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Review

CC Chemokine Receptor 4 (CCR4) as a Possible New Target for Therapy

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Abstract: Chemokines and their receptors participate in many biological processes, including the modulation of neuroimmune interactions. Approximately fifty chemokines are distinguished in humans, which are classified into four subfamilies based on the N-terminal conserved cysteine motifs: CXC, CC, C, and CX3C. Chemokines activate specific receptors localized on the surface of various immune and nervous cells. Approximately twenty chemokine receptors have been identified, and each of these receptors is a seven-transmembrane G-protein coupled receptor. Recent studies provide new evidence that CC chemokine receptor 4 (CCR4) is important in the pathogenesis of many diseases, such as diabetes, multiple sclerosis, asthma, dermatitis, and cancer. This review briefly characterizes CCR4 and its ligands (CCL17, CCL22, and CCL2), and their contributions to immunological and neoplastic diseases. The review notes a significant role of CCR4 in nociceptive transmission, especially in painful neuropathy, which accompanies many diseases. The pharmacological blockade of CCR4 seems beneficial because of its pain-relieving effects and its influence on opioid efficacy. The possibilities of using the CCL2/CCL17/CCL22/CCR4 axis as a target in new therapies for many diseases are also discussed.

Keywords: CCR4; CCL17; CCL22; CCL2; chemokines; opioids; neuropathy

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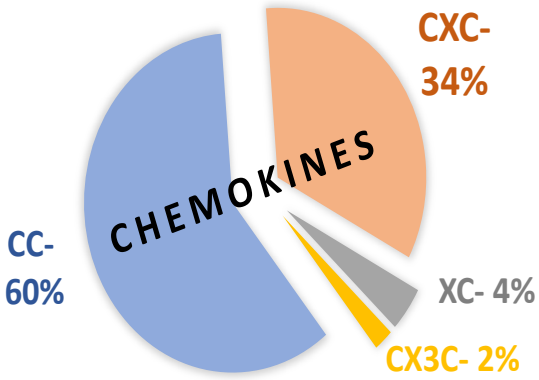
1. Chemokines and Their Receptors

The 20 receptors for chemokines have been described and divided into four main families: CC, CXC, XC, and CX3C [1]. Each of these receptors are bound to a G protein at the C-terminus and interacts with its intracellular elements. The structure of these receptors includes a single helical polypeptide chain that crosses the cell membrane seven times with two disulfide bridges located between the N-terminal domain and the second extracellular loop and between the first and third extracellular loops [2,3]. Approximately 50 ligands of chemokine receptors have been identified and classified into four basic families: CC, CXC, XC, and CX3C [1]. Some chemokines have pleiotropic properties and activate different receptors (Figure 1), including CCL3/CCR1, CCR5; CCL4/CCR5, CCR8; CCL5/CCR1, CCR3, CCR5; CCL7/CCR1, CCR2; CCR3; CCR5; and CCL11/CCR2/CCR3/CCR5, and some chemokines activate only one receptor, such as CX3CL1-CX3CR1, CXCL25-CXCR9, and CXCL13-CXCR5 [3]. After binding with their ligand, chemokine receptors activate a cascade of intracellular signaling pathways, e.g., mitogen-activated protein kinase (MAPK), phospholipase C (PLC), and phosphatidylinositol 3-kinase (PI3-K), which lead to a wide range of cellular processes, such as chemotaxis, adhesion, cell activation or cell polarization, which amplify the production of cytokines [4–6].

Chemokine receptors play key roles in several diseases, including allergies, atherosclerosis, viruses, cancer, various infections, and inflammation [7]. Research indicates that immune cells and glia (microglia and astrocytes) express most chemokine receptors in the central nervous system, but many of these receptors are also located on neurons [8–12].

FAMILY	CHEMOKINE	RECEPTORS
CC-	CCL1, I-309	CCR8
	CCL2, MCP-1	CCR1, CCR2, CCR4
	CCL3, MIP-1α	CCR1, CCR5
	CCL4, MIP-1β	CCR1, CCR5, CCR8
	CCL5, RANTES	CCR1, CCR3, CCR5
	CCL6, -	CCR1
	CCL7, MCP3	CCR1, CCR2, CCR3, CCR5
	CCL8, MCP-2	CCR1, CCR2, CCR3, CCR5
	CCL9, -	CCR1
	CCL10, -	unknown
	CCL11, Eotaxin	CXCR3, CCR3, CCR5
	CCL12, -	CCR2
	CCL13, MCP-4	CCR1, CCR2, CCR3, CCR5
	CCL14, HCC-1	CCR1
	CCL15, HCC-2	CCR1, CCR3
	CCL16, HCC-4	CCR1
	CCL17, TARC	CCR4
	CCL18, DC-CK1	unknown
	CCL19, MIP-3β	CCR7
	CCL20, MIP-3α	CCR6
	CCL21, 6Ckine	CXCR3, CCR7
	CCL22, MDC	CCR4
	CCL23, MPIF-1	CCR1
	CCL24, Eotaxin-2	CCR3
	CCL25, TECK	CCR9
	CCL26, Eotaxin-3	CCR3, CCR10
	CCL27, CTACK	CCR10
	CCL28, MEC	CCR3, CCR10, CCR10



