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REVIEW

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Progress of CCL20-CCR6 in the airways: a promising new therapeutic target

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Abstract

The chemokine CCL20, a small cytokine that belongs to the C–C chemokine family, interacts with its homologous receptor CCR6, which is expressed on wide range of cell types. According to current research, the CCL20-CCR6 has been established as acritical player in a diverse range of inflammatory, oncogenic, and autoimmune diseases. Within the respiratory system, CCL20-CCR6 demonstrates heightened expression in conditions such as allergic asthma, chronic airway inflammation, non-small cell lung cancer (NSCLC), chronic obstructive pulmonary disease (COPD), and other respiratory diseases, which is conducive to the inflammatory mediators recruitment and tumor microenvironment remodeling. Numerous studies have demonstrated that therapeutic interventions targeting CCL20 and CCR6, including antibodies and antagonists, have the potential to mitigate disease progression. Despite the promising research prospects surrounding the CCL20-CCR6 chemokine axis, the precise mechanisms underlying its action in respiratory diseases remain largely elusive. In this review, we delve into the potential roles of the CCL20-CCR6 axis within the respiratory system by synthesizing and analyzing current research findings. Our objective is to provide a comprehensive understanding of the CCL20-CCR6 axis and its implications for respiratory health and disease. And we aspire to propel research endeavors in this domain and furnish valuable insights for the development of future therapeutic strategies.

Keywords CCL20, CCR6, Immunoreaction, Inflammation, Respiratory system

Introduction

Respiratory diseases are one of the most prevalent illnesses in daily life. As the global economic level and population grow, air pollution and environmental degradation exacerbate the incidence and impose a substantial economic burden. In the European Union, expenditures on respiratory diseases amount to approximately 6% of the annual healthcare budget [1]. Chronic Obstructive Pulmonary Disease (COPD), one of the common respiratory diseases, ranked as the fourth leading cause of death in the United States in 2018, impacting over 10% of the population [2]. Therefore, the treatment of respiratory diseases and the advancement of novel therapeutic agents remain challenging.

The role of chemokines in regulating leukocyte trafficking has been extensively documented in the scientific literature [3]. Over 20 chemokine receptors and 50 chemokine ligands have been identified and characterized until now [4]. Notably, many chemokines exhibit promiscuous binding capabilities, interacting with multiple receptors, while receptors themselves can bind to various ligands. Therefore, the highly selective interaction between CCL20 and CCR6 is a focal point of our research endeavors. It has been confirmed that bronchial and alveolar epithelial cells express CCL20 [5]. After bronchial epithelial cells were stimulated, the expression of CCL20 increased, exerting a chemotactic effect that induced the recruitment of various inflammatory factors

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and activated both the innate and adaptive immune systems [6].

The CCL20-CCR6 axis is expressed by a diverse array of immune cells and plays pivotal roles in numerous systems and organs throughout the human body. In the psoriasis (PS), interleukin-17A (IL-17A) stimulates the production of CCL20 by epidermal keratinocytes, recruiting $CCR6^+$ Th17 cells to the affected skin, exacerbating the inflammatory process [7]. Furthermore, the expression of CCL20-CCR6 has been confirmed in other diseases characterized by Th1/Th17-related immune responses, such as Crohn's disease (CD), atopic dermatitis (AD), systemic lupus erythematosus (SLE), and vitiligo [8–16]. A comprehensive understanding of the mechanisms underlying the CCL20-CCR6 axis in inflammatory responses is crucial for the identification of potential therapeutic targets. Beyond its role in inflammatory diseases, the activation of CCL20-CCR6 in the tumor microenvironment has been implicated in the proliferation, migration, and invasion of cancer cells [17]. For instance, CCL20-CCR6 promotes the development of gastric adenocarcinoma (GAC) by modulating the tumor microenvironment in gastric cancer [18]. In hepatocellular carcinoma (HCC), CCL20-CCR6 influences disease progression by regulating macrophage survival and Treg cells recruitment [19]. Collectively, these findings suggest that CCL20-CCR6 is directly involved in the pathogenesis of a wide range of diseases, sparking our interest in further exploring its functions and potential therapeutic applications.

Currently, drugs such as corticosteroids, immunosuppressants, and monoclonal antibodies available on the market may exhibit limited tolerability and efficacy [20]. Meanwhile, research on the CCL20-CCR6 axis in the respiratory system is still in nascent stages. This paper aims to summarize the advancements in the study of CCL20-CCR6 in the respiratory system, encompassing the research and developmental progress of related drug inhibitors, systematically elucidating the origin, function, and role of CCL20-CCR6 in various respiratory diseases. The feasibility of CCL20-CCR6 as a potential therapeutic target is discussed, offering a novel therapeutic perspective for the future treatment of respiratory diseases.

Method

A comprehensive literature search was conducted in the PubMed and Web of Science databases, focusing on all relevant English-language publications since January 1, 2000. The search utilized the keywords "CCL20," "CCR6," "respiratory diseases" and "inhibitors" to ensure a thorough capture of all pertinent studies on CCL20-CCR6 in respiratory research. Duplicate literature was meticulously eliminated to avoid redundancy. To refine the search strategy, an iterative process was employed, building upon the initial keyword search. Additionally, to trace the origins of relevant literature, earlier references were included in the review. The types of literature cited encompassed articles, reviews, letters, and other forms, ensuring a diverse and comprehensive range of sources. Two independent reviewers screened the titles, abstracts, and keywords of the shortlisted articles to ensure their relevance and quality. Articles were excluded based on the following criteria: 1. Articles with outdated results lacking a sufficient theoretical foundation. 2. Articles whose research findings aligned with the current mainstream thinking, but the knowledge points were no longer up-to-date (e.g., older views suggesting lung squamous cell carcinoma as the most prevalent type of lung cancer, whereas current understanding highlights lung adenocarcinoma as the most common). 3. Retracted articles. These exclusion criteria were applied to ensure maximum alignment with the subject matter of this study. No topics are registered for this study.

The origin of the chemokine CCL20 and its receptor CCR6

Chemokines are small cytokines that induce the directional chemotaxis of responsive cells. Based on the position of the NH2-terminal cysteine (Cys) residues in their sequences, chemokines are categorized into four main classes: C–C motif (CC), C-X-C motif (CXC), C motif (C), and CX3C chemokines [21]. The chemokine CCL20, located on human chromosome 2, is a member of the C–C chemokine family. It is also known by several other names, including liver activation-regulated chemokine (LARC), macrophage inflammatory protein-3 (MIP-3), Exodus-1, and small-inducible cytokine subfamily A member 20 (SCYA20), and identified as a chemokine through bioinformatics [22, 23]. CCL20 is primarily expressed in various epithelial cells, including keratinized cells, lung epithelial cells, and intestinal epithelial cells [24–27].

The CC chemokine receptor 6 (CCR6), alternatively known as STRL22, resides on chromosome 6q27 and functions as a homologous receptor for CCL20. It is also characterized as a 7-transmembrane domain G-protein coupled receptor, primarily expressed in leukocytes, and binds to CCL20 to mediate leukocyte migration [28]. In tissues, it is predominantly expressed in the lymph nodes, appendix, and spleen, while showing lower levels of expression in the thymus, testis, and small intestine [29].

CCL20 engages in two types of interactions as a small molecule chemokine. On the one hand, the C-terminus of CCL20 binds to glycosaminoglycans (GAGs), thereby localizing CCL20 to the cell surface or extracellular

matrix and creating a concentration gradient that facilitates the recruitment of its homologous receptors [30]. On the other hand, the N-terminus of CCL20 interacts with the side chain of CCR6 through hydrogen bonds and salt bridges, binding to the shallow pocket of CCR6 andactivating it [31]. This structural foundation ensures a strong binding affinity between CCL20 and CCR6 (Fig. 1). CCL20 is highly specific for CCR6 [32], which has long been recognized as its primary interacting receptor [33]. However, recent studies have identified the atypical chemokine receptor ACKR4 as an additional receptor for CCL20. β-arrestin mediates the recruitment of CCL20 to ACKR4, effectively removing excess CCL20 from the body and regulating chemokine concentration [34, 35]. Interestingly, CCL20 shares significant structural similarity with β-defensins. Certain defensins, such as human β-defensin 1 (HBD-1) and human β-defensin 2 (HBD-2), can bind to CCR6 receptors [36]. Notably, HBD-2, which boasts the highest expression level among defensins in the lung, exhibits chemotactic activity upon binding to CCR6. This interaction subsequently recruits T cells and dendritic cells (DCs) to the site of inflammation [36, 37] Additionally, mouse antimicrobial peptides β-defensins 2 and 3 also bind to CCR6, though they have a lower affinity for CCR6 compared to CCL20 [38]. This implies a potential defensin with higher CCR6 affinity could functionally replace the CCL20-CCR6 axis, warranting further investigation.

The role and function of CCL20 and CCR6

CCL20 is a small-molecule peptide with diverse biological functions, including chemotaxis, and expressed by various immune cells. It is commonly associated with conditions including rheumatoid arthritis, psoriasis, and inflammatory bowel disease [39–41]. CCL20 accumulates at both sites of inflammation and immune activation, with its concentration positively correlated with inflammatory diseases severity [42]. It is stably expressed across cell types and rapidly induced upon pathogen invasion, stimulating Th17 cells to express CCR6 and recruiting CCR6-expressing cells to the inflammation site [43]. CCR6 signaling activates small GTPases and actin polymerization to regulate leukocyte migration and influence inflammation development [44]. Furthermore, recent studies have demonstrated that the homing of mature regulatory T cells (Tregs) to the thymic Treg pool occurs via a CCL20/CCR6-dependent pathway, which is crucial for maintaining immune tolerance and homeostasis [45]. This further supports the significant role of the CCL20/CCR6 axis in autoimmune inflammatory responses.

CCL20 is poorly expressed in normal tissues, but the expression of CCL20 in tumor tissues is much higher thannormal tissue, which can be used as an independent predictor of downstream cancer signaling pathways activation [46]. It has been confirmed that CCL20 plays a role in a variety of cancers, such as colorectal, pancreatic, liver, breast, ovarian, and lung cancers [47–51]. CCL20 directly targets endothelial cells through its cognate receptor, CCR6, and activates signaling pathways that can stimulate or enhance peritumoral angiogenesis in the tumor microenvironment, nourish tumor cells, and promote tumor cell metastasis and migration [52]. In addition, a recent study showed that mutations in the CCR6 gene cause abnormal activation of CCR6 and high expression in malignant B lymphocytes, leading to unbalanced cell proliferation and malignant transformation [53]. However, the exact B lymphocyte population that

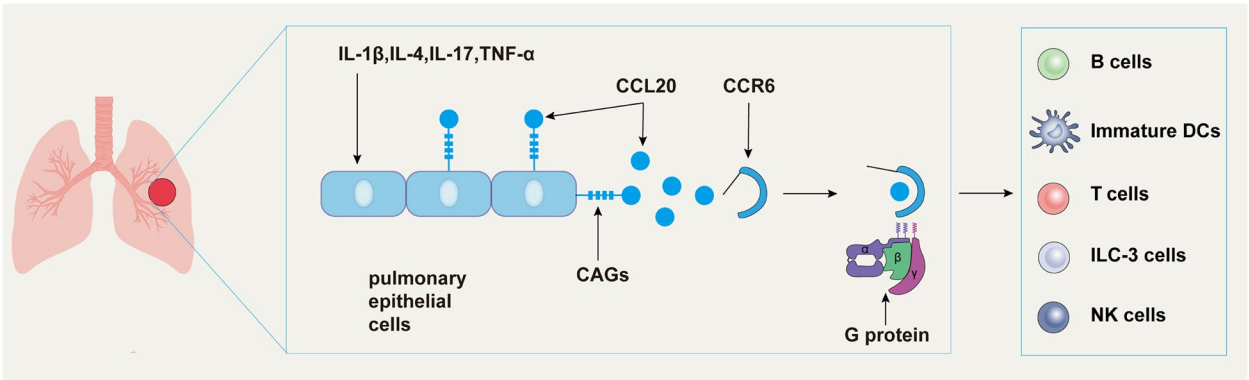

Fig. 1 Lung epithelial cells secrete CCL20 to recruit CCR6-expressing cells. Glycosaminoglycans (GAGs) are present on the surface of lung epithelial cells. Upon stimulation, these cells secrete large amounts of CCL20. GAGs bind to CCL20 and anchor it to the cell surface. This accumulation of CCL20 creates a concentration gradient within the extracellular matrix, recruiting CCR6-expressing cells. CCR6 contains a molecular switch that remains closed in the absence of CCL20. However, upon CCL20 binding, CCR6 couples with downstream G proteins, activating signaling pathways that mediate cellular responses

expresses CCR6 in a sustained T cell-dependent immune response remains to be determined.

The CCL20-CCR6 axis is intricately involved in numerous signaling pathways (Fig. 2). Specifically, it promotes osteoblast differentiation via the PI3K-AKT pathway [54]. In mouse psoriasis models, the inhibition of the JAK-STAT3 pathway has been verified to decrease CCL20 secretion [55]. Furthermore, Helicobacter pylori induces the production of CCL20 in gastric epithelial cells through NF-κB signaling dependency [56]. In lung cancer cells, CCL20 stimulates cancer cell proliferation and migration by activating the MAPK-ERK signaling pathway [57]. Additionally, Farnesyl diphosphate synthase (FDPS) induces CCL20 expression through the Wnt/β-catenin pathway, leading to the promotion of macrophage infiltration [58]. EGFR/Ras signaling plays a pivotal role in inducing CCL20 production across multiple cancer types and contributes to the establishment of the tumor microenvironment by stimulatingcytokines and chemokines secretion [52].

In summary, CCL20-CCR6 interactions have far-reaching consequences in multiple human organs health and play important roles in maintaining the integrity of the immune system in the internal environment, directing the migration of inflammatory cells in vivo, and promoting the differentiation of tumor cells.

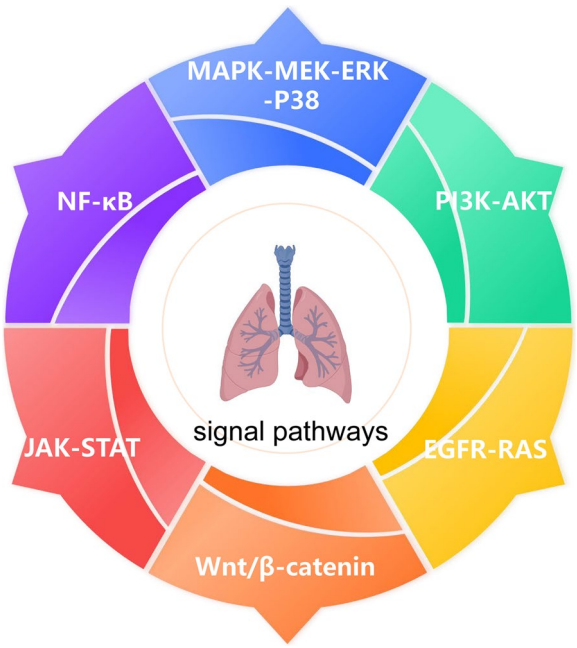

Fig. 2 The signaling pathway involved in CCL20-CCR6 in lung disease

Progress of CCL20-CCR6 in the respiratory tract

The role of CCL20-CCR6 in asthma and allergic inflammation of the airways

Asthma is a chronic inflammatory disease marked by persistent mucus hypersecretion and airway hyperresponsiveness [59]. While current treatments primarily involve steroids, some patients still experience inadequate control of their symptoms, highlighting the urgent need for new therapeutic targets [60]. The pathogenesis of asthma is complex, with the inflammatory factor IL-1β recognized as a key mediator in the disease's inflammatory processes [61]. CCL20 is produced by airway epithelial cells [62], and its activation is closely associated with IL-1β-mediated inflammatory responses [63]. Joan Reibman et al. have demonstrated that CCL20 is regulated by pro-inflammatory cytokines such as IL-1β and TNF-α, as well as pro-allergic cytokines including IL-4 and IL-13. When the airway epithelium is exposed to inflammatory factors or environmental particles, CCL20 expression is upregulated through the ERK1/2 and p38 MAPK pathways, leading to rapid binding to the CCR6 receptor. Conversely, inhibition of the ERK1/2 and p38 MAPK pathways results in reduced CCL20 expression [5]. Additionally, Shen et al. observed in a mouse model of HDM-induced asthma that CCR6 + Treg cells were significantly increased in lung tissue and activated by CCL20. This activation led to IL-17 secretion from Th17 cells, thereby exacerbating asthma [64]. Another study investigating house dust mite (HDM)-induced CCL20 secretion in allergic asthma reported that HDM induces CCL20 secretion through the Akt-ERK1/2-C/EBPβ pathway [65]. This process recruits immature dendritic cells (DCs) to interact with airway bronchial smooth muscle cells. Conversely, anti-CCL20 treatment alleviates airway hyperresponsiveness and reduces the infiltration of inflammatory cells.

Interestingly, Zijlstra et al. have found that sputum levels of CCL20 are significantly higher in asthmatics following treatment with inhaled glucocorticoids and positively correlated with the dosage of the hormone used [66]. Alen et al. reported that CCL20 expression and airway mucus secretion were significantly increased in asthmatics in a controlled study comparing asthmatics and healthy individuals, with IL-1β induction [67]. They observed that both CCL20 expression and mucus secretion levels were greater in patients with moderate asthma compared to those with mild asthma. These findings suggest that CCL20 expression may contribute to chronic airway mucus secretion, potentially explaining why airway secretion did not improve substantially with steroid treatment in some asthma patients. Thus, the CCL20-CCR6 axis plays a critical role in asthma-related

inflammation and mucus hypersecretion, and anti-CCL20 therapy could offer new approaches to asthma treatment.

Progress of CCL20-CCR6 in non-small cell lung cancer (NSCLC)

Lung cancer is a leading cause of cancer-related deaths, with approximately 90% of these deaths attributed to smoking [68]. A related study demonstrated that nicotine-derived nitrosamines (NNK) significantly increase CCL20 expression in human lung epithelial cells [69]. CCL20 expression was found to be higher in smokers compared to non-smokers, and it was elevated in non-small cell lung cancer (NSCLC) patients with a history of smoking compared to those with no smoking history [69]. Interestingly, the expression levels of CCL20 and CCR6 were higher in the adenocarcinoma (AC) group compared to the squamous cell carcinoma (SCC) group, which may account for the more aggressive nature of this histopathological subtype of lung cancer [70]. Most CCR6 mutations are nonsense mutations or frameshift insertions/deletions clustered in the C-terminal region, leading to truncated products that lack the C-terminal phosphorylation motif [71]. CCR6 mutants exhibit remarkable resistance to cell death. Upon stimulation with CCL20, CCR6 mutants W335X and R159S show enhanced transformation and proliferation compared to the wild type [53].

In lung cancer cells, the expression level of CCL20 is positively correlated with both the tissue stage and disease severity [69]. CCL20 not only promotes the proliferation and migration of lung cancer cells but serves as a significant prognostic marker in non-small cell lung cancer (NSCLC) [72]. NSCLC cells produce CCL20 through autocrine or paracrine mechanisms, which activate signaling pathways including ERK1/2-MAPK, Wnt, and PI3K, to promote epithelial-mesenchymal transition (EMT) [73]. However, the knockout of CCL20 has been observed to impair signal transduction pathways, including AKT and STAT3, ultimately inhibiting cell proliferation and migration [46]. A recent investigation has demonstrated that the use of CCR6 inhibitors in conjunction with erlotinib enhances drug sensitivity in resistant cancer cells [74]. This combination therapy exhibits a trend toward inducing cell cycle arrest and cellular growth reduction, suggesting a promising therapeutic approach. In the mouse lung cancer model, chimeric antigen receptor (CAR-T) cells expressing CCR6 significantly reduced tumor cell infiltration, lysed CCL20-secreting tumor cells, prolonged survival, and enhanced anti-lung cancer activity [75]. In conclusion, CCL20-CCR6 displays heightened expression levels in both mouse models and lung cancer patients. Blocking the expression of CCL20/CCR6 has been verified to exert specific anticancer effects.

Progress of CCL20-CCR6 in COPD

Chronic obstructive pulmonary disease (COPD) is a persistent inflammatory lung disease characterized by irreversible airflow limitation, with smoking being a major risk factor for its development [76]. Korytina et al. reported that the minor allele C of CCL20 (rs6749704) was associated with an increased risk of COPD exclusively in smokers [77]. Additionally, individuals carrying the CCR6 G allele (rs3093024) had a significantly higher smoking index. Chronic exposure to cigarette smoke promotes CCL20 expression and enhances the secretion of inflammatory cells, including macrophages, neutrophils, dendritic cells, and $CD8^+$ T cells [27, 78–83]. These cells also secrete neutrophil elastase and matrix metalloproteinases (MMPs), which further damage lung parenchyma and contribute to COPD [84]. While previous studies have predominantly observed DC-mediated increases in CCL20 expression in asthma, Demedts et al. were the first to report that elevated CCL20 levels in COPD lead to the accumulation of dendritic cells (DCs) at sites of airway inflammation [85]. The extent of this elevation was positively correlated with COPD severity. Additionally, since CCR6 is expressed on DCs, CCR6 receptor-deficient mice exhibited significant attenuation of airway inflammation and fibrosis [86].

Airway remodeling is a key pathological feature of COPD, primarily characterized by chronic inflammation and fibrosis around the small airways [87]. During this process, Brand et al. identified CCL20-positive fibroblasts in the lamina propria of the airway epithelium [88]. They observed that CCL20 was most prominently expressed in fibroblasts that had been stimulated by the inflammatory factor IL-1β and subsequently activated through TGF-β induction by integrin αvβ8. The avβ8-mediated activation of TGF-β at the CCL20 promoter induces the formation of the SMAD4/NF-κB transcription complex, which enhances CCL20 transcription, creates a positive feedback loop, and exacerbates airway fibrosis in a murine model of COPD [89]. This provides strong evidence that CCL20 plays a crucial role in airway remodeling. Additionally, in a rat model of COPD induced by LPS, theCCL20 blocker significantly reduced dendritic cells (DCs) accumulation caused by the CCL20-CCR6 interaction and alleviated emphysema [90]. In conclusion, CCL20-CCR6 plays a certain role in the initiation and progression of COPD, albeit the research on CCL20-CCR6 in the context of COPD remains relatively scarce.

Progress of CCL20-CCR6 in pulmonary tuberculosis

Tuberculosis is caused by infection with Mycobacterium tuberculosis (Mtb), encompassing both active tuberculosis (TB) and latent tuberculosis infection (LTBI) [91]. During Mtb infection, chemokines and corresponding receptors have been extensively recognized for their role in facilitating the recruitment of inflammatory cells and the formation of granulomas at the site of infection [92]. In the Mycobacterium bovis BCG-infected mice airway model, Stolberg et al. detected that CCL20-CCR6 exhibited peak expression one week post-infection [93]. Intriguingly, their study revealed that CCR6 knockout ($CCR6^{-/-}$) mice appear to play a significant antibacterial role in innate immunity, albeit not essential for adaptive immunity. Because innate immunity is considered pivotal for the establishment of early immune responses against Mycobacterium tuberculosis [94].

In tuberculosis (TB) patients, CCL20 was significantly upregulated compared to healthy controls in peripheral blood mononuclear cells (PBMCs) and monocyte-derived macrophages (MDMs) [95]. Furthermore, CCR6 expression was induced in memory T lymphocytes in a dose-dependent manner, promoting the migration of T lymphocytes to the site of infection [95]. Various types of macrophages have been implicated in TB status [96, 97]. Yang et al. employed single-cell RNA sequencing (ScRNA-seq) to identify a unique subpopulation of macrophages in bronchoalveolar lavage fluid (BALF) following Mycobacterium tuberculosis (Mtb) infection [98]. They discovered that MM macrophages in latent TB infection (LTBI) patients can regulate $CD8^+$ T lymphocytes through the CCL20-CCR6 axis, thereby playing an anti-TB role. Additionally, several studies have demonstrated that CCR6 is expressed on the surface of $CD4^+$ T cells in the airway during LTBI [99, 100]. Notably, $CCR6^{-/-}$ mice infected with Mtbare able to effectively clear the bacteria [93].

Progress of CCL20-CCR6 in pulmonary sarcoidosis

Pulmonary sarcoidosis is an interstitial lung disease characterized by a CCR6-dependent immune response involving the coactivation of $CD4^+$ Th1 and Th17 cells [101]. Monica et al. detected elevated levels of CCL20 in bronchoalveolar lavage fluid (BALF) from patients with active pulmonary sarcoidosis [102]. They found that $CCR6^+$ T lymphocytes recruited by CCL20 accumulated in the nodular lung microenvironment and were involved in the progression of immunoinflammatory alveolitis and granuloma formation. Ding et al. found that elevated CCL20 expression in patients with stage II nodular disease stimulated activation of the PI3K/Akt pathway, leading to a Th17/Treg imbalance and impairing the immunosuppressive effects of Treg cells, which promotes granulomatosis [103]. Recent studies have shown that serum amyloid A (SAA) upregulates CCL20 expression, which then induces migration and activation of Treg and Th17 cells by binding to the CCR6 receptor and activating the TGF-β/Smad pathway, leading to the formation of characteristic non-caseating granulomatous lesions [104]. Anti-CCL20 therapy has shown some degree of efficacy in reversing these effects.

Progress of CCL20-CCR6 in invasive pulmonary aspergillosis

Invasive pulmonary aspergillosis is commonly seen in immunocompromised individuals, with Aspergillus fumigatus being the most frequent causative agