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Authors

Choi, Jinjung

Selmi, Carlo

Leung, Patrick

et al.

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Chemokine and chemokine receptors in autoimmunity: the case of primary biliary cholangitis

Jinjung Choi[1,2], **Carlo Selmi**[3,4], **Patrick Leung**[1], **Thomas P. Kenny**[1], **Tania Roskams**[5], and **M. Eric Gershwin**[1]

[1]Division of Rheumatology, Allergy and Clinical Immunology, University of California Davis, CA

[2]Division of Rheumatology, CHA University Medical Center, Bundang, Korea

[3]Rheumatology and Clinical Immunology, Humanitas Research Hospital, Rozzano, Italy

[4]BIOMETRA Department, University of Milan, Italy

[5]Translational Cell and Tissue Research, University of Leuven, Belgium

Summary

Chemokines represent a major mediator of innate immunity and play a key role in the selective recruitment of cells during localized inflammatory responses. Beyond critical extracellular mediators of leukocyte trafficking, chemokines and their cognate receptors are expressed by a variety of resident and infiltrating cells (monocytes, lymphocytes, NK cells, mast cells, and NKT cells). Chemokines represent ideal candidates for mechanistic studies (particularly in murine models) to better understand the pathogenesis of chronic inflammation and possibly become biomarkers of disease. Nonetheless, therapeutic approaches targeting chemokines have led to unsatisfactory results in rheumatoid arthritis, while biologics against pro-inflammatory cytokines are being used worldwide with success. In this comprehensive review we will discuss the evidence supporting the involvement of chemokines and their specific receptors in mediating the effector cell response, utilizing the autoimmune/primary biliary cholangitis setting as a paradigm.

Keywords

innate immunity; chemokine receptor; tolerance breakdown; biologics; monoclonal antibody; autoimmune cholangitis

The chemokine alphabet

Chemokines (*chemeia*, alchemy, and *kinesis*, movement) represent a large family of cytokines that control leukocyte recruitment. Based on the common capability to induce

Corresponding author: M. Eric Gershwin, M.D., Division of Rheumatology, Allergy and Clinical Immunology, University of California at Davis School of Medicine, Genome and Biomedical Sciences Facility, 451 Health Sciences Drive, Suite 6510, Davis, CA 95616; Telephone: 530-752-2884; Fax: 530-752-4669; megershwin@ucdavis.edu.

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migration of various cells (chemotaxis), these small (8–14 kDa) proteins were cumulatively coined ‘chemokines’, derived from “chemotactic cytokines”. Chemokines share structural similarity and possess a pattern of cysteine residues near the amino-terminal (-NH2) domain, responsible for their tridimensional structure [1].

In 1961, the first chemokine, platelet factor-4 (PF-4), was identified by Deutsch and Kain [2]. At the earliest stages of chemokine discovery, names were created arbitrarily based on the producing cell type or the proposed function, as in the cases of platelet factor-4, monocyte chemoattractant protein 1 (MCP-1), stromal derived factor 1 (SDF-1) and mucosal epithelial chemokine (MEC). With the development and progress of EST (expressed sequence tag) databases and bioinformatics in the 1990s, significantly more chemokines were identified by molecular cloning. Interleukin-8 (IL-8/CXCL8) was first discovered in 1987 as a leukocyte chemoattractant characterized by the basic three-dimensional structure showing the conserved monomeric fold [3]. Since then, chemokines have grown to a large family now comprising over 50 members. Chemokine receptors are seven transmembrane spanning G protein-coupled receptors and expressed mainly on immune and inflammatory cells, although they have been found on non-immune cells such as resident cells within the liver [4–7].

In 2000, a systematic chemokine nomenclature was proposed and ligands are now named according to subclass (CC, CXC, CX3C, or C) followed by L for ligand and a unique number. In a complementary fashion, the chemokine receptor nomenclature uses CC, CXC, XC, or CX3C followed by R (for receptor) and then a number [8] (Figure 1). This nomenclature was not applicable to both humans and mice as it was designed primarily for human chemokines based on their genomic localization and was later updated for mice through chemokine genomic organization using the murine genome.

Structural characteristics of Chemokines

Chemokines include over 50 small, prevalently basic, heparin-binding proteins spanning 70–125 amino acids with molecular weights ranging from 6 to 14 kDa [9]. Based on the number and location of conserved cysteine residues near the N-terminus of the protein, chemokines are grouped into four subfamilies, designated CC, CXC, C, and CX3C (where X is any amino acid residue and C is cysteine) [10]. The biological effects of chemokines on their target cells follow the binding to specific G protein-linked transmembrane receptors called chemokine receptors. The majority of known chemokines belong to the CC and CXC subgroups, particularly with the first two cysteine residues adjacent to each other (CC) in 28 chemokines numbered CCL1 to 28. Although CC chemokines primarily induce monocyte chemotaxis, MCP-1 (CCL2), MIP-1α (CCL3) and RANTES (CCL5) may also exert chemotactic activity towards T cells and NK cells [11,12] and MIP-3α attracts IL-17-producing Th17 cells [13].

In the case of CXC chemokines, the first two conserved cysteine residues are separated by one non-conserved amino acid residue (C-X-C) and this applies to 17 CXC chemokines as chemoattractants for neutrophils. CXC chemokine ligands can be further subdivided based upon the presence or absence of the specific three amino acid sequence, glutamic acid-

leucine-arginine (the 'ELR' motif) preceding the first conserved cysteine residue. These structural differences are important because they determine the biological activity of CXC family members. Most of the CXC chemokines have the ELR sequence near the N terminus, termed the ELR-positive CXC chemokines (ELR^+), such as GRO-alpha (CXCL1), GRO-beta (CXCL2), GRO-gamma (CXCL3), ENA-78 (CXCL5), GCP-2 (CXCL6), NAP-2 (CXCL7), and IL-8 (CXCL8) which are potent chemoattractants for neutrophils and potent promoters for angiogenesis, whereas CXC chemokines that lack the ELR motif (ELR^-), such as platelet factor 4 (CXCL4), MIG (CXCL9) and IP-10 (CXCL10), are potent inhibitors of angiogenesis [14].

C chemokines lack the first and third cysteine, containing only disulfide bond with two cysteine residues at their N-terminus, whereas two disulfide bonds are present between the first and third, and the second and fourth cysteine residues, respectively, in CXC and CC chemokines. The C chemokine family includes only two members, i.e. lymphocyte-specific chemotactic peptide XCL1 (lymphotactin-alpha) and XCL2 (lymphotactin-beta) [15].

Finally, CX3C chemokines are characterized by the unique position of cysteine residues in which the two N-terminal cysteine residues are separated by three variable amino acids. To date, the only member of CX3C family is fractalkine (CX3CL1) which is unique among chemokines because it is synthesized as a membrane-bound molecule presented on a mucin-like stalk which functions as an adhesion molecule for capturing leukocytes, while the soluble form functions as a chemoattractant [16].

Functional classes of chemokines

Chemokines may be broadly arrayed into two functional groups, i.e. inflammatory and homeostatic [8] but discrimination is not strict and some overlapping is encountered [8,17]. Inflammatory chemokines are produced under inflammatory conditions by infiltrating and resident cells in response to pro-inflammatory mediators (IL-1 and TNF-α), bacterial products (LPS) and infectious agents (viruses). They are actively involved in the recruitment of monocytes, neutrophils, NK cells and other effector cells into site of inflammation and injury. Typical inflammatory chemokines include CCL2, CCL3, CCL4, CCL5, CXCL1, CXCL2 and CXCL8 [18]. In particular, ELR^+ CXC chemokines could promote the early stage of wound healing and granuloma formation, whereas CXC chemokines without the ELR motif might be produced in the late stage to antagonize angiogenesis [19]. On the other hand, homeostatic chemokines are constitutively and differentially expressed at steady levels in the bone marrow, lymphoid and nonlymphoid tissues (skin and mucosa) and act specifically on lymphocytes and dendritic cells, being involved in hematopoiesis, immune surveillance, and adaptive immune responses [20]. Their homeostatic role is to modulate the physiological migration of cells as part of normal tissue development and functional maintenance. Homeostatic chemokines inlcude CCL14, CCL19, CCL20, CCL21, CCL25, CCL27, CXCL12 and CXCL13.

Chemokine receptors

In 1991, the first chemokine receptors were identified with the discovery of two human interleukin-8 receptors on the surface of granulocytes, which were initially referred to as IL-8RA (now CXCR1) and IL-8RB (now CXCR2) [21,22]. Soon after that, the first CC chemokine receptor, i.e. macrophage inflammatory protein 1 alpha/RANTES receptor, was reported [23]. To date, 19 human chemokine receptors have been identified and the biological effects of chemokines are mediated by their binding to cell surface receptors that belong to the family of G protein-coupled receptors (GPCR) containing 7 transmembrane (7TM) domains, which trigger intracellular signals that direct cellular migration and other cellular functions [1]. Chemokine receptors are named according to a systemic nomenclature and they are also grouped into four subfamilies depending on the type of chemokine ligand they recognize. Thus, receptors for CC chemokines are referred to as CCR, receptors for CXC as CXCR, receptors for XC as XCR, and receptors for CX3C as CX3CR. The numbering is based on the date of deposition of the chemokine receptor sequence within the nucleic acid databases [24].

Chemokine receptors are typically activated only by class restricted ligands, except for Duffy antigen receptor complex (DARC), which binds both CC and CXC chemokines with high affinity [25]. A majority of chemokines share the same receptor for their chemotactic function, although several chemokines specifically bind to only one receptor with a one-on-one ratio. For instance, CXCR4 selectively binds to CXCL12 but CXCR3 binds to MIG (CXCL9), IP-10 (CXCL10) and I-TAC (CXCL11). Even when multiple ligands interact with a single receptor, diverse effects are produced because the binding affinity and the resulting effects differ across ligands. As an example, the chemokine receptors of inflammatory chemokines show a propensity to have a great number of chemokine ligands.

Most chemokines exert their chemotactic function as agonists, but some may have an ambivalent function with agonist and antagonist capacity depending on the different receptors. For instance, chemokine ligands such as CXCL9, 10, and 11 function as an agonist for CXCR3, while being antagonists for CCR3 [26]. CXCR3 is expressed preferentially on Th1 cells, but CCR3 is typically associated with Th2 cells. Consequently, this observation indicates that chemokines that attract Th1 cells via CXCR3 may concomitantly inhibit the recruitment of Th2 cells in response to CCR3 ligands, thus favoring T cell polarization and differentiation [26]. In contrast, homeostatic chemokine receptors bind only one or two chemokine ligands. Homeostatic receptors (CXCR4, CXCR5 and CCR7) are expressed on B cells, T cells, and mature dendritic cells. Some homeostatic chemokine receptors bind specifically to only one ligand such as CXCR4-CXCL12 (SDF-1) and CXCR5-CXCL13 (BCA-1) whereas others share the binding domain with more than one chemokines, such as CCR7-CCL19 (ELC) or CCR7-CCL21 (SLC) [27,28]. CCR7 controls the migration of naive T cells and antigen-activated dendritic cells to the T cell-rich areas of secondary lymphoid organs [29]. In contrast, CXCR5 and its ligand, CXCL13, play an essential role in B cell migration and thus the organization of B cell follicles in lymph nodes and spleen [30].

The genetics of chemokines and chemokine receptors

Chemokine genes are clustered within specific regions on the mammalian chromosomes. Two major gene clusters are present for CXC and CC genes which encode inflammatory CXC or CC chemokines, called the major-cluster chemokines (Figure 2). They are tightly located mainly on the human chromosomes 4q12-q21 (CXC) and 17q11-q21 (CC), respectively [31,32]. Each major cluster can be additionally divided into two discrete subregions. Therefore, the CXC major cluster is composed of GRO and IP-10 subregions, and the CC gene cluster contains MIP and MCP subregions.

In the **human GRO subregion**, nine functional genes, such as CXCL8, CXCL6, CXCL4L1, CXCL4, CXCL7, CXCL5, CXCL3 and CXCL2, are mapped. These chemokines can have a potent chemotactic activity for neutrophils as they interact with CXCR1 and CXCR2 [33].

In human and mouse **IP-10 subregion**, four functional genes, CXCL9, CXCL10, CXCL11 and CXCL13, are present. CXCL9, CXCL10 and CXCL11, as stated earlier, have been known as dual-function chemokines based on the fact that they are agonists for CXCR3, preferentially and act as antagonists for CCR3 [26]. CXCL13 is known to be a homeostatic chemokine trafficking and homing of B cells to the secondary lymphatic follicles associated with its cognate receptor, CXCR5, which is required for lymphoid follicle formation, follicular helper T cell (Tfh) and T cell-dependent B cell activation [34]. The gene for CXCL13 is located apart from the other members of IP-10 region on human chromosome 4 [35].

In the **MIP subregion of the CC gene cluster**, at least eight genes, such as CCL5, CCL16, CCL14, CCL15, CCL23, CCL18, CCL3 and CCL4, are located [33]. These chemokines, which act via G-protein-coupled cell surface receptors (CCR1, 3, 5) expressed by lymphocytes and monocytes/macrophages, are known for their chemotactic and proinflammatory effects but can also promote homoeostasis. In the human MCP subregion of the CC gene cluster, there are six genes, such as CCL2, CCL7, CCL11, CCL8, CCL13 and CCL1. In the mouse MCP subregion, the gene for CCL12 is additionally located, but the gene for human CCL13 does not exist. Chemokines in the CC cluster act as an inflammatory chemokines with exception of CCL1, which is involved in fibrogenesis [36]. Other group of genes for homeostatic chemokines are located separately or in small clusters on unique chromosomal locations (the non-cluster chemokines) [37].

Eighteen chemokine receptor genes with chemotactic functions have been identified in the human genome, such as 10 CCR, 6 CXCR, 1 XCR, and 1 CX3CR genes. Besides, five atypical chemokine receptor genes encoding DARC, CCBP2, CCRL1, CCRL2, CXCR7 have also been identified [38,39]. One major gene cluster of chemokine receptors is located mainly on the human chromosome 3. Most of the receptors in the major cluster interact with inflammatory cytokines, excluding CCR9, CXCR6 and XCR1 which could bind homeostatic chemokines. The other chemokine receptor genes are found as single genes or in mini-clusters on the human chromosome 2 (CXCR4, CXCR2, CXCR1, and CXCR7), 6 (CCR6), 11 (CXCR5), 17 (CCR10 and CCR7) and x (CXCR3) [40,41]. In mouse, the genomic organization of chemokine receptor genes is very similar to that of the human genes. In

addition, there is one additional gene termed Ccr1l1 (CCr1-like 1) in the mouse genome, which is located between Ccr1 and Ccr3 in the major gene cluster [42].

The majority of chemokine and chemokine receptor genes rank among the most rapidly evolving genes in phylogeny. Variation in gene sequence is common among individuals for most chemokine and chemokine receptors. However, the degree of polymorphism varies greatly among different genes.

Atypical chemokine receptors

In addition to conventional chemokine receptors which share conserved signaling pathway through G-protein coupled chemokine receptors (GPCRs), a smaller subgroup of chemokine receptors referred to as 'atypical chemokine receptors (ACR)' does not signal through the GPCRs upon ligation of cognate chemokines and lacks chemotactic activity. [43]. Because all seven-transmembrane domain-containing members of the ACR subfamily have modified or missing DRYLAIV motif, a highly conserved determinant of G protein coupling found in conventional GPCRs at the boundary between the third transmembrane domain and the second intracellular loop (ICL), ACR are not able to couple to G-proteins and could not then activate the typical G-protein-mediated signaling and cellular responses [44]. Even though not directly inducing chemotactic activity, ACR have preserved the ability to activate β-arrestin-dependent signaling pathways, which is required for biological functions of chemokine internalization and scavenging activity [45,46] leading to generation of chemokine gradients in tissues through the process of binding, sequestration, scavenge, transcytosis, or presentation of their chemokine ligand [45]. To date, the ACR subfamily includes five receptors, D6, Duffy Antigen Receptor for Chemokines (DARC), CXCR7 and CC-Chemokine Receptors like-1 and 2 (CCRL1 and CCRL2).

D6 was cloned in 1997 initially from placenta and hematopoietic stem cells [42,47] but more recent data confirmed that it is expressed in skin, gut, lung, liver, spleen, kidney, heart, muscle, brain, placenta, predominantly on lymphatic endothelial cells [42] and binds to inflammatory CC chemokines (CCR1–5) while failing to bind homeostatic CC chemokines or CXC, CX or CX3C chemokines. The expression of D6 may scavenge chemokines during their lymphatic flow in order to limit leukocyte trafficking and to adhere to the endothelial lining of lymphatics, which thus functions to aid in the resolution of inflammatory reactions. Mice that lack D6 demonstrate markedly increased inflammatory reactions, which might be associated with the exaggerated chemokine response at inflammation site [48].