FAMILY	CHEMOKINE	RECEPTORS
CXC-	**CXCL1,** GROα	**CXCR2**
	CXCL2, GROβ	**CXCR2**
	CXCL3, GROγ	**CXCR2**
	CXCL4, PF4	**unknown**
	CXCL5, ENA-78	**CXCR1, CXCR2**
	CXCL6, GCP-2	**CXCR1, CXCR2**
	CXCL7, NAP-2	**CXCR1, CXCR2**
	CXCL8, IL-8	**CXCR1, CXCR2**
	CXCL9, Mig	**CXCR3**
	CXCL10, IP-10	**CXCR3**
	CXCL11, I-TAC	**CXCR3**
	CXCL12, SDF-1α/β	**CXCR4**
	CXCL13, BCA-1	**CXCR5**
	CXCL14, -	**unknown**
	CXCL15, -	**unknown**
	CXCL16, -	**CXCR6**
XC-	**XCL1,** SCM-1α	**XCR1**
	XCL2, SCM-1β	**XCR1**
CX3C-	**CX3CL1,** Fractalkine	**CX3CR1**

Figure 1. Classification of chemokine family—chemokines (systematic and original names) and their receptors. Abbreviations of original names of chemokines: BCA-1, B-cell-attracting chemokine 1; CTACK, cutaneous T-cell-attracting chemokine; DC-CK1, dendritic-cell-derived CC chemokine 1; ENA-78, epithelial-cell-derived neutrophil attractant 78; GCP, granulocyte chemotactic protein; GRO, growth-related oncogene; HCC, haemofiltrate CC chemokine; IL, interleukin; IP-10, interferon-inducible protein 10; I-TAC, interferon-inducible T-cell alpha chemoattractant; LEC, liver-expressed chemokine; LCC-1, liver-specific CC chemokine-1; MCP, monocyte chemoattractant protein; MDC, macrophage-derived chemokine; MEC, mammary-enriched chemokine; Mig, monokine induced by interferon γ; MIP, macrophage inflammatory protein; MPIF, myeloid progenitor inhibitory factor; NAP, neutrophil-activating peptide; PF4, platelet factor 4; RANTES, 'regulated on activation, normally T-cell-expressed and -secreted'; SCM-1α/β, single C motif-1 α/β; SDF, stromal-cell-derived factor; TARC, thymus- and activation-regulated chemokine; TECK, thymus-expressed chemokine.

The involvement of several chemokine receptors, such as CCR1 [13,14], CCR2 [4,15,16], CCR5 [17,18], CCR8 [19], CXCR2 [9], CXCR3 [20], CXCR4 [21,22], and XCR1 [23], has been documented in nociception and neuropathic pain of different origins (Table 1). Blockade of

these receptors relieves pain and shows beneficial effects in numerous diseases, such as colitis [24], rheumatoid arthritis [25,26], allergies [27], HIV [28,29], leukemia [30], and multiple sclerosis [31]. Because of the important role of chemokines and chemokine receptors in various physiological functions and their association with many pathological conditions, these factors have become targets in the search for new treatments for several human diseases. However, the role of many of these factors is not fully known, and one of the most interesting factors of this group is the C-C chemokine receptor type 4 (CCR4). CCR4 influences the development of the inflammatory process [32], and subsequent researchers demonstrated the important role of this receptor in the processes of nociception [33–35], immunological diseases [36–39], and cancer [38–40]. Data indicate that CCL17 and CCL22 are selective CCR4 ligands [37,41]. However, it was suggested that CCL2, which was widely regarded as the major ligand of CCR2, also acted via CCR4 [42], which is interesting because these chemokines are important agents in physiology and pathology (Figure 2). Therefore, the role of this receptor and its endogenous ligands is discussed in the following chapters.

