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Commentary

Chemokines as novel therapeutic targets in inflammatory diseases

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Abstract

Chemokines and their receptors are a large family of inflammatory molecules responsible for a number of biological functions, including the accumulation of leukocytes at tissue sites. Over the past 10 years, a number of studies have indicated a role for chemokines and chemokine receptors in the pathophysiology of several inflammatory diseases, examples of which are multiple sclerosis, atherosclerosis, rheumatoid arthritis, and gastrointestinal diseases including hepatic disease. For this reason, it is not surprising that modulation of their pharmacology could be a prime target for drug discovery. This commentary provides a brief synopsis of our current knowledge of the role of chemokines and their receptors in the inflammatory process, and highlights the pros and possibly cons of chemokine and chemokine receptor antagonism in the therapeutic approach to several inflammatory diseases.

Keywords: Chemokines; Chemokine receptors; Leukocytes; Inflammation; Chemokine receptor antagonists; Inflammatory diseases

1. Introduction

Leukocyte recruitment into tissue is a cardinal feature of acute and chronic inflammatory diseases. Chemokines constitute a family of small (~8–15 kDa) structurally related proteins that have emerged as one of the most important regulators of leukocyte trafficking and activation [1–3]. In addition to their central role in controlling the recruitment of basal and inflammatory cells, chemokines have also been implicated in the tissue repair process, and abnormalities linked to cancer and autoimmune infections [3,4]. The chemokine superfamily is divided into four subfamilies (C-X-C, C-C, C, and C-X_3-C), based on the arrangement of their amino terminal cysteine residues. To date, over 40 chemokines have been identified [5,6]. The vast array of chemokine activities is mediated by the interaction of over 40 different chemokines with a relatively modest number of 18 G-protein-coupled receptors [5–7]. With only 18 chemokine receptors characterized to date, it is not surprising that most chemokine receptors can interact with multiple ligands and some chemokine ligands can bind to multiple receptors.

Chemokines are produced by immune and nonimmune cells, and can have profound and long-lasting biological effects both in the cellular environment of their release and at distant sites. The ability of chemokines and their receptors to participate in an exceptional range of physiological and pathological processes has led to new insights concerning the therapeutic potential of these proteins. In the last decade, tremendous progress has been made in the design of a number of inhibitors that can be used to limit chemokine and/or chemokine receptor function in *in vivo* disease models. Strategies that have been used to reduce chemokine/receptor activity include neutralizing antibodies, peptide antagonists, non-peptide antagonists, virally derived peptides, and gene-deficient mice [8–11]. Using such strategies, recent studies have provided irrefutable evidence that chemokines and their receptors are pivotal mediators in the pathophysiology of several inflammatory diseases (some of this information is summarized in Table 1). In most cases, a complete absence or deficiency of most of these chemokines/receptors was found to reduce the severity of disease. This mini-review summarizes

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Abbreviations: APAP, acetaminophen; BCA-1, B cell attracting chemokine-1; EAE, experimental autoimmune encephalomyelitis; ENA-78, epithelial cell-derived neutrophil activating protein; Hp, *Helicobacter pylori*; IL-8, interleukin-8; IP-10, interferon-inducible protein-10; KC, keratinocyte-derived chemokine; MCP-1, monocyte chemoattractant protein-1; MIG, monokine induced by interferon; MIP, macrophage inflammatory protein; MS, multiple sclerosis; RA, rheumatoid arthritis.

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Table 1
A simplified view of the effects of chemokine/receptor antagonism or deletion on inflammatory disease[a]

Inflammatory disease	Chemokine or receptor targeted	Pathological finding
Inflammatory bowel disease	CCR5	↑ T cell; ↓ colonic ulcer
	CCR1/5	↓ Mϕ, MC, N; ↓ colonic ulcer
	CXCR2	↓ N
	MIP-1α	↓ N; ↓ colonic ulcer
APAP-induced liver injury	CCR2	↑ Liver injury
	CXCR2	↑ Liver injury
LPS-induced liver injury	TARC	↓ T cell; ↓ liver injury
Atherosclerosis	CXCR2	↓ Mϕ; ↓ atherosclerotic lesion
	CCR2	↓ Mϕ; ↓ atherosclerotic lesion
	MCP-1	↓ Mϕ; ↓ atherosclerotic lesion
Tissue transplant rejection	CCR1	↓ Rejection
	CXCR3	↓ Rejection
	RANTES	↓ Mϕ, T cell; ↓ rejection
Arthritis	RANTES	↓ Histopathological score
	CCR2	↓ Mϕ, T cell; ↓ histopathological score
	CCR1/CCR5	↓ Histopathological score
	IL-8	↓ N; ↓ histopathological score
	ENA-78	↓ Histopathological score
LPS-induced sepsis	CCR4	↓ Mϕ; ↓ mortality
CLP-induced sepsis	MDC	↓ Mϕ, N; ↑ mortality
CLP-induced sepsis	MCP-1	↓ Mϕ; ↑ mortality
CLP-induced sepsis	C10	↑ Mortality
EAE	CCR5	No effect on severity of disease
	MIP-lα	No effect on severity of disease
	CCR2	↓ Mϕ, T cells; ↓ severity of disease
	CCR1	↓ Severity of disease
	MCP-1	↓ Mϕ; ↓ severity of disease
	IP-10	↓ Mϕ; ↓ severity of disease

[a] Outcome on a number of inflammatory diseases of the effects of chemokine/chemokine receptor antagonism/deletion. The role played by various chemokines/chemokine receptors on inflammatory cell recruitment and tissue injury after antagonism or deletion is shown in pathological finding. These data are based on a number of animal studies [2–4,6–8,10,12,20–26,30–34,37–40]. N, neutrophils; Mϕ, macrophages; MC, mast cells; LPS, lipopolysaccharide; and CLP, cecal ligation and puncture.

evidence from both the laboratory and the clinical setting that supports the concept that ''chemokines and their receptors are potential targets that can be exploited for therapeutic intervention in inflammatory diseases.''

2. Chemokines in inflammatory diseases

2.1. Hepatic diseases

Despite several reports that inflammatory cell recruitment to the liver is a common feature of liver diseases [6,12], the mechanisms underlying the recruitment of inflammatory cells to hepatic tissue following injury are still far from clear. Recent advances in the understanding of chemokine biology have raised hopes of uncovering the specific role of chemokines and their receptors in the pathophysiology of hepatic inflammation and injury.

CXCL8/interleukin-8 (IL-8) is one of the first chemokines to be recognized as a possible mediator of hepatitis [13]. During initial clinical studies in which the expression of CXCL8/IL-8 was assessed in livers from patients with alcoholic hepatitis, the levels of CXCL8/IL-8 were observed to be consistently higher than those observed in normal livers [13,14]. Furthermore, serum measurement of CXCL8/IL-8 was found to be closely associated with the severity of liver injury during alcoholic hepatitis [15]. The authors [13] hypothesized that CXCL8/IL-8 expressed by damaged liver parenchyma cells may be a chemoattractant for neutrophils. Increased expression of a number of mononuclear cell attracting chemokines (CCL2/monocyte chemoattractant protein-1 (MCP-1), CCL8/MCP-2, and CCL7/MCP-3) has also been observed in liver biopsies from patients with primary biliary cirrhosis [16] and fulminant hepatic failure [17]. In addition, Tsuneyama *et al.* [16] observed that biliary epithelial cells in the portal tract were labeled positively for these chemokines. Chemokine expression was assessed in liver biopsies from patients with active chronic hepatitis C [18], and augmented hepatic expression of CXCL10/interferon-inducible protein-10 (IP-10) and CXCL9/monokine induced by interferon (MIG) was observed in the sinusoidal endothelium [18,19]. *In vitro*, human hepatic sinusoidal endothelial cells were found to secrete CXCL10/IP-10 and CXCL9/

MIG in response to stimulation with interferon-γ in combination with either IL-1 or tumor necrosis factor-α. The authors [18] concluded that CXCL10/IP-10 and CXCL9/MIG expressed by the sinusoidal endothelium could be a chemoattractant for T lymphocytes. Furthermore, assessment of the expression of CXCR3 (a receptor for IP-10 and MIG) in hepatic biopsies from patients with active chronic hepatitis C, indicated that CXCR3 was expressed on infiltrating T lymphocytes [18], perhaps a hint that increased expression of CXCL10/IP-10 and CXCL9/MIG during chronic hepatitis C infection may promote the continuous recruitment of CXCR3-expressing T cells into the hepatic lobule.

That chemokines and their receptors play a major role in hepatic inflammation and injury has been established by a number of laboratory studies in a variety of animal models of hepatitis. The inhibition of CCL17/thymus-activated regulated chemokine (TARC) during bacteria-induced fulminant acute liver injury in mice reduced the recruitment of CCR4-expressing $CD4^+$ T cells in the liver and also reduced hepatic injury [20]. Likewise, a crucial role for ELR^+-CXC chemokines in the pathophysiology of liver diseases is suggested by the effectiveness of CXCL2/macrophage inflammatory protein-2 (MIP-2), CXCL1/keratinocyte-derived chemokine (KC), and CXCL5/epithelial cell-derived neutrophil activating protein (ENA-78) antibodies in causing the attenuation of inflammation and tissue injury associated with hepatic ischaemia–reperfusion injury [21,22]. Through the use of neutralizing antibodies, it has also been reported that the CCL3/MIP-1α/CCR5 axis contributes to T cell recruitment and hepatic injury during graft-versus-host disease [23].