DARC was initially discovered as the Duffy (Fy) blood group antigen and named after the first hemophiliac patient, Duffy, who was thought to develop antibodies to this antigen [49]. As the Duffy blood group antigen became known as a chemokine receptor that can bind many ligands, it was renamed as Duffy antigen receptor for chemokines (DARC). Human DARC binds a large number of proinflammatory CC and CXC chemokines [50]. DARC was originally identified on red blood cells, but has also been found as an abundant receptor on vascular endothelial cells, which are the primary site of leukocyte transmigration in most tissues [51]. The expression of DARC on erythrocytes functions to bind and remove chemokines from sites of overproduction, such as inflammatory sites [52]. Besides, the

function of DARC on endothelial cells facilitates the migration of chemokine-positive cells from tissues to the vascular lumen [43].

CXCR7 was originally identified as a GPCR isolated from a canine thyroid cDNA library and was considered to be an orphan receptor, named RDC1 [53]. Based on the sequence similarity and genomic localization of RDC1 between species, RDC1 was suggested to be a chemokine receptor. Moreover, RDC1 has been shown to bind to CXCL11/I-TAC, a ligand for CXCR3, and CXCL12/SDF-1, a ligand for CXCR4 [54]. Thus, RDC1 was recently renamed CXCR7, according to the current chemokine receptor nomenclature [55], despite lack of evidence of coupling to G proteins and cell activation. Instead of the canonical DRYLAIV motif present in classical chemokine receptors, CXCR7 has DRYLSIT sequence which could not induce classical signaling responses following ligand binding [54]. CXCR7 expression has been found on subsets of T and B cells, activated endothelial cells, fetal hepatocytes, placenta and vascular endothelium [27,54,56–58]. CXCR7 is also expressed on the surface of many tumor cells as a membrane-associated receptor protein [59]. Recent studies showed that CXCR7 acts exclusively as a decoy receptor, whereas other studies demonstrated that it also mediates the action of CXCL12 or CXCL11 [60,61]. Nevertheless, other research groups have still reported that CXCR7 is closely related to cancer proliferation, adhesion, invasion, metastasis and angiogenesis [58,62,63], or angiogenesis [64,65].

Chemokines/chemokine receptors in PBC

Primary biliary cholangitis (PBC) is a chronic cholestatic autoimmune disease selectively targeting the small and medium-size bile ducts [66,67] with the histological appearance of chronic nonsuppurative destructive cholangitis mediated by mononuclear inflammatory cells such as T cells, B cells, natural killer (NK) cells, macrophages, and eosinophils around the biliary tracts [68] driven by chemokines [69]. The potential contribution of chemokines and inflammation to the progression of PBC in chemokine-chemokine receptor network may provide important clues in biliary epithelial cell (BEC) injury in PBC and will be discussed in further detail in the next chapters (Figure 3).

MCP-1 (CCL2)

Monocyte chemoattractant protein (MCP-1/CCL2) is a potent chemoattractant chemokine that regulates the migration and infiltration of monocytes, T lymphocytes, NK cells and dendritic cells to the sites of inflammation and works as a key factor in initiating the various inflammatory responses [7,70]. MCP-1 is expressed predominantly by macrophages when stimulated by proinflammatory cytokines such as IL-1β, IL-6, and TNF-α, but can also be produced by a variety of other cells and tissues, including fibroblasts, endothelial cells, bronchoalveolar epithelial cells, renal tubules, hepatocytes, kupffer cells, and BEC [4,7,71–75].

At PBC immunohistochemistry, MCP-1-positive inflammatory cells can be detected mainly in portal tracts and accentuated around the damaged bile ducts, as well as around epitheloid granulomas that characterize the PBC liver [76]. In recent studies of human with biliary

disorders and in animal models of biliary fibrosis, BECs play an active role in expressing profibrogenic proteins and chemokines such as IL-8 and MCP-1. BEC-expressed chemokines cause mononuclear cells to infiltrate into the damaged sites in PBC [69] and BEC senescence contributes to non-suppurative destructive damage in PBC by altering microenvironment in conjunction with the upregulation of senescence-associated secretory phenotype (SASP) such as cytokines (IL-1 and IL-6), chemokines (IL-8 and MCP-1), growth factors, and profibrogenic factors [77,78]. Senescent BECs increase expression of MCP-1/CCL2 and CX3CL1 which may cause corresponding CCR2 and CX3CR1-expressing cells to infiltrate and inflame in small bile duct lesions in PBC (Table 1) [77,79].

MIP-1α (CCL3), MIP-1β (CCL4) and RANTES (CCL5)

Macrophage Inflammatory Proteins-1α (MIP-1α/CCL3) initially described in 1988 as MIP-1, along with the closely related MIP-1β (CCL4), is a proinflammatory chemokine of the CC subfamily. Both proteins are markedly produced by neutrophils, lymphocytes, dendritic cells, mast cells, NK cells and macrophages, and can be induced by various proinflammatory cytokines (IL-1, TNF-α, IFN-γ) or by exposure to bacterial lipopolysaccharide (LPS) [80]. **RANTES (CCL5)** is an 8 kDa protein classified as a CC chemokine, and identified along with MIP-1α and MIP-1β as the major HIV-suppressive factors produced by $CD8^+$ T cells [81]. Like MIP-1α and MIP-1β, RANTES is also secreted by a variety of cells including macrophages, activated NK cells, T cells, and certain types of tumor cells [82,83]. MIP-1α and 1β and RANTES play active roles in recruitment of inflammatory cells to the site of inflammation because their signals are delivered through CCR1 and CCR5 [84]. In particular, CCR5, a seven-transmembrane G-protein-coupled receptor, is used as their common receptor and predominantly expressed on Th1 cells, macrophages, dendritic cells and eosinophils [85]. MIP-1α and RANTES could modulate magnitude and cytokine polarity of the T cell response [86]. MIP-1α may have a direct effect on T cell differentiation by the finding that addition of MIP-1α to activated T cells promoted development of IFN-γ-producing cells [87].