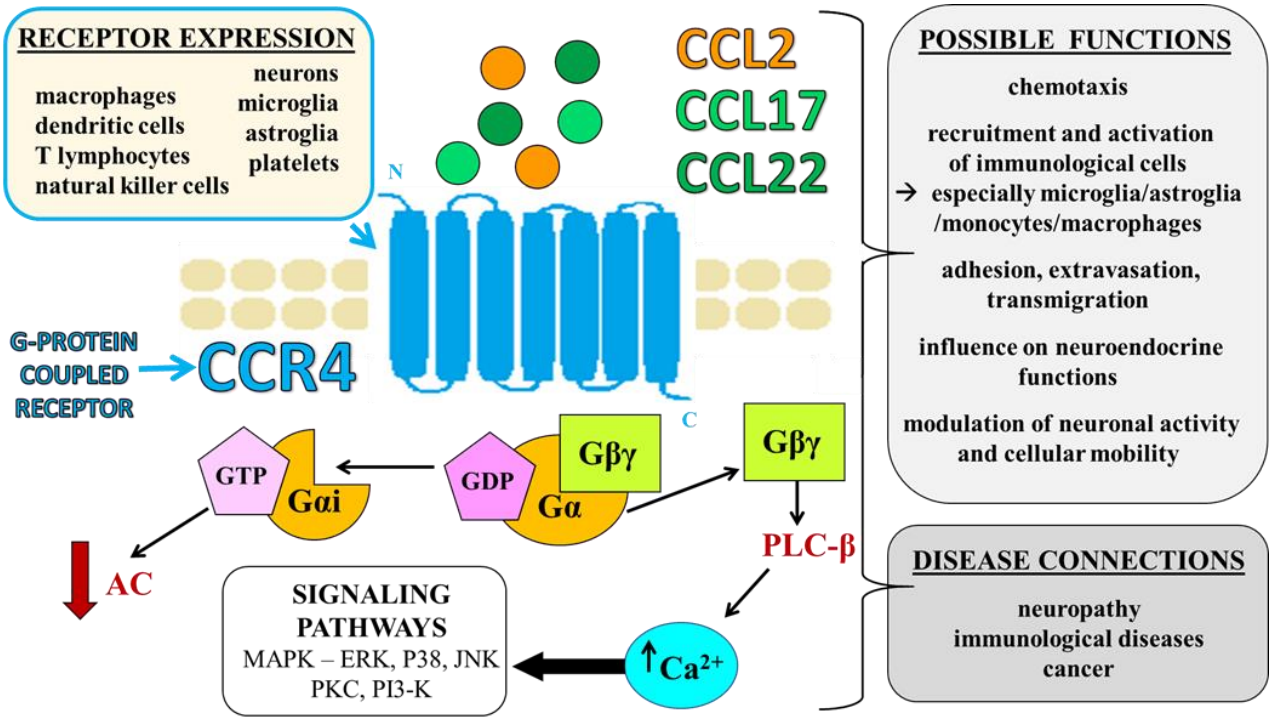


Figure 2. CCR4—mechanisms of action, possible roles, cellular expression, and disease connections. Abbreviations: chemokine receptor 4—CCR4; chemokine (C-C motif) ligand 22 (CCL2); chemokine (C-C motif) ligand 17 (CCL17); chemokine (C-C motif) ligand 22 (CCL22).

2. CCR4 and Its Ligands—Identification, Expression, and Functions

According to the current classification, CCR4 belongs to the CC group and was cloned from a human basophilic cell line [43–45]. Its presence has been demonstrated on T lymphocytes (Th2, Th17, and Tregs), platelets, natural killer (NK) cells, monocytes, macrophages, dendritic cells [37,41,46], neurons [47], microglia [48], and astroglia [41,48]. Notably, CCR4 has been found at different levels of the nervous system, such as in the dorsal root ganglia [49], spinal cord [50], and brain [51], which suggests its pivotal roles in physiology and pathology. CCR4 belongs to the family of transmembrane metabotropic receptors that respond to cell signals via G proteins [43]. CCR4 consists of a single polypeptide chain that crosses the membrane seven times. The amino terminus is extracellular, and the carboxyl terminus is intracellular. Notably, CCR4 may occur in at least two different conformational types. The major population is activated by CCL17 and CCL22, and the second population is responsive only to CCL22 [52]. The contribution of CCR4 to the pathogenesis of autoimmune encephalitis [41,50,53], multiple sclerosis [41], asthma [54], and atopic dermatitis [36]

has been shown. Clinical trials revealed the important role of CCR4 in cancers, such as leukemia/lymphoma [38], breast cancer [39], and renal cancer [40]. Notably, Kiguchi et al. (2017) showed a CCR4 increase in the spinal cords of monkeys with diabetes [55], but its role in nociception was not described until 2020.

2.1. Selective Ligands of CCR4—CCL17 and CCL22

The gene encoding CCL17, thymus, and activation-regulated chemokine (TARC) was discovered in 1996 in the thymus on human chromosome 16q13 [37,56]. CCL17 is released by lymphocytes, peripheral blood mononuclear cells, dendritic cells, and neurons [41,57,58]. CCL17 is involved in various infectious and autoimmune diseases [57,59–61], inflammatory bowel disease, and atherosclerosis. This chemokine is responsible for chemotaxis and Ca^{2+} influx into cells expressing CCR4 [62].

The second selective CCR4 ligand, macrophage-derived chemokine-MDC (CCL22), is also found on human chromosome 16q13 [37,56] and shows a 37% similarity at the amino acid level with CCL17 and a high affinity for CCR4 [56,62,63]. Monocytes release CCL22, which acts as a chemoattractant for T cells, NK cells, and dendritic cells [41,64]. Similar to CCL17, this chemokine is also highly expressed in the thymus and bone marrow cells. Increased CCL22 expression has been observed in allergies and inflammatory skin responses [64] in the lungs of patients with allergic asthma and atopic dermatitis [36,54]. The overexpression of CCL22 prevented autoimmune β cell destruction and the development of type 1 diabetes in a mouse model [65]. Activated M2 phenotype macrophages associated with the Th2 response and tissue regeneration produce CCL22 in large amounts [66,67]. CCL22 controls Treg recruitment in various human tumors [68,69].

Notably, CCL17 and CCL22 show different properties in receptor desensitization, and CCL22 predominates over CCL17 in the ligand-induced internalization of CCR4 [52,70]. Increased levels of both chemokines were demonstrated in the serum of fibromyalgia patients [71]. Recent pharmacological studies showed that a single intrathecal injection of CCL17 and CCL22 induced pain-related behavior in naive mice [33].

