PPD or *Schistosoma* egg antigen (SEA) develop a granuloma formation that is associated with the production of either Th1 or Th2-cytokine, respectively (Chensue et al., 1994a,b; Henderson et al., 1991, 1992). The importance of Th1/Th2 cytokines in the development of the granuloma formation has been confirmed by using antibodies against Th1/Th2 cytokines and gene technology (Chensue et al., 1992, 1995a,c, 1997a,b; Fallon et al., 2000; Lukacs et al., 1997a). Thus, specific cytokine phenotype apparently dictates the progression of cell-mediated pulmonary immune response.

Histologically, the Th1-type granuloma typically consists of macrophages and lymphocytes, whereas the

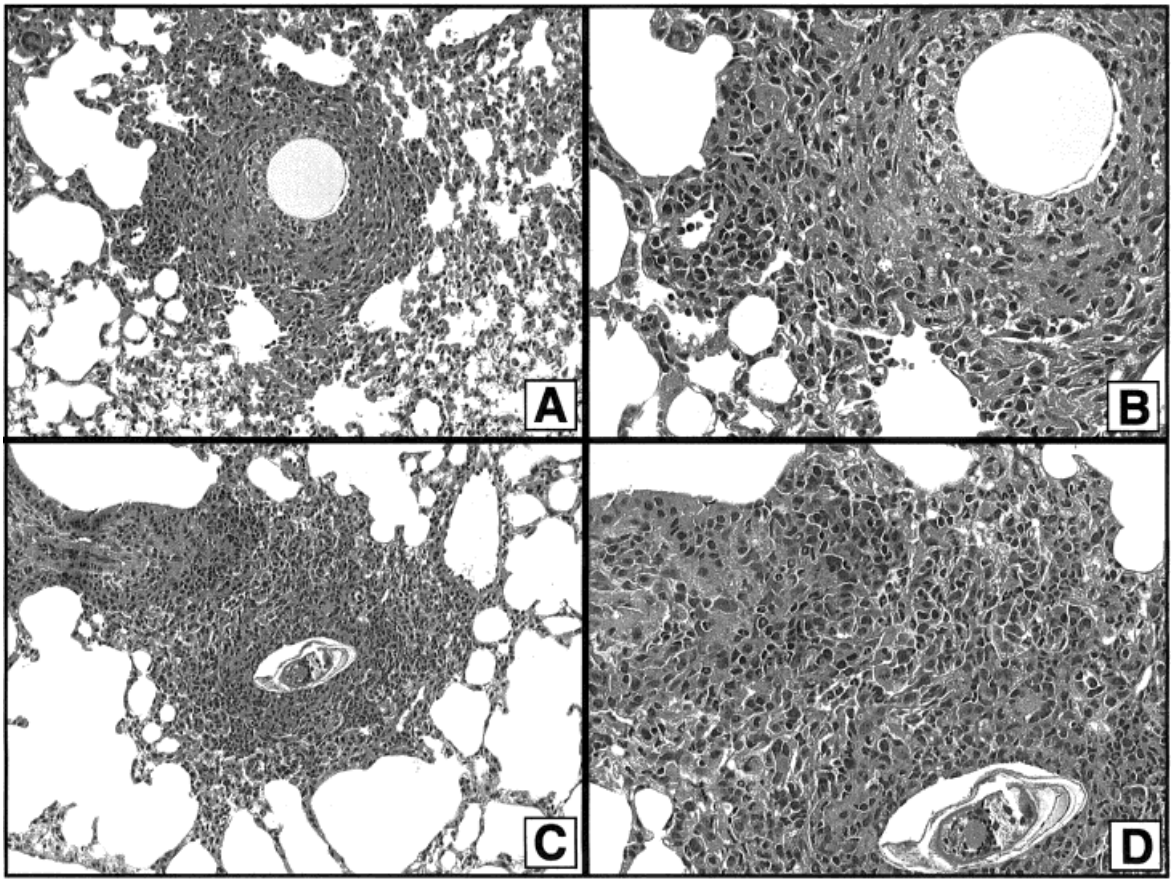

Fig. 1. Histology of experimental models of pulmonary granuloma. Mice were sensitized to PPD from *Mycobacteria* or *Schistosoma mansoni* egg and were challenged i.v. with PPD (Th1-type) or *Schistosoma mansoni* egg (Th2-type). The photos are representative of Th1-type (**A,B**) and Th2-type (**C,D**) granuloma models (H&E staining). Magnification: A and C, ×200; B and D, ×400.

Th2-type granuloma contains mononuclear cells and eosinophils (Fig. 1), suggesting that different chemokines are likely to be involved in the development of the granuloma formation. Recent studies have begun to provide insight into the mechanism(s) whereby chemokines, especially CC chemokines, play an essential role in the granuloma formation in experimental models. CC chemokine production in the lung has been preferentially observed between the models. The level of RANTES in Th1-type granuloma was greater than that in Th2-type granuloma (Chensue et al., 1999), while higher levels of MCP-1 (Chensue et al., 1996; Hogaboam et al., 1999a) and eotaxin (Ruth, 1998) were detected in Th2-granuloma. Consistently, the expression of CCR2 and CCR3, a receptor for MCP-1 and eotaxin, respectively, is preferentially up-regulated in Th2-granuloma (Ruth et al., 1998; Hogaboam et al., 1999a). Evidence from neutralizing studies using antibodies against specific chemokines and from mice with specific disrupted chemokines/receptors gene has allowed us to understand the involvement of chemokines in the evolution of granuloma formation. Table 3 summarizes the current results of the studies addressing the role of chemokines in these models. The data suggest that MCP-1 contributes more to the Th2-type granuloma than Th1-type granuloma, as mice treated with anti-MCP-1 antibodies and mice deficient in MCP-1 gene showed reduced granuloma formation in the Th1-type model whereas no change was observed in the Th1-type model after anti-MCP-1 treatment (Chensue et al., 1995b, 1996; Lu et al., 1998). Correspondingly, CCR2 deficient mice showed a decreased size of granuloma in the Th2-type model (Warmington et al., 1999). Interestingly, IL-4 production was decreased in these studies, and, in turn, IL-4 blockade in mice developing Th2-type granuloma reduced the production of MCP-1 (Chensue et al., 1996). Thus, an immunoregulatory role of MCP-1/CCR2 appears to be related, in part, to the development of Th2-type granuloma. In the Th1-type model, neutralization of MCP-1 did not inhibit the granuloma formation while CCR2 −/− mice showed a smaller granuloma than wild-type, which was associated with decreases in the level of IFNγ and IL-2 (Boring et al., 1997; Chensue et al., 1996). The data suggest that chemokines other than MCP-1 that can bind CCR2 (i.e., MCP-2, MCP-3, MCP-4, and MCP-5) may be involved in the progression of Th1-type granuloma. MIP-1α and RANTES appear to be preferentially involved in the development of Th1-type granuloma. MIP-1α deficient mice developed a smaller

TABLE 3. Chemokines and their receptors in the development of Th1- and Th2-type pulmonary granuloma models[1]

Targetting chemokines	Depletion[2]	Granuloma size (vs. control)	Th1/Th2 cytokine profile	References
Th1-type granuloma				
MCP-1	Antibodies	No change	No change	Chensue et al. (1996)
MIP-1α	Gene knockout	↓	Decreased IFNγ/IL-2, increased IL-4/IL-5	Hogaboam et al. (1999c)
RANTES	Antibodies	↓	No change	Chensue et al. (1999)
Eotaxin	Antibodies	↓	Decreased IFNγ	Ruth et al. (1997)
CCR2	Gene knockout	↓	Decreased IFNγ/IL-2	Boring et al. (1997)
Th2-type granuloma				
MCP-1	Antibodies	↓	Decreased IL-4/IL-5	Chensue et al. (1995b, 1996)
	Gene knockout	↓	Decreased IL-4/IL-5	Lu et al. (1998)
MIP-1α	Gene knockout	No change	Decreased IL-4/IL-5	Hogaboam et al. (1999c)
RANTES	Antibodies	↑	Decreased IL-4/IL-5/IL-10/IL-13	Chensue et al. (1999)
Eotaxin	Antibodies	↓	Decreased IL-5	Ruth et al. (1997)
CCR1	Gene knockout	↓	Decreased IL-4, increased IFNγ	Gao et al. (1997)
CCR2	Gene knockout	↓	Decreased IL-4	Warmington et al. (1999)

[1]Mice were sensitized to PPD from *Mycobacteria* or *Schistosoma mansoni* egg and were challenged i.v. with PPD (Th1-type) or SEA (Th2-type). Granuloma size was measured by lung sections. Cytokines were measured in the lung or draining lymph nodes.
[2]Results were obtained from mice using neutralizing antibodies against specific antibodies, or mice desrupted chemokine/receptor gene.

