Archivum Immunologiae et Therapiae Experimentalis, 2000, **48**, 451–456
PL ISSN 0004-069X

Review

T Cell Chemokine Receptor Expression in Human Th1- and Th2-Associated Diseases

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Abstract. The interaction between chemokines and their receptors is an important step in the control of leukocyte migration into sites of inflammation. Chemokines also mediate a variety of effects independent of chemotaxis, including induction and enhancement of Th1- and Th2-associated cytokine responses. Recent studies have shown that human Th1 and Th2 clones, activated under polarizing conditions with polyclonal stimuli *in vitro*, display distinct patterns of chemokine receptor expression: Th1 clones preferentially express CCR5 and CXCR3, while many Th2 clones express CCR4, CCR8 and, to a lesser extent, CCR3. These differential patterns of chemokine receptor expression suggest a mechanism for selective induction of migration and activation of Th1- and Th2-type cells during inflammation and, perhaps, normal immune homoeostasis. Studies have begun to examine T cell chemokine receptor expression *in vivo* to determine the relevance of these *in vitro* observations to human Th1- and Th2-associated diseases. In this review, we critically examine recent reports of T cell chemokine receptor expression in human autoimmune disorders (multiple sclerosis and rheumatoid arthritis) and atopic disorders (allergic rhinitis and asthma) which are believed to arise from inappropriate Th1- and Th2-dominated responses, respectively.

Key words: multiple sclerosis; rheumatoid arthritis; atopy; chemokines; chemokine receptors; T cells.

Introduction

The chemokines are a family of low molecular weight proteins. Their name derives from "**chemo**attractant cyto**kines**", as these cytokines were originally characterized based on their ability to selectively induce chemotaxis of specific cell types. Human chemokines are classified into four subfamilies based on the location of the first two conserved N-terminal cysteine residues in their sequence: CXC (α) chemokines (currently 14 members), CC (β) chemokines (23 members) and the CX3C and C chemokine subfamilies which have one member each, fractalkine and lymphotactin, respectively. Chemokines are produced by a wide range of tissue and inflammatory cells both constitutively and in response to diverse stimuli[12, 30].

In sharp contrast to other cytokines, most chemokines are promiscuous in receptor usage. However,

Abbreviations used: CCR – CC chemokine receptor, CXCR – CXC chemokine receptor, CSF – cerebrospinal fluid, IFN – interferon, ILm – interleukin, IP-10 – interferon-γ-induced protein of 10 kDa, I-TAC – interferon-induced T cell α chemoattractant, MCP – monocyte chemotactic protein, MDC – monocyte-derived chemokine, Mig – monokine induced by interferon γ, MIP – macrophage inflammatory protein, MS – multiple sclerosis, RA – rheumatoid arthritis, RANTES – regulated upon activation normal T cell expressed and secreted, SLC – secondary lymphoid tissue chemokine, TARC – thymus and activation-regulated chemokine, Th – T helper.

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Table 1. Chemokine receptor expression on human Th1 and Th2 cell lines and clones

T cells	Chemokine receptor	Principal ligands
Th1	CCR5	MIP-1α, MIP-1β, RANTES
	CXCR3	IP-10, Mig, I-TAC
Th2	CCR3	eotaxin, RANTES, MCP-2, 3, 4
	CCR4	TARC, MDC
	CCR8	I-309
Th1 and Th2	CCR1	MIP-1α, RANTES, MCP-3
	CCR2	MCP-1, 2, 3, 4
	CCR7	SLC, MIP-3β

CXC chemokines exclusively bind CXC receptors (CXCR1-5) and CC chemokines exclusively bind CC receptors (CCR1-10). All leukocytes, and many other cell types, express a proportion of these receptors and are, hence, capable of responding to many chemokines. Apart from their key role in orchestrating adhesion and transendothelial migration of leukocytes to sites of inflammation, chemokines have myriad other effects, including regulation of angiogenesis[26], hematopoiesis[34] and inhibition of tumor cell growth[2]. There is also increasing evidence that select chemokines are capable of modulating the development and maintenance of Th1 and Th2 cytokine responses. In mouse studies, OVA--specific transgenic T cells primed in the presence of MIP-1α developed a Th1 phenotype, whereas MCP-1--primed cells developed a Th2 phenotype[17]. MCP-1 knock-out mice were unable to mount Th2 responses at all[14]. In human studies, IP-10 selectively promoted antigen or mitogen-induced IFN-γ production over IL-4 production, suggesting a role for this CXC chemokine in the maintenance of Th1 responses[9].

Selective responsiveness to chemokines is suggested by differential chemokine receptor expression on human Th1 and Th2 clones and cell lines *in vitro*. Under often highly polarizing conditions and in response to polyclonal stimuli, human Th1 cell lines and clones preferentially express CXCR3 and CCR5, whereas Th2 cells preferentially express CCR4 and CCR8 and, to a lesser extent, CCR3[5, 6, 38] (Table 1). Receptors common to both subsets include CCR1, CCR2 and CCR7. The question of whether these distinct patterns of chemokine receptor expression are reflected *in vivo* during Th1 and Th2 immune responses is a highly topical area of investigation. This review focuses on recent advances in this area, specifically on the nature of T cell chemokine receptor expression in Th1-linked autoimmune disorders (multiple sclerosis and rheumatoid arthritis) and Th2-linked atopic disorders (allergic rhinitis and atopic asthma).

T Cell Chemokine Receptor Expression Patterns in Human Disease

Autoimmune disorders

Multiple sclerosis (MS) and rheumatoid arthritis (RA) are autoimmune-related disorders of unclear etiology in which tissue-specific pathology results from chronic inflammatory responses. In MS, myelin-specific T cells participate in demyelination within the central nervous system, contributing to progressive irreversible tissue damage that results in neurological impairment[27, 45]. RA is characterized by T cell-mediated inflammation in synovium and subsequent destruction of cartilage and joints[32]. Individuals suffering from RA experience considerable joint pain and loss of mobility and dexterity.

Cumulative evidence suggests that the tissue pathology of both MS and RA is caused specifically by inappropriate or misdirected Th1-type immune reactions[20]. This includes findings that increased production of IFN-γ precedes the clinical symptoms of MS, that injection of IFN-γ exacerbates the disease[24, 33], and that IFN-γ-producing $CD4^+$ T cells predominate in RA synovial fluid[19]. It has been speculated that infiltration of Th1-type cells into the inflammatory sites of MS and RA is promoted by an enhanced and localized expression of chemokines that preferentially bind (and activate?) putative Th1-associated chemokine receptors. There is preliminary evidence of selective expression of CXCR3 and CCR5 ligands in these autoimmune disorders. In comparison with brain tissue and cerebrospinal fluid (CSF) from normal subjects, IP-10, Mig, MIP--1α and RANTES were highly expressed in CSF and were associated with brain tissue lesions of patients with active MS[3, 42]. In contrast, the Th2-associated chemokines eotaxin and TARC were not detectable in MS brain lesion biopsies. Similarly, expression of the CCR5 ligands MIP-1α and RANTES were found at high levels in synovial fluid of RA but not osteoarthritis patients[44].

Recent studies, seeking to investigate the pathogenesis of MS and RA, have examined chemokine receptor expression on T cells localized to sites of inflammation and on circulating T cells in these autoimmune disorders. Using immunohistochemistry, BALASHOV et al.[3] as well as SORENSEN et al.[42] found marked up-regulation of CXCR3 and CCR5 expression on T cells in MS brain lesions. CCR5 was also expressed on macrophages, which likely co-migrate with T cells and contribute to local inflammation. Compared with blood T cells of MS patients, a higher proportion of $CD4^+$ and

$CD8^+$ T cells in CSF stained positive for CXCR3 and CCR5[42].

More investigation is required to definitively identify the functional phenotype(s) (i.e. Th1 vs. Th2) of the T cells involved in this immunopathology and, indeed, the antigen-specificity of these cells. It is not clear whether these T cells are myelin-specific or react with other undefined antigens. While T cells infiltrating MS lesions appear to have a low to undetectable expression of putative Th2-associated chemokine receptors such as CCR3 and CCR4[3, 42], analysis of T cell cytokine production patterns in MS has been restricted to circulating T cells only, so this remains an important issue to resolve. Following polyclonal activation, $CCR5^+$ T cells of MS patients demonstrated elevated IFN-γ production compared with $CCR5^-$ T cells from the same subjects[3] and $CCR5^+$/IFN-γ double positive T cells were identified by intracellular flow cytometry[3, 43]. In one study, $CXCR3^+$ T cells from only two of four MS subjects produced IFN-γ in response to combined anti-CD3/anti-CD28 stimulation, suggesting that $CXCR3^+$ cells may not always display a Th1 phenotype *in vivo*[3].

In RA, several studies have analysed chemokine receptor expression on T cells (defined as $CD3^+$, $CD4^+$ or $CD8^+$ cells) in synovial tissue sections and synovial fluid and found consistently high levels of CXCR3 and CCR5 expression[23, 25, 35, 44]. By flow cytometry, these two chemokine receptors were found to be co-expressed on ~80% of synovial fluid cells, a level much higher than that found in blood, suggesting an accumulation of $CXCR3^+$/$CCR5^+$ T cells in the synovial fluid of RA subjects[35]. In addition, T cells isolated from synovial fluid were found to migrate *in vitro* in response to MIP-1α and IP-10, ligands for CCR5 and CXCR3, respectively[23]. The synovial fluid T cells had very low levels of CCR3 and CCR4 expression[23, 44]. Following anti-CD3 stimulation, intracellular flow cytometry demonstrated that these cells had a Th1 phenotype (i.e. high IFN-γ-staining/low IL-4 staining)[44].

Given the redundancy inherent in the chemokine system, the question arises: are CCR5 and/or CXCR3 **necessary** for T cell trafficking to inflammatory sites in MS or RA? Approximately 10% and 1% of Caucasians are heterozygous and homozygous, respectively, for a 32 base-pair deletion allele of the CCR5 gene (termed CCR5 Δ32). Individuals homozygous for the CCR5 Δ32 allele do not express functional CCR5 receptors and heterozygous individuals have reduced levels. Expression of this allele has been linked to resistance to HIV-1 because the virus uses CCR5 as a co-receptor for entry into cells[21, 40]. Several investigators have examined the relationship between the mutant CCR5 allele and MS and RA inflammation. Despite elevated levels of CCR5 expression on T cells in these autoimmune disorders, there is no significant difference in the allele frequency of the CCR5 Δ32 gene between MS or RA patients and the control population[4, 10, 13, 25, 41]. However, CCR5 Δ32 heterozygous individuals may experience reduced MS- and RA-associated clinical symptoms[10, 41]. These data suggest a possible role for CCR1 and CCR3 in the context of reduced CCR5 expression or, alternatively, that CXCR3 alone is sufficient for migration of Th1-type cells to inflammatory sites in MS or RA. In support of the latter possibility, CXCR3 is expressed on more T cells than CCR5 at both MS and RA inflammatory sites[35, 42] and the lack of CCR5 expression does not hinder Th1 differentiation. Functional IFN-γ and IL-2-secreting Th1-type cells develop in CCR5 Δ32 homozygous individuals[31].

While enhanced expression of CXCR3 and CCR5 is clearly evident at sites of inflammation in MS and RA, how the levels of these receptors on blood T cells of patients compare to those on circulatory T cells of healthy individuals is much less clear. At present, there are a very limited number of cross-sectional studies published on this topic. Additionally, issues such as longitudinal stability of chemokine receptor expression and the effects of differential T cell counts between subjects need to be addressed. Interpretation of the currently available data is complicated by the use of different T cell markers (e.g. CD3 as opposed to CD4 or CD8). However, in one study, CCR5 expression on $CD3^+$ cells was found to be significantly elevated in the blood of progressive MS subjects, but not relapsing-remitting MS subjects, compared with controls[3]. Hence, the ability to measure elevated (or decreased?) chemokine receptor expression on peripheral blood T cells may demonstrate a potential to serve as a relatively unobtrusive indicator of inflammatory disease and, thus, deserves further investigation.

Atopic disorders

Atopic disorders such as allergic rhinitis and asthma are diseases characterized by sustained, inappropriate IgE responses to common environmental antigens (allergens). Upon re-exposure to allergen, local inflammation results in clinical symptoms, including sneezing and postnasal drainage in individuals with rhinitis and coughing, wheezing, shortness of breath and chest tightness in asthma sufferers. Atopic diseases are strongly associated with Th2-type immune responses induced by allergens locally and systemically[7, 18]. The Th2 cytokines IL-4, IL-5 and IL-13 stimulate a range

of effects associated with atopy, including isotype switching to IgE production and promotion of eosinophil development[36]. The role that chemokines play in the predisposition towards the development of atopic disease (or resistance thereto), in selective leukocyte recruitment and, ultimately, in the development of prophylactic or therapeutic strategies for atopy has only recently begun to be examined.

A wide range of chemokines produced by endothelial and epithelial cells, fibroblasts and inflammatory cells are up-regulated in rhinitis and asthma[12]. These include eotaxin, RANTES, MCP-3 and MCP-4, all of which bind the type 2 immunity-associated chemokine receptor CCR3. Eotaxin, in particular, is highly expressed in the nasal epithelium of allergic rhinitis patients and in the bronchial epithelium of asthmatics[28, 47]. In asthmatics, plasma eotaxin levels correlated with eosinophil counts and impairment of lung function[29]. Eotaxin is unique in that it exclusively binds CCR3, a receptor widely expressed on mast cells, basophils and eosinophils[15]. A subset of peripheral blood Th2-like cells are also reported to express CCR3[39]. Although expression of this chemokine receptor on T cells is controversial[1, 37], CCR3 levels have been shown to be up-regulated on T cells from normal non-allergic individuals in response to the combined stimulus of IL-2 and IL-4 *in vitro*[16]. These IL-2- and IL-4-stimulated T cells were highly responsive to eotaxin-induced chemotaxis, demonstrating functionality of CCR3 on T cells.

Evidence for the involvement of $CCR3^+$ T cells in atopic disorders comes largely from immunohistochemistry studies. Although most $CCR3^+$ cells in allergic tissue are eosinophils[47], small numbers of $CD3^+$ $CCR3^+$ T cells were found in bronchial biopsies of asthmatic individuals and biopsy specimens from lesional skin of patients with atopic dermatitis[46, 47]. $CCR3^+$ T cells appear to co-localize with eosinophils in sites of allergic inflammation[11]. While the cytokine production profile of these $CCR3^+$ T cells is unknown, $CCR3^+$ T cells were absent from the Th1 environment of rheumatoid arthritis synovium[11]. The above studies did not examine the expression of other chemokine receptors in allergic biopsy tissue.

Further studies are clearly required to definitively demonstrate a role for $CCR3^+$ T cells in allergic inflammation. T cells in systemic sclerosis skin biopsies did not express CCR3, suggesting that CCR3 expression is not required in all Th2-mediated inflammatory disorders[1]. The potential contribution of other Th2-associated chemokine receptors (i.e. CCR4 and CCR8) in atopic disorders is unknown. In one study, the CCR4 ligand MDC was detected at high levels in the sera of subjects suffering from atopic dermatitis, suggestive of a role for CCR4 in allergic inflammation[8]. In a murine model of allergic airway disease, sequential expression of CCR3 followed by CCR4 on lung-infiltrating Th2 cells was demonstrated with repeated antigen stimulation[22]. Whether a similar co-ordinated expression of these Th2-associated chemokine receptors occurs during allergic inflammation in humans remains to be investigated.

Concluding Remarks

The studies summarized in this review provide preliminary evidence that preferential chemokine receptor expression occurs on T cells *in vivo* during some human diseases associated with Th1- and Th2-polarization of the response. This suggests functional relevance for the distinct expression profiles first identified on T cell lines and clones. As some chemokines bind both Th1- and Th2-associated receptors (e.g. RANTES binds CCR3 and CCR5), chemokine receptor expression at the site of inflammation or in blood may be a more representative indicator of the type of immune response than chemokine production *in vivo*.

It should be noted that the studies discussed in this review have demonstrated the presence of specific chemokine receptors in inflammatory infiltrates (i.e. an association) but not their absolute **requirement** or a cause and effect relationship. Whether co-ordinated expression of more than one chemokine receptor is required for migration to inflammatory sites is unclear. Taken together, *in vivo* and *in vitro* studies indicate that chemokines and their receptors play important roles in multiple facets of T cell-mediated immune responses. Further investigation will define the precise contributions of specific chemokine/chemokine receptor interactions to Th1 and Th2 responses.

Acknowldegment. This research was supported by the Canadian Institutes of Health Research (CIHR). J. Darren Campbell holds a Manitoba Health Research Council Fellowship.

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Received in June 2000
Accepted in July 2000