2.2. Nonselective Ligand of CCR4—CCL2

CCL2 also activates CCR4 [42,72,73]. Due to the pleiotropic properties of this chemokine, it is one of the best studied. CCL2, also known as monocyte chemoattractant protein-1 (MCP-1), is a chemotactic and activating factor for monocyte differentiation into macrophages after penetration into tissue, memory T lymphocytes, and NK cells. The main source of CCL2 is monocytes/macrophages [74], but it is also expressed by endothelial and epithelial cells, fibroblasts, smooth muscle, astroglia, and microglia [75,76]. This chemokine is associated with the increased growth and progression of breast, ovarian, and prostate cancer [77–79]. CCL2 may be a therapeutic target for the treatment of various diseases, including multiple sclerosis [10], rheumatoid arthritis [80], atherosclerosis [81], and diabetes [82]. An increased level of CCL2 in various structures of the nervous system was observed in an animal model of neuropathic pain, which was associated with the activation of glial cells [17,83,84]. Pharmacological studies showed that intrathecal injections of CCL2 induced pain-related behaviors in naïve mice, long-lasting thermal hypersensitivity [85], and microglial activation. Notably, intrathecal injections of a CCL2-neutralizing antibody effectively reversed pain-related behavior in neuropathic mice [86,87]. Although the well-known pronociceptive properties of this chemokine are primarily associated with CCR2 [4,15,16], recent research provides evidence that CCL2/CCR4 signaling is also involved in these effects [35].

3. Pharmacological Blockade of CCR4 and Its Ligands Using CCR4 Antagonists and Blocking Antibodies

Purandare and Somerville (2006) described four main groups of CCR4 antagonists distinguished on the basis of their chemical properties: aryl sulfonamides, substituted aminoheterocycles, thiazolidinones, and lactams [88,89]. There have been many reports of

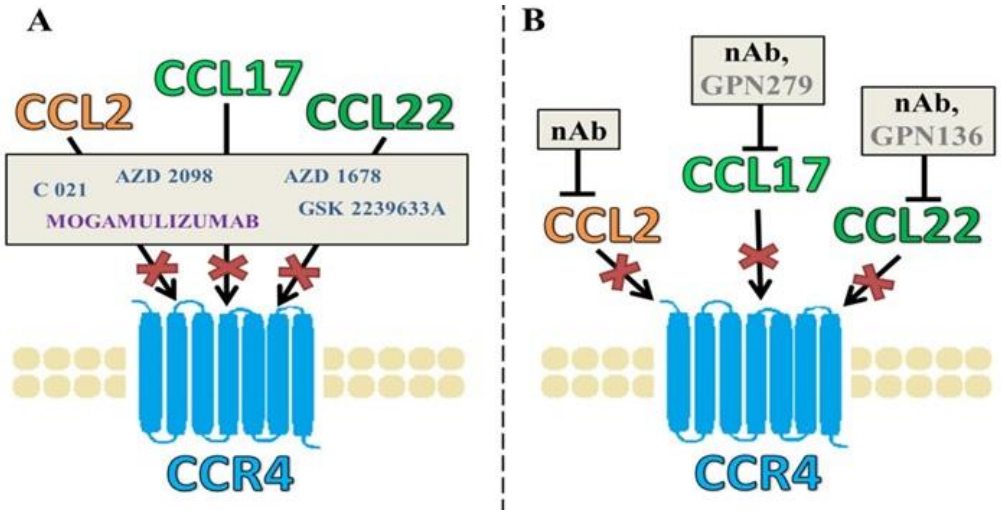
CCR4 antagonist development, primarily from two groups. The first group is a collection of lipophilic heteroarenes from Bristol Myers Squibb, Astellas, and Daiichi Sankyo, and the second group is aryl sulfonamides produced by various companies, such as Astra Zeneca, Ono, and GlaxoSmithKline [90–96]. However, most of these antagonists are not clinically approved due to their complex mechanism of action. The indazole aryl sulfonamide GSK 2239633 has been used in phase one clinical trials in asthma and allergic inflammation models, but these studies were terminated due to multiple problems with their mechanisms of action [41,93].

C021 is often used as a potent CCR4 antagonist in experimental studies. Its characteristics indicate that it is a cell-permeable diaminoquinazoline compound ([1,4′-bipiperidine]-1′-*N*-cycloheptyl-6,7-dimethoxy-4-quinazolinamine dihydrochloride). C021 inhibited CCL22/CCR4-mediated chemotaxis in murine and human cultures [96,97]. C021 reduced microglial activation and proinflammatory cytokine upregulation in animal models of hepatic encephalopathy [42] and neuropathic pain [33,35]. Moreover, it was recently discovered that two new substances, namely AZD-2098 and AZD-1678, are CCR4 antagonists, and research aiming to clarify their characteristics is still ongoing [98].

Research into the development of monoclonal antibodies against CCR4 is also in progress [99,100]. Clinical trials of the humanized CCR4 antibody mogamulizumab were approved in Japan for the treatment of T-cell lymphomas, leukemia [100,101], and advanced solid tumors [100]. The mechanism of action of mogamulizumab involves CCR4-positive Treg cells. However, inhibition of Treg cell function may produce side effects, including skin rash due to a reduction in the number of these cells, which emphasizes their multidirectional mechanism of action [102]. Mogamulizumab may also have applications in the treatment of allergic diseases, such as asthma and atopic dermatitis [37]. However, this medication remains at an early stage of clinical use and requires much more extensive research focused on application and in combination with other drugs to maximize its benefits and minimize its negative effects [41] (Figure 3).