Although chemokines and their receptors mediate hepatic inflammation and injury, some studies have also revealed a possible protective role for chemokines and their receptors in hepatitis. Thus, inhibition of CXCR2 or CXCL2/MIP-2 expression during acetaminophen (APAP)-induced acute liver injury causes an increase in the degree of liver hemorrhage and necrosis [24]. Further evidence that chemokine receptors play an important protective role in the context of experimental hepatitis derives from targeted gene deletion studies. Hogaboam *et al.* [25] demonstrated that the induction of acute hepatitis with APAP in CCR2 gene-deficient mice leads to increased hepatic inflammation and injury. Furthermore, exogenous administration of CXCR2 ligands (CXCL8/IL-8, CXCL2/MIP-2, and CXCL5/ENA-78) has been found to cause enhanced liver regeneration and reduced hepatic injury in the APAP model, most likely by facilitating hepatocyte proliferation [24]. Novel and important findings such as these provoke new questions and stimulate speculation. An obvious question arising from these findings is whether peptide chemokine agonists could be applied therapeutically in the clinical setting due to their very short half-life and rapid clearance from the circulation. Gene therapy in which adenoviral vectors are used to deliver specific chemokine genes to sites of inflammation is now being explored. For example, the administration of CXCL2/MIP-2 cDNA by an adenovirus vector resulted in less hepatic injury [12]. In this regard, such an approach looks promising.

2.2. Rheumatoid arthritis

Rheumatoid arthritis (RA) is best characterized as a chronic inflammatory disease in which the infiltration of the synovial membrane with mononuclear leukocytes and pannus formation over the underlying cartilage and bone have been implicated in the injury associated with this disease. The inflammatory process observed in RA is mediated, in part, by chemotactic factors released by inflamed tissues. Over the years, a significant body of evidence has been generated to support a role for chemokines and their receptors in the pathogenesis of RA. Chemokine expression in synovial tissue from human and experimental RA was found to be increased markedly over that observed in normal tissue [4,26–29]. Further evidence implicating chemokines in the pathogenesis of RA has come from chemokine/receptor antagonist studies. Gong *et al.* [30] demonstrated that treatment of mice with a CCL2/MCP-1 receptor antagonist modified the severity of the disease, as demonstrated by reduced joint swelling, tissue destruction, and pannus formation. Administration of Met-RANTES, a CCR1/CCR5 antagonist or a CCL5/RANTES antibody, was also found to be effective at reducing the severity of the disease in mice [31] and in rats [26]. The CXC chemokines have also been implicated in the pathogenesis of RA. This can be likely linked to the intense influx of blood-borne neutrophils into the synovial joint, detected during the active phases of the disease. Halloran *et al.* [32] reported that expression of CXCL5/ENA-78-like protein correlated with the progression of inflammation of the joints. Furthermore, anti-human ENA-78 antibody administered before onset of the disease modified the severity of RA in rats, while administration of anti-ENA-78 antibody after clinical onset of RA did not modify the disease [32]. CXCL8/IL-8 antibody was shown to attenuate joint swelling and neutrophil infiltration that occurred in monosodium urate crystal-induced arthritis in rabbits [33]. Data derived from studies involving chemokine receptor knockout mice show that mice lacking the CXCL8/IL-8 receptor, CXCR2, have fewer neutrophils infiltrating into an artificial air-pouch during acute urate crystal-induced gouty synovitis [34]. Similarly, the CXCR2 ligand KC is released by resident macrophages to attract neutrophils, in another model of gouty arthritis [35].

Taken together, the efficacy of CCR2, CCR1, CCR5, CXCR2, CXCL8, and CXCL5 antagonists in disease models of RA indicates that these chemokines/receptors are reasonable therapeutic targets. In 2000, a phase II clinical trial of the humanized CXCL8/IL-8 antibody ABX-IL-8

for use in the treatment of RA was initiated (Abgenix Inc., California, USA).