The pathway via CCL5 and its receptors (**CCR1 and CCR5**) has been demonstrated to be implicated in the onset of liver fibrosis in experimental models using CCR1- and CCR5-deficient mice, confirming the activation of CC chemokines (MIP-1α/1β and RANTES) in human fibrogenesis [88]. Interestingly, it is also evident that the expression of CCR5 is augmented on circulating effector memory T cell ($CD45RO^{high}CD57^+$ $CD8^{high}$ T cells) in PBC cases and these T cells, which respond specifically to PDC-E2, accumulate around the portal area in PBC [89].

The transmigration of PBC liver-infiltrating mononuclear cells (LMNC) is significantly enhanced when stimulated with MIP-1α, MIP-1β and RANTES. In addition, BECs from PBC cases cocultured with autologous LMNCs produced significantly higher levels of MIP-1α and MIP-1β, RANTES as well as IP-10 [69]. Based on these findings, it is likely that BEC-induced chemokines may be active players in PBC pathogenesis and elicit migration and infiltration of mononuclear cells, and further leading to the expansion of autoreactive T cells contributing to liver lesions in PBC.

MIG (CXCL9) and IP-10 (CXCL10)

Gamma interferon (IFN-γ)-inducible protein 10 (IP-10) and monokine induced by IFN-γ (MIG) are members of CXC chemokine family. They were identified as products of genes induced by macrophages following exposure to IFN-γ [90,91]. They have potent chemotactic activities for activated T lymphocytes and NK cells [91]. They are similar in molecular structure and also have a common receptor, CXCR3, which is highly expressed on activated T cells and NK cells [92–95]. Early studies reported that increased expression of MIG and IP-10 is associated with IFN-γ production skewing to Th1-type immune response and found in patients with psoriasis and viral or bacterial infections [96–99]. MIG and IP-10 are preferentially expressed by human hepatic sinusoidal endothelial cells [5] and hepatocytes. Activated Kupffer cells along with sinusoidal endothelial cells are able to secrete MIG and IP-10 in response to IFN-γ [5,100,101]. Notably, activated hepatic myofibroblasts produce CXC (IL-8, MIG and IP-10) and CC (MCP-1, MIP-1α and RANTES) chemokines [7].

MIG and IP-10 mRNA expression is enhanced in inflamed liver [102,103] and their serum levels are increased during flares of chronic hepatitis B, suggesting that MIG and IP-10 are involved in recruitment of proinflammatory leukocytes into the liver [104]. In patients with PBC, the levels of circulating IP-10 and MIG are significantly increased, and expression of CXCR3 in livers is also increased, supporting the view that IFN-γinducible chemokines (CXCL9, CXCL-10, and CXCL11) and their specific receptor (CXCR3) could contribute to the activation and attraction of Th1 cells to the site of inflammation in the liver.

Fractalkine (CX3CL1)

Fractalkine is the only one member of CX3C chemokine family and signals through CX3CR1 [16,105]. Fractalkine exists in two different forms, one as the membrane-bound form that functions as an adhesion molecule for capturing circulating leukocytes and one soluble form containing the chemokine domain generated through the cleavage of extracellular portion by metalloproteinases such as ADAM10 or ADAM 17 [105,106]. Fractalkine is widely expressed in macrophages, dendritic cells, epithelial cells and endothelial cells [107–109]. The secretion can be greatly upregulated in response to inflammatory cytokines such as IL-1β, TNF-α and IFN-γ or LPS [110,111]. The presence of fractalkine is also found in rheumatoid arthritis synovium [109]. Upregulation of fractalkine and its receptor CX3CR1 in inflammatory cells (monocyte, T cells and NK cells) and target tissue expression may contribute to immune-related inflammatory diseases and promote trafficking and retention of CX3CR1-expressing cells to the site of inflammation [112]. Upregulation of fractalkine/CX3CR1 has been advocated to participate in the development of atherosclerosis [113], rheumatoid arthritis [109], systemic lupus erythematosus [114], and colon cancer [115]. In patients with PBC, the expression of fractalkine is upregulated in biliary epithelial cells (BEC), followed by the CX3CR1-expressing CD4+ and CD8+ T cells, suggesting that recruitment of mononuclear cells to bile ducts via fractalkine/CX3CR1 may contribute to the autoimmune inflammation of bile ducts [69,116,117]. Such a proinflammatory activity of BECs in PBC was demonstrated to be secondary to the intervention of liver-infiltrating mononuclear cells [69].

CXCR3

CXCR3 is a G protein-coupled receptor for CXC chemokines. CXCR3 exists mainly in two forms, A and B. While both bind to the CXC chemokines such as MIG (CXCL9), IP-10 (CXCL10), and I-TAC (CXCL11), CXCR3-B also binds CXCL4 [118]. Binding of chemokines to CXCR3 may lead to the diversity of cellular effects. CXCR3 is expressed primarily on activated T lymphocytes, NK cells and dendritic cells [94,119]. CXCR3 is activated by three IFN-γ-inducible ligands (MIG, IP-10, I-TAC). At the sites of inflammation, CXCR3-expressing T cells have been abundantly demonstrated and selectively recruited by MIG and IP-10 (CXCR3 ligands) [5,120].

According to the differentiation of $CD4^+$ effector subsets and then depending on their different inflammatory cytokine production, CXCR3 is differently upregulated and associated with the migration of effector cells to the sites of inflammation or infection [121–123]. Th1 cells preferentially express CXCR3 and CCR5, whereas Th2 cells favor the expression of CCR3 and CCR4 [95,124]. Interaction of CXCR3 and its signature ligands directs the migration and accumulation of Th1 cells into sites of Th1-mediated inflammation, which has been shown in inflammatory synovial tissues of rheumatoid arthritis, inflamed renal tissues of lupus nephritis and hepatic inflammation of chronic liver diseases [120,125,126]. These observations were supported by experimental evidence in which CXCR3 deficiency, using $CXCR3^{-/-}$ mice backcrossed into the MRL/*lpr* background, was associated with milder glomerulonephritis through interference with trafficking of Th1 and even Th17 cells into the kidney [127]. These findings suggest that IFN-γ-CXCR3-chemokine interaction play an important role for the recruitment of inflammatory cells into the focus of inflammation and contribute to Th1 and even Th17 immune-mediated diseases, further implying a possible approach to a therapeutic target.

Furthermore, studies in PBC patients demonstrated CXCR3-positive mononuclear cells were densely infiltrated into the damaged bile ducts in early rather than in advanced stages [128]. The frequency of CXCR3-expressing cells in peripheral blood and the inflamed portal areas, along with its chemokine ligands such as MIG and IP-10, significantly increased [129,130]. These data undoubtedly support that CXCR3-chemokine pair interaction may play a role in the generation of PBC.

Recent study identified that CXCR3 can be expressed on a subset of FOXP3+ Tregs which are detected at peripheral sites of chronic inflammation such as chronic hepatitis [126,131–133]. NKT cells have been also implicated in liver injury of hepatitis [134] as activated liver NKT cells secrete IFN-γ that can induce IFN-γ-inducible chemokines such as IP-10, which then induce the $CXCR3^+$ Treg recruitment into the inflamed portal area via a cytokine-chemokine pathway [132]. These observations support the possibility that interaction between NKT and Treg cells may contribute to the pathogenesis of autoimmune hepatitis and PBC. However, it is still unclear if the trafficking Tregs could fulfill their suppressive function of immune responses locally into inflamed liver [135,136].

CX3CR1

Chemokine CX3C motif receptor 1 (CX3CR1) is known as a fractalkine receptor and is a unique member of the GPCR family through which migration and adhesion of cells such as monocytes and lymphocytes are mediated [105,137]. CX3CR1 is mainly expressed on monocytes, T lymphocytes, dendritic cells, NK cells and mast cells [105,117,138,139]. CX3CR1 has been demonstrated to be preferentially expressed in Th1 cells which respond to fractalkine. CX3CR1-expressing cells also show perforin and granzyme B [140,141]. The expression of CX3CR1 is increased on monocytes during chronic inflammatory diseases such as rheumatoid arthritis, inflammatory kidney diseases and renal allograft rejection, coronary artery diseases, and inflammatory bowel diseases [105,109,142–144]. Studies reported that the co-localization and upregulation of fractalkine and CX3CR1 are also predominant in BECs and mononuclear cells, respectively, in PBC as well as chronic hepatitis C-liver injury patients [116,145]. It was reported that the expression of fractalkine and CX3CR1 was upregulated in injured bile ducts of PBC, CX3CR1-expressing mononuclear cells including $CD4^+$ and $CD8^+$ T cells were densely infiltrated into bile ducts and within the biliary epithelium. These findings suggest that migration and accumulation of CX3CR1-expressing cells around bile ducts, mediated by upregulated fractalkine/CX3CR1 interaction, may play a pivotal role in the pathogenesis of PBC and bile duct injury.

Expert commentary

There is extensive literature on the importance of chemokines and their cognate receptors in multiple autoimmune disorders and in a variety of other human diseases involving different degree of immune dysregulation [146–160]. In this paper we have focused on PBC, but with the understanding that the lessons in PBC are proof of principle on the molecular interactions and the cellular basis of chemokines and their receptors in other autoimmune diseases. Indeed, the interaction of chemokines with their chemokine receptors on inflammatory cells is believed to play a role in the establishment and maintainance of inflammation in PBC regulated by the microenvironmental milieu including cytokines and inflammatory mediators as ligands. Nonetheless, evidence supporting this view is currently limited and the mechanisms of immune activation and inflammatory response via chemokine/chemokine receptors in PBC remain enigmatic.

Over the past decade, a number of studies were directed to examine the contribution of chemokines in PBC, as in other autoimmune or chronic inflammatory conditions and this may be representative of the orchestrated symphony of immune cells and mediator that is expected to be at the bases of tolerance breakdown and autoimmunity development. Interaction between chemokines and chemokine receptors is involved in the pathogenesis of PBC by directing the migration and positioning of diverse inflammatory and immune cells into the small bile ducts. These infiltrating cells are able to produce a vast array of chemokines, develop chronic inflammation and then progressively proceed to fibrosis, which eventually leads to the vanishing of bile ducts. Beyond the recruitment of immune cells, recent data suggest that chemokine receptors can be expressed on non-immune cells such as hepatocytes, stellate cells, sinusoidal endothelial cells, and BEC, and they are able to express chemokine ligands [6,126].

Five-year view

The fundamental role of chemokines is to guide selective cells to specific tissues and the growing understanding of their roles in mediating the immune response raised high hopes towards personalized medicine to treat deficits in a range of biological processes within the immune system, such development, polarization, activation, and differentiation. Under autoimmune conditions, the chemokine-chemokine receptor interactions play important roles in trafficking of autoreactive lymphocytes into the focus of inflammation, and contribute to the determination of infiltrating pathological cell types and their communication with resident cells, leading to cellular and humoral immune responses resulting in autoimmune inflammation. In spite of the rapid progress in our understanding the functions of chemokines and their receptors in the immune system physiologically and pathologically, further elucidation of the molecular mechanisms and their regulation in vivo are awaited. In the meantime, monoclonal antibodies and small molecules are being proposed to treat chronic autoimmune diseases, as well exemplified by the large number of approaches used in rheumatoid and psoriatic arthritis [161], but data are largely inconclusive. A stronger contamination between areas of clinical and basic research may provide answers to the remaining major questions in PBC as in other areas; this may ultimately lead to the fulfillment of the domino prophecy in which finding the key to one autoimmune disease may well lead to a faster understanding of other unrelated conditions.

Abbreviations

ACR	Atypical chemokine receptors
BEC	Biliary epithelial cells
CCL	CC motif chemokine ligand
CCR	CC motif chemokine receptor
CXCL4L1	a homologue of CXCL4 chemokine or Platelet Factor 4 Variant 1
FOXP3	forkhead box protein 3
GPCR	G-protein coupled chemokine receptors
IFNγ	Interferon gamma
MCP	Monocyte chemoattractant protein
MIP	Macrophage inflammatory protein
NK	Natural killer cells
PDC-E2	Pyruvate dehydrogenase complex
PBC	Primary biliary cholangitis
RANTES	Regulated on activation, normal T cell expressed and secreted

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Reference annotations

* Of interest

** Of considerable interest

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Key issues

- The 2000 systematic chemokine nomenclature defines ligands according to subclass (CC, CXC, CX3C, or C) followed by L for ligand and a unique number;
- In a complementary fashion, the chemokine receptor nomenclature uses CC, CXC, XC, or CX3C followed by R (for receptor) and then a number;
- Beyond critical extracellular mediators of leukocyte trafficking, chemokines and their cognate receptors are expressed by a variety of resident and infiltrating cells (monocytes, lymphocytes, NK cells, mast cells, and NKT cells);
- Chemokine interactions have been implicated in a diverse range of biological processes in the immune system, such as immune cell development, polarization, activation, and differentiation;
- The majority of chemokine and chemokine receptor genes rank among the most rapidly evolving genes in phylogeny;
- Eighteen chemokine receptor genes with chemotactic functions have been identified in the human genome, such as 10 CCR, 6 CXCR, 1 XCR, and 1 CX3CR genes;
- In addition to conventional chemokine receptors which share conserved signaling pathway through G-protein coupled chemokine receptors (GPCRs), a smaller subgroup of chemokine receptors referred to as 'atypical chemokine receptors (ACR)' does not signal through the GPCRs upon ligation of cognate chemokines and lacks chemotactic activity;
- At PBC immunohistochemistry, MCP-1-positive inflammatory cells can be detected mainly in portal tracts and accentuated around the damaged bile ducts, as well as around epitheloid granulomas that characterize the PBC liver;
- The transmigration of PBC liver-infiltrating mononuclear cells (LMNC) is significantly enhanced when stimulated with MIP-1α, MIP-1β and RANTES;
- In patients with PBC, the expression of fractalkine is upregulated in biliary epithelial cells (BEC), followed by the CX3CR1-expressing CD4+ and CD8+ T cells.

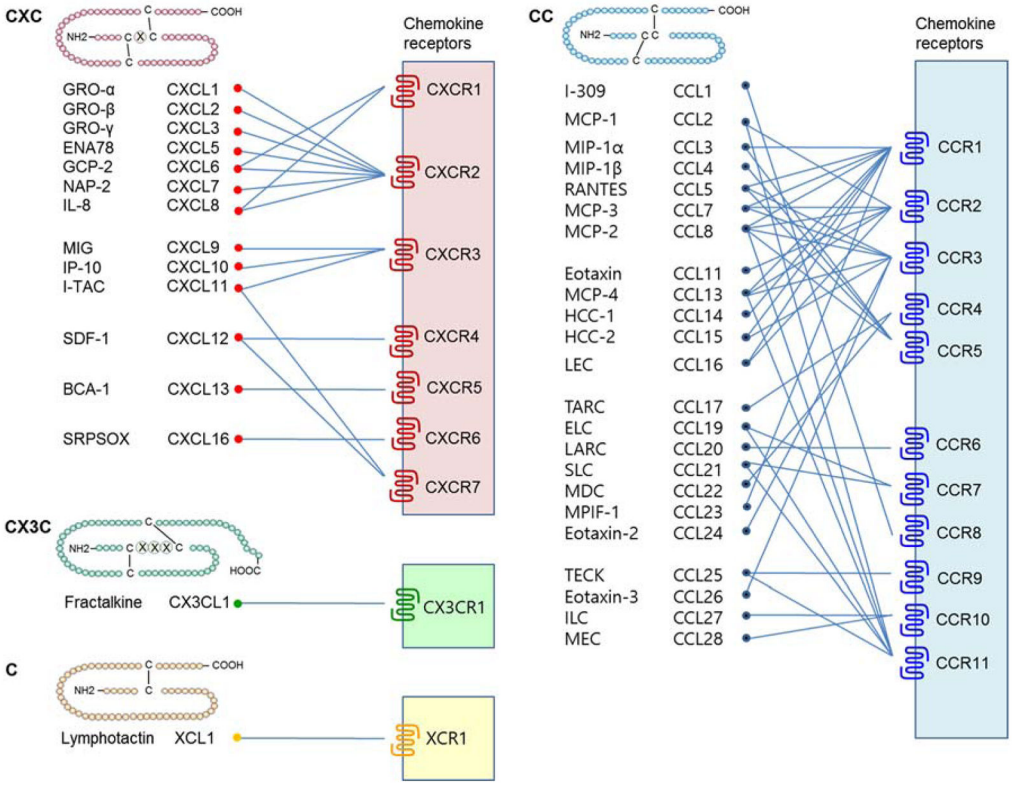

Figure 1.

Chemokine receptors are classified according to the chemokine family they bind, followed by an R (for receptor) and a number that corresponds to the order of its discovery. Specific chemokine ligand-receptor interaction lead to directional cellular migration, activation, and various biological responses via different intracellular signaling pathways.

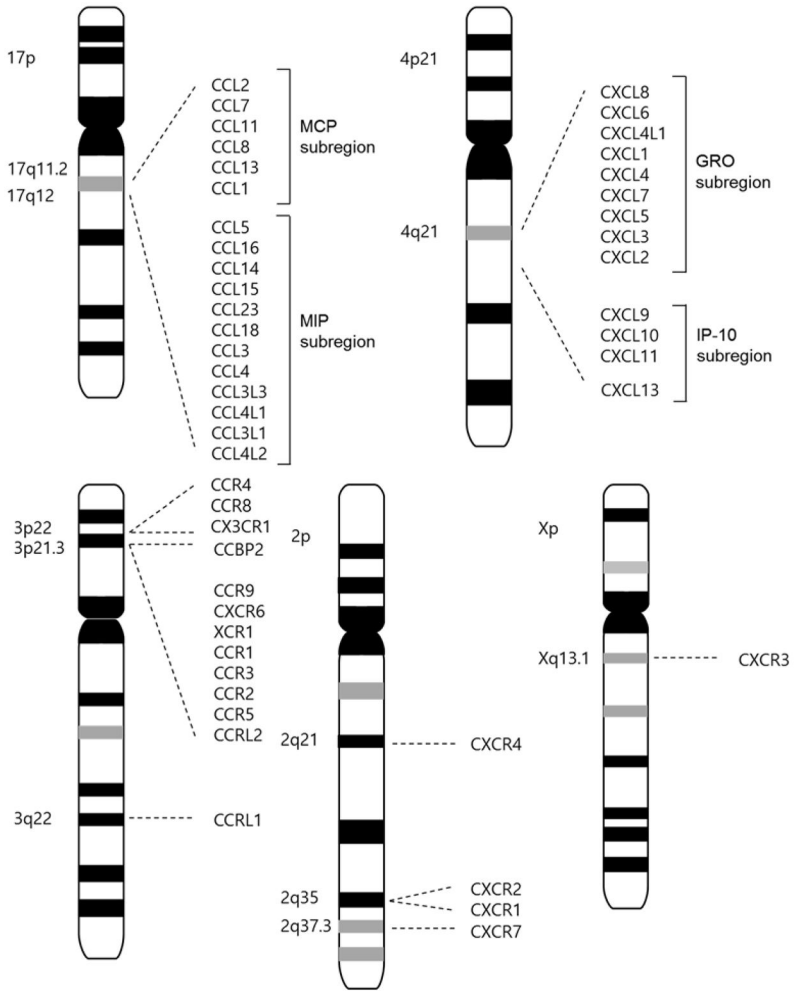

Figure 2.

Gene mapping of the human chemokines (CC and CXC chemokine gene clusters) and chemokine receptors on chromosomes 3, 4, 17, and X.

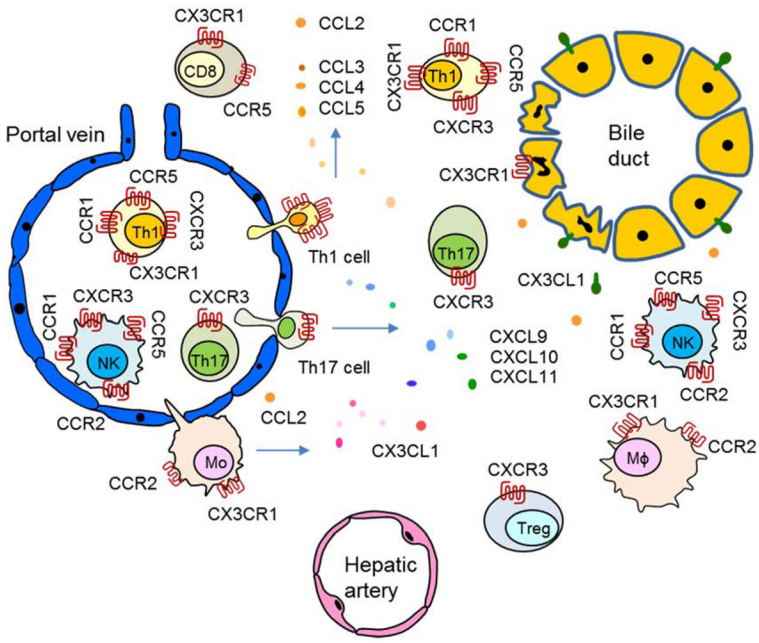

Figure 3.

Chemokines and chemokine receptors in the pathogenesis of primary biliary cirrhosis. Interaction of chemokines infiltrating immune cells, predominantly composed of Th1 cells, Th17 cells, NK cells, CD8+ T cells and monocytes, with their cognate chemokine receptors is found around the portal tract, eventually resulting in the immune-mediated destruction of small bile ducts.

Table 1

Main chemokines and receptors observed in primary biliary cirrhosis.

Chemokine	Common names	Receptor	Cells expressing receptors
CCL2	MCP-1	CCR2	Monocytes/macrophages, DCs, NK, basophils, HSCs
CCL3	MIP-1α	CCR1, CCR5	Th1 cells, NK, DCs, CD8 T cells, monocytes
CCL4	MIP-1β	CCR1, CCR5	Th1 cells, NK, DCs, CD8 T cells, monocytes
CCL5	RANTES	CCR1, CCR5	Th1 cells, NK, DCs, CD8 T cells, monocytes, HSCs
CCL20	MIP-3α	CCR6	Th17 cells, DCs, δ T, B cells, HSCs
CXCL9	MIG	CXCR3	Th1/Th17 cells, NK, DCs, Treg Kupffer cells, hSCs, LSECs
CXCL10	IP-10	CXCR3	Th1/Th17 cells, NK, DCs, Treg Kupffer cells, HSCs, LSECs
CXCL11	I-TAC	CXCR3	Th1/Th17 cells, NK, DCs, Treg Kupffer cells, HSCs, LSECs
CX3CL1	Fractalkine	CX3CR1	Monocytes/macrophages, NK Kupffer cells, BECs

DC, dendritic cells; NK, natural killer cells, HSCs, hepatic stellate cells; LSECs, liver sinusoidal endothelial cells; BECs, biliary epithelial cells.