CCL2/CCL17/CCL22 Neutraligands and Neutralizing Antibodies

Chemokine-neutralizing molecules (neutraligands) that target CCL17 and CCL22 have been created [103]. In vitro experiments showed that neutraligands, such as GPN279 and GPN136, inhibited CCL17- and CCL22-induced intracellular calcium responses, endocytosis, and T-cell migration [103]. Neutraligands inhibited inflammation in a mouse model of asthma [103]. The injection of a neutralizing antibody (nAb) to CCL2 into animals with developed neuropathic pain reduced hypersensitivity. CCL2 neutralization was effective against hepatocellular cancer in a mouse model [104]. The blockade of CCL17 using an antibody decreased the proliferation of carcinoma HeLa and SiHa cells [105], and anti-CCL22 treatment ameliorated the development of experimental autoimmune encephalomyelitis [106]. Due to the beneficial properties of the neutraligands and neutralizing antibodies against CCL2, CCL17, and CCL22, these agents seem especially important targets for future therapies (Figure 3).



C	EXPERIMENTAL STUDY AND CLINICAL TRIALS
CCR4 ANTAGONISTS	
GSK2239633	asthma – clinical trials
AZD-2098	kidney cancer – clinical trials
AZD-1678	lack of data
C021	neuropathic pain – experimental study hepatic encephalopathy – experimental study diabetes neuropathy – experimental study
MONOCLONAL ANTIBODY AGAINST CCR4	
MOGAMULIZUMAB	T-cell lymphomas and leukemia – clinical trials
NEUTRALIZING ANTIBODY AGAINST CHEMOKINES	
CCL2 nAb	neuropathic pain – experimental study breast cancer – experimental study glioma – experimental study hepatocellular cancer – experimental study
CCL17 nAb	osteoarthritis pain – clinical study carcinoma – clinical study
CCL22 nAb	autoimmune encephalomyelitis – experimental study
NEUTRALIZING MOLECULES (NEUTRALIGANDS)	
GPN136	asthma – experimental study
GPN279	asthma – experimental study

Figure 3. CCR4 as a possible new target for therapy-available pharmacological tools for study. (**A**) blockade of the CCR4 by its antagonists (AZD-2098 [98], AZD-1678 [98]; C021 [33–35,42]; GSK 2239633 [41,93]) and by monoclonal antibodies against CCR4 (mogamulizumab [37,38,100–102]); (**B**) neutralization of CCR4 ligands by antibodies (CCL2 [104,107–109], CCL17 [105,110,111], CCL22 [106]) and using neutralizing molecules of its ligands (GPN279—target CCL17 and GPN136 -target CCL22 [103]). (**C**) the table summing the experimental study and clinical trials. Abbreviations: chemokine receptor 4—CCR4; chemokine (C-C motif) ligand 22 (CCL2); chemokine (C-C motif) ligand 17 (CCL17); chemokine (C-C motif) ligand 22 (CCL22); neutralization antibodies (nAb).

4. CCR4 and Nociceptive Processes

Despite the significant progress in this field in recent decades, the effectiveness of treatments for neuropathic pain and the available pain medications are not satisfactory. The complex pathomechanisms of neuropathic pain directly affect the efficacy of pharmacotherapy. The International Association for the Study of Pain defines neuropathic pain as pain that arises from a "lesion or disease of the somatosensory nervous system", and it is divided into central or peripheral pain depending on the location of the impairment. While available methods control inflammatory pain, the possibility of relieving neuropathic pain remains an issue and requires the development of new effective analgesics. Understanding the mechanisms of this pain, with a particular emphasis on the contributions of immunological factors, creates an opportunity to identify new methods for more accurate pharmacotherapies for neuropathy.

Interactions between the immune and nervous systems are crucial in neuropathic pain development and persistence. A disturbance in the communication between these systems may underlie many pathological conditions [112]. Growing evidence indicates that the activation of non-neuronal cells, especially glial cells, also plays a crucial role in the development and maintenance of neuropathic pain [113–115].

An increasing number of studies indicate that chemokines strongly modulate the pain response (e.g., CCL2, CCL5, CCL4, CCL3, and CXCL1) [14,23,109,116]. Intrathecal injections of CCR4 ligands (CCL17 and CCL22) [33,35] cause a rapid and strong hypersensitivity to mechanical and thermal stimuli as measured by von Frey and cold plate tests in naïve mice, which supports their pronociceptive properties. We confirmed the strong pronociceptive character of CCL2 [35], which is consistent with previously published results [15]. Our team demonstrated for the first time that the pronociceptive effects of all three chemokines were attenuated by a previous administration of the CCR4 antagonist C021. These results were not surprising for CCL17 and CCL22. However, we also showed that CCL2 may be a pronociceptive ligand of CCR4 since CCL2-evoked pain-related behaviors were diminished when preceded by the administration of C021. Our data found that each of these chemokines played an important role in nociceptive processes, which suggests that CCR4 blockade has therapeutic utility.

Previous studies demonstrated that both single and repeated intrathecal and intraperitoneal administration of the CCR4 antagonist C021 reduced hypersensitivity to mechanical and thermal stimuli in the von Frey and cold plate tests in rats [33] and mice [35] subjected to a chronic constriction injury (CCI) of the sciatic nerve or diabetic neuropathic pain models. The use of C021 in streptozotocin-induced diabetic neuropathy also improved locomotor activity in the RotaRod test [34]. This result is important from a clinical point of view because patients with diabetes mellitus often experience a decline in locomotor performance with the development of neuropathic pain [117,118].

Our biochemical studies were performed in rats exposed to CCI and revealed increased levels of *CCL17* and *CCL22* in the dorsal root ganglia during the development of neuropathy [33]. These results suggest that these chemokines are involved in the initiation of neuropathic pain after a peripheral nervous system injury. However, the levels of *CCL17* and *CCL22* in the spinal cords of rats and mice in this model were not changed in the early and late stages of neuropathy [33,35]. Seven days after streptozotocin administration, which induced diabetic neuropathy, the spinal levels of *CCL17* and *CCL22* were not changed [34]. However, an increase in *CCL2* in the spinal cord was observed in a neuropathic pain model, and these changes were maintained up to day 28 after injury [13]. An increase in CCL2 was also observed on day seven in a diabetic neuropathy model [34]. These results highlight the important role of the CCL2/CCR4 axis in nociception at the spinal cord level.

CCR4 may play a key role in nociceptive transmission in the peripheral nervous system, which may be related to elevated levels of *CCL17/22* [33] and *CCL2* [15] in the dorsal root ganglia. Notably, a CCR4 antagonist is more effective when administered intraperitoneally, which is not similar to other chemokine antagonists, such as RS5043930

for CCR2 [119] or maraviroc for CCR5 [18]. The results of our research suggest that CCR4 is a very interesting and unique target in the search for future painkillers.

Recent studies, including ours, suggest that an imbalance between pronociceptive factors (e.g., IL-1beta, IL-18, IL-6, and NOS2) and antinociceptive factors (e.g., IL-1RA, IL-18BP, and IL-10) released from various immune and nonimmune cells is involved in the development of neuropathic pain [14,18,120,121]. Therefore, their modulation may have therapeutic benefits. Repeated intrathecal administration of C021 reduced hypersensitivity to mechanical and thermal stimuli in CCI-exposed rats and the level of a macrophage/microglia activation marker, IBA-1, in the spinal cord and dorsal root ganglia [33] with no effect on the levels of astroglial markers (GFAP) or T lymphocytes (CD4, CD8). Intrathecal administration of C021 also reduced the level of pronociceptive interleukins, such as IL-1beta and IL-18, in the spinal cord but not in the dorsal root ganglia. Repeated intraperitoneal treatment with C021 produced similar results for spinal macrophages/microglia. C021 significantly reduced the levels of IBA-1, but not GFAP, 12 days after ligation of the sciatic nerve [35]. Notably, a lower level of CCL2 was also measured, which suggests that this chemokine plays a key role in the initiation and maintenance of neuropathy. Therefore, targeting CCR4 is a promising strategy to provide a new basis for understanding neuropathic pain pathomechanisms with potentially new therapeutic utility.

The coadministration of different drugs is often necessary for neuropathic pain therapy. Opioid analgesics are less effective in neuropathy than other types of pain [122–125], and the mechanisms of this phenomenon are poorly understood. The reduced efficacy of opioids in neuropathy, and their numerous side effects associated with the use of high doses, limit their usefulness, which is a serious clinical problem [126,127]. Many studies, including ours, demonstrated that the analgesic properties of morphine were largely influenced by activated microglial cells and the release of pronociceptive factors, such as interleukins (e.g., IL-1beta and IL-18) [123,128–130] and chemokines (e.g., CCL2 and CCL5) [109]. The administration of neutralizing antibodies against CCL2 and CCL5 enhances the effectiveness of opioids [109]. Recent data emphasize that cytokines alter the effectiveness of opioids and the development of tolerance to their analgesic effects, which has been demonstrated in various animal models of pain [124,131–136]. Our research in CCI-exposed rats and mice showed that single, intrathecal and intraperitoneal administration of C021 enhanced the analgesic effect of morphine and buprenorphine [33,35]. We confirmed that the repeated intraperitoneal administration of morphine led to the development of opioid tolerance in mice after nerve injury [35]. Repeated administration of C021 alone for 12 days diminished nociceptive hypersensitivity. Although this effect was weaker in the few first days than morphine, it remained constant until the end of the experiment. Notably, the intraperitoneal administration of C021 with morphine or buprenorphine for 12 days significantly prolonged the analgesic effects of these opioids, and mice showed better locomotor activity on the RotaRod test.

Overall, our results indicate that targeting CCR4 and its ligands is a promising strategy to provide relief from neuropathic pain and may beneficially influence the analgesic effect of opioids, which represents a promising basis for the development of a more effective combined therapy for neuropathic pain.

5. CCR4 and Immunological Diseases

As previously mentioned, CCR4 is expressed by Th2 cells [63], regulatory T cells (Tregs) [137], mast cells [138], and skin-homing lymphocyte Ag–positive T cells [139]. Therefore, it plays an important role in inflammatory diseases, such as atopic dermatitis [140–142], asthma [54,143], and allergic airway inflammation [144], which are often associated with massive infiltration of Th2-type CD4+ T cells [145]. Studies using murine atopic dermatitis models showed that CCR4 deficiency or the use of a CCR4 antagonist ameliorated allergic responses. These results showed that CCR4 functioned in skin allergy inflammation by recruiting CCR4-expressing Th2 cells and Th17 cells [36,142]. There was also an increase in the expression of eosinophils, mast cells, Th2 cells, CCL17, and CCL22

in atopic dermatitis [36]. The CCR4/CCL17/CCL22 interaction is significant in the late phase of allergic airway inflammation, which was demonstrated using blocking antigens specific for CCL22 and CCL17 [52,66]. The blockade of CCL17 or CCL22 using neutralizing antibodies effectively reduced leukocyte recruitment to the lungs following allergen exposure [66,146]. Notably, CCL17 and CCL22 influence CCR4-expressing immune cells in the lungs and skin to evoke protective pulmonary responses to pathogens by recruiting Th2 and CD4+ T cells [39,137,147].

Encephalitis is a broad group of inflammatory diseases of the central nervous system. The causes of this condition may be an infection or an autoimmune disease. Experimental autoimmune encephalomyelitis (EAE) is a model that shares many characteristic features with multiple sclerosis (MS) [41,148]. The mechanism of EAE development involves the infiltration of mononuclear cells into the spinal cord, such as macrophages, dendritic, CD4+, and CD8+ T cells, which cause inflammation and demyelination [148,149]. An increase in CCL22 and CCR4 expression was demonstrated in the central nervous system in mice that develop chronic recurrent forms of autoimmune encephalitis, which demonstrates the involvement of CCL17/CCL22/CCR4 in the pathogenesis of this disease [148]. Experiments in animal models showed that CCR4 knockout mice were fully resistant to EAE and showed reduced neuritis and demyelination [148]. Increasing evidence from clinical trials indicates the involvement of the CCL17/CCL22/CCR4 axis in the pathogenesis of multiple sclerosis [41,50,150]. Cerebrospinal fluid levels of CCL22 and CCL17 are elevated in patients suffering from multiple sclerosis [41,50,151]. However, an increase in CCL22 levels was observed only in women [41].

CCR4 is also important in the pathogenesis of vitiligo, which is characterized by skin depigmentation. CCR4 and CCL17 were highly expressed in the skins of patients with vitiligo. The CCL17/CCR4 axis is also important for the onset of vitiligo in mice, and CCR4 neutralization reversed depigmentation in animals [152]. The levels of CCL17 and CCR4 were significantly upregulated in the pathogenesis of the oral lichen planus compared to the control patients [153].

The role of another CCR4 ligand, CCL2, in immunological diseases is primarily understood from its actions via CCR2. There is a direct association between the expression of hypoxia-inducible factor 1 and CCL2 during allergic lung inflammation in mice [154]. Mas receptor activation significantly attenuated CCL2-dependent macrophage recruitment in acute allergic airway inflammation via the JNK pathway [155].

Taken together, the interaction between CCR4, its ligands, and its modifications are important in the pathomechanism and treatment of immunological diseases.

6. CCR4 and Neoplastic Diseases

Adult T-cell leukemia/lymphoma (ATL) is caused by human T-lymphotrophic virus type 1 [38,101,102]. T-cell lines derived from patients with ATL are characterized by a high CCR4 expression at the mRNA and protein levels [37,102]. CCR4 is also expressed in the tumor cells of most ATL patients [37,102]. CCR4 is especially expressed on Treg lymphocytes and contributes to the influx of cells to the site of inflammation. Treg cells play an essential role in the maintenance of immune balance, but these cells interfere with the host's antitumor immunity in malignant tumors and provide an environment for tumor growth [156,157]. Mogamulizumab was the first approved glycoengineered therapeutic antibody that targets CCR4. Clinical studies indicate that it recognizes the extracellular N-terminus of this receptor and provides beneficial effects in the treatment of ATL patients [101] It also demonstrated efficacy in the treatment of relapsed and refractory aggressive T-cell lymphomas [37,102]. An awareness of the importance of Treg cells in various cancers will allow for the rational design of more effective therapies. Reducing the number of Treg cells in cancer patients may be a promising strategy for immune enhancement and better immune therapy, even at the cost of autoimmunity, but with beneficial effects against the development of cancer cells [38,102].

CCR4 is also involved in the pathomechanism of hepatocellular carcinoma. Despite many studies, the basis of this disease is not clear. Frequent intrahepatic metastases lead to high mortality and poor prognosis of patients. Enhanced expression of CCL22 in the tumor tissues of patients with hepatocellular carcinoma was reported in some studies and was associated with accelerated tumor growth [158]. CCR4 promotes this malignancy and facilitates metastasis [159]. Notably, downregulated CCR4 consistently decreases the invasive capacity of hepatocellular carcinoma cells, and a CCR4 antagonist had antitumor effects in a murine model [160]. These findings suggest CCR4 is a potential new diagnostic and prognostic marker in hepatocellular carcinoma, and its targeting may be a new therapeutic strategy for blocking metastasis [159].

The expression of chemokine receptors (CXCR4, CCR7, and CCR10) was previously associated with breast cancer metastases [39]. Recent studies showed that CCR4 also promoted the growth of breast tumors in mice, and CCL17 overexpression enhanced the chemotactic response of neoplastic cells [39]. Notably, the pathomechanism of metastatic breast cancer involves primary tumor growth in mammary pads, which activates the expression of CCL17 and CCL22 in the lungs [39]. It is important to emphasize that Treg cell activation inhibits antitumor T-cell immune responses [161,162]. CCR4-mediated chemotaxis is not sufficient to produce metastasis because it requires CCR4-positive Treg cells, which suppress the cytotoxicity of NK cells that eliminate tumor cells [39,163]. The killing of CCR4-expressing cells via the delivery of CCL17-fused toxins or Treg depletion prevents lung metastasis [39]. Strategies that target CCR4-positive Treg cells may have significant benefits in the control of breast cancer metastasis by protecting adaptive immune responses [39,164].