granuloma than the wild-type which was associated with decreased IFNγ and IL-2, and in contrast, increased IL-4/IL-5, whereas no change was found in the Th2-type granuloma although the level of IL-4 and IL-5 was decreased (Hogaboam et al., 1999c). MIP-1α is shown to enhance the production of IFNγ by activated T cells (Karpus et al., 1997). RANTES blockade decreased the granuloma size in the Th1-type model, while increasing the Th2-type lesion that was accompanied by the increase in the level of IL-4, IL-5, IL-10, and IL-13 (Chensue et al., 1999). Convincingly, infusion of RANTES reduced the Th2-type lesion, but not the Th1-type lesion, and augmented type 1 and impaired type 2 responses in the lymph nodes. In vitro, RANTES caused selective, dose-related inhibition of IL-4 that was largely dependent on ligation of CCR1 receptors (Chensue et al., 1999). CCR1 deficient mice, the receptor for MIP-1α and RANTES, showed decreased granuloma formation in the Th2-type model, which was associated with the decreased level of IL-4 while increasing IFNγ (Gao et al., 1997). Neutralization of eotaxin decreased the IFNγ level in regional lymph nodes and granuloma size in Th1-type model, as well as reduced the IL-5 level and granuloma size in the Th2-type model (Ruth et al., 1998). All these findings suggest that chemokines/receptors influence the granuloma formation not only through direct effects on leukocyte chemotaxis, but also through altering the Th1/Th2 cytokine balance.

CHEMOKINES DIRECT THE IMMUNE RESPONSE

In addition to altering the Th1/Th2 cytokine balance in the evolution of immune responses, chemokines apparently direct the immune system toward a specific response. In particular, CC chemokines are capable of regulating T cell activation and function during specific immune responses. Earlier studies have demonstrated that RANTES can directly activate T cells in vitro, specifically activating relevant signal transduction pathways (Bacon et al., 1995, 1996). Other evidence suggests that CC chemokines, such as MIP-1α, MIP-1β, RANTES, and MCP-1 enhance adjuvant activity and increase T cell activation and IL-2 production (Taub et al., 1996a,b). MCP-1 is shown to inhibit the production of IL-12 in peritoneal macrophages (Chensue et al., 1996). MCP-1 can induce the production of suppressive cytokines TGFβ that may impact on the production of Th1 type responses, such as IL-12 production (Gharaee-Kermani et al., 1996). Chemokines may also influence the differentiation of native T cells to Th1 or Th2 cells, as MCP-1 contributes to the production of IL-4 from antigen activated T cells, while MIP-1α enhances IFNγ production (Karpus et al., 1997; Lukacs et al., 1997b; Hogaboam et al., 1998). In vivo, MCP-1 regulates oral tolerance in the development of experimental autoimmune encephalomyelitis through the regulation of IL-12 production as well as antigen-specific Th1 cell responses (Karpus et al., 1998). MCP-1 attenuates the severity of septic response via decreasing the production of IL-12, IFNγ, and TNFα (Matsukawa et al., 2000a; Zisman et al., 1997). Interestingly, MCP-1 transgenic mice failed to clear bacteria, possibly reflecting an altered ability to generate the Th1 immune response (Rutledge et al., 1995). Our recent data in pulmonary granuloma models have shown that the over-expression of MCP-1 at specific phases of the developing responses appears to differentially alter the outcome of the immune responses (Matsukawa et al., 2000b). When MCP-1 was over-expressed at the beginning of the immune response at a time when T cells would first be in contact with antigen, a decreased size of granuloma was observed in the Th1-type model while increasing the Th2-type granuloma. The regulation of Th1/Th2-type cytokine by MCP-1 is likely the mechanism, as activated T cells recovered from MCP-1 treated mice showed decreased production of IFNγ and IL-12 in the Th1-type model, and, in contrast, increased production of IL-10 and IL-13 in the Th2-type model. When MCP-1 was over-expressed during the elicitation phase of the responses, neither the Th1-type nor the Th2-type granuloma was altered, suggesting that the function of MCP-1 may depend upon the stage and type of immune response (Matsukawa et al., 2000b). Thus, chemokines, in particular MCP-1, appear to have multiple effects on a developing immune response and influence the direction of an immune response.

CONCLUDING REMARKS

In addition to its original chemotactic activity toward specific types of cell populations, chemokines have a broad spectrum of activities ranging from immune cell homing and immune recognition in lymphoid tissue to the regulation of immune responses against specific antigens. Therefore, chemokines aid in determining the direction and intensity of the acquired immune responses. Chemokines are also well known to govern innate immunity (Mahalingam and Karupiah, 1999). Innate immune responses are tightly linked to acquired immune responses, suggesting that chemokines may play a key role in connecting these immune responses. There is little doubt that a further understanding of the chemokine biology will shed light on the therapeutic approach for the treatment of refractory pulmonary diseases.

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