2.3. Multiple sclerosis

The recruitment of macrophages and T lymphocytes into the CNS during the development of multiple sclerosis (MS) is a critical feature of this chronic inflammatory disease [36]. The pathological association between the expression of chemokines/receptors, the distribution of inflammatory cells in the CNS, and the development of clinical disease in MS has long been recognized [8,36,37]. In the last few years, using targeted gene deletion approaches, success has been achieved in understanding the functional role of chemokines and their receptors in an animal disease model of MS (experimental autoimmune encephalomyelitis, EAE). Mice lacking the CCL2/MCP-1 receptor, CCR2, are protected from EAE as demonstrated by decreased clinical and histological disease incidence and severity, as well as reduced T cell and monocyte infiltration [37,38]. Thus, CCR2 plays a crucial role in the pathogenesis of EAE. Furthermore, mice lacking the CCR1 receptor are also less susceptible to injury and inflammation in EAE [39]. In contrast, both CCL3/MIP-1α-deficient and CCR5-deficient mice were fully susceptible to EAE as shown by comparable disease severity and infiltration of the CNS by granulocytes and mononuclear cells in both knockout and wild-type mice [40]. This observation in animal studies correlates with the observation in humans where people who are naturally deficient in the CCR5 chemokine receptor are not protected against MS attack [41]. To explore the role of CXCL10/IP-10 in EAE, Fife *et al.* [42] administered an anti-CXCL10/IP-10 antibody to mice with EAE. They observed that this treatment decreased clinical and histological disease incidence, severity, as well as infiltration of mononuclear cells into the CNS. These compelling experiments confirm that chemokine receptors such as CCR1 and CCR2 and the chemokine CXCL10/IP-10 are important mediators in the pathophysiology of EAE, and thus, potential targets for therapeutic intervention.

2.4. Hp-mediated infection

Helicobacter pylori (Hp), a Gram-negative bacterium, has been implicated in the pathogenesis of chronic active gastritis and other gastroduodenal diseases including peptic ulcer, gastric carcinoma, and gastric lymphoma. Colonization of the gastric mucosa by Hp is consistently accompanied by gastric inflammation comprised of neutrophilic infiltrates in the gastric epithelial layer and mononuclear cell accumulation in the lamina propria, with varying degrees of epithelial cell degeneration and injury [43,44]. The acquisition of Hp-induced gastritis is thought to occur in early life where it passes unnoticed clinically. Studies aimed at understanding the mechanism of Hp-induced gastritis have found that Hp can induce mucosal damage by producing substances that directly damage epithelial cells and through the release of inflammatory mediators such as chemokines that promote the recruitment and activation of inflammatory cells [45,46].

The concept that chemokines and their receptors exert important pro-inflammatory effects during Hp-mediated gastritis is largely supported by clinical observations of increased expression of chemokines such as CXCL8/IL-8, CXCL5/ENA-78, CXCL10/IP-10, and CXCL13/B cell attracting chemokine-1 (BCA-1) in mucosal biopsies [47–49]. Both epithelial cells and infiltrating leucocytes have been found to be cellular sources of these chemokines [47–49]. Further support for a role of chemokines in the pathogenesis of Hp-mediated gastritis comes from several clinical studies in which gastric chemokine expression was found to correlate with the magnitude of gastritis and inflammatory cell recruitment [44,50,51]. Therefore, targeting these chemokines and/or their receptors might prove clinically beneficial in Hp-mediated infections.

Increased expression of chemokines is also seen in other forms of Hp-mediated gastrointestinal inflammation. For instance, the expression of CXCL8/IL-8 and CCL3/MIP-1α is increased in mucosal biopsies from patients with Hp-mediated peptic and duodenal ulcers [52,53]. Furthermore, biopsies from patients with Hp-associated gastric lymphoma exhibited increased expression of the CXC chemokine CXCL13/BCA-1 [54]. The extent to which the actions of chemokines and their receptors contribute to the pathophysiology of Hp-mediated inflammation is difficult to infer because of the lack of functional study data from animal models. However, it is noteworthy that the eradication of Hp results in the resolution of mucosal inflammation and reduced chemokine expression [55,56].

3. Epilogue

In the last decade, we have witnessed major advances in the understanding of the pathophysiological role of chemokines and their receptors in several disease states. Chemokine/receptor gene-deficient mice are enabling us to determine the roles of individual chemokines and their receptors in the complex network of interactions that orchestrate the inflammatory process. Although results from gene-deficient mice have extended our understanding of the roles of specific chemokine/receptor genes in disease progression/regression, it seems clear that pharmacological approaches will also be required to provide proof-of-concept for these potential drug targets. Inhibiting the actions of specific chemokines and their receptors using a pharmacological approach has met with considerable success, as is seen in animal disease models such as inflammatory bowel disease, hepatic diseases, allergic diseases, and arthritis. Furthermore, chemokine agonists also appear to have beneficial effects involving tissue repair, as has been observed in experimental hepatic

diseases. Based on the current concepts, chemokine agonists and antagonists targeted against chemokines and their receptors have the potential to become therapeutically important in the treatment of several inflammatory diseases. Nevertheless, it remains to be seen whether clinical trials will ultimately bear out this promise.

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