An enhanced CCR4 expression is also correlated with the clinical stage and outcome of nonsmall cell lung cancer patients compared to controls [163]. A higher expression of the *CCR4* gene was confirmed in patients with lung adenocarcinoma [165]. The chemokines CCL17 and CCL22 regulate CCR4-expressing immune cells in the lungs to evoke protective pulmonary responses to pathogens.

CCR4 is also highly expressed in human renal cell carcinoma biopsies and plasma samples, which is associated with the extent of immune cell infiltration [40]. This enhancement is considered a poor survival prognosis for patients [166]. The levels of CCL17 and CCL22 are also changed in renal cancer tissue, and the CCL17/CCL22 ratio in plasma is associated with poor prognosis [40]. This finding is in agreement with studies of other solid tumors, where CCR4 is also highly expressed. Therefore, an anti-CCR4 antibody has antitumor activity. Although CCR4 inhibition does not reduce the proportion of infiltrating leukocytes, it alters the phenotype of myeloid cells and increases NK cells and Th1 cytokine levels, which potentially evokes antitumor activity [40]. The anti-CCR4 antibody, alone or in coadministration with other immune modulators, may be a potential treatment approach to cancer therapy.

The CCL2-CCR2 signaling axis plays a role in the promotion of pathological angiogenesis in neoplastic disease, and the survival and invasion of tumor cells, without taking CCR4 into account [167]. However, the latest studies by Ling and colleagues [168]. Showed that the CCL2/CCR4 axis, not CCL2/CCR2, induced the signaling cascade responsible for cell motility and metastasis in head and neck squamous cell carcinoma. Targeting CCR4 was also effective in disrupting CCL2-induced growth and metastasis without promoting cancer relapse [168]. Further research is undoubtedly necessary to evaluate the role of the CCL2/CCR4 axis in other cancers.

7. Future Perspectives and Treatment Strategies

The CCL2/CCL17/CCL22/CCR4 interaction is a promising target for the treatment and prevention of immune diseases, cancer, and neuropathic pain (Table 1). Therefore, the search for drugs that interact via CCR4 is a very interesting research area. Although the results of animal models are encouraging and show very promising results, many challenges must be resolved before CCR4-targeted therapies may be successfully developed

for patients. Most compounds are in the preclinical phase of research. The expression of CCR4 on Th2 cells makes it a potential therapeutic target for allergic diseases. Due to the expression of CCR4 on Treg cells, the blockade of CCR4 may also be beneficial in enhancing the effectiveness of anticancer vaccines. As mentioned earlier, studies have already identified several small molecule antagonists of the CCR4 receptor and have tested and evaluated these agents in animal models of allergic diseases. Based on the research results, we conclude that CCR4 and its ligands are involved in the pathogenesis of many diseases of various etiologies. Promising studies offer hope for a new strategy for effective polytherapy in patients suffering from neuropathic pain, several immunological diseases, and cancer.

Table 1. Summary of the involvement of CCL2, CCL17, and CCL22 in different health problems in the cases of pain, immunity, and tumor studies.

LIGAND	PAIN	IMMUNITY	TUMORS
CCL17 **T**hymus and **A**ctivation-**R**egulated **C**hemokine **(TARC)** **CELL TYPES** neurons, lymphocytes, basophils, mononuclear cells, dendritic cells	**CLINICAL STUDY**		
	fibromyalgia—clinical trials [71]	asthma [143] dermatitis [140] autoimmune diseases [57,59–61] atherosclerosis [61]	breast cancer [169] hepatocellural carcinoma [170] colon cancer– clinical trials [171]
	EXPERIMENTAL STUDY		
	neuropathic pain [33–35] inflammatory pain [172]	asthma [173]	pituitary adenoma [174] glioblastoma [175] gastric cancer [176]
CCL22 **M**acrophage-**D**erived **C**hemokine-**(MDC)** **CELL TYPES** lymphocytes, basophils, NK, mononuclear cells, dendritic cells	**CLINICAL STUDY**		
	fibromyalgia [71]	atopic dermatitis [137] allergy [64] asthma [143,177] dermatitis [178] pneumonia [179]	breast cancer [169] hepatocellural carcinoma [170] colon cancer [171] gastric cancer [176]
	EXPERIMENTAL STUDY		
	neuropathic pain [33–35]	autoimmune encephalomyelitis [106]	melanoma [180] t-cell lymphoma [181] hepatocellular carcinoma [182] bladder cancer [183]
CCL2 **M**onocyte **C**hemoattractant **P**rotein-**1 (MCP-1)** **CELL TYPES** T lymphocytes, NK cells monocytes/macrophages, endothelial/epithelial cells, fibroblasts, smooth muscle, astroglia and microglia	**CLINICAL STUDY**		
	lumbar disk herniation [184] traumatic spinal cord injury [185]	multiple sclerosis [186] tuberculosis [187] myocardial infarction [188] aids [189] multiple sclerosis [190] nephropathy [191] inflammatory bowel disease [192] allergic asthma [193] rheumatoid arthritis [194]	colorectal cancer [195] ovarian cancer [195] esophagus cancer [195] pancreatic cancer [195] breast cancer [195]
	EXPERIMENTAL STUDY		
	neuropathic pain [15,16,109,119] arthritis bone cancer pain [196]	insulin resistance [197] asthma [198] autoimmune encephalomyelitis [199]	meningioma [200] colon cancer [201] carcinomas [202] melanoma [203] bladder cancer [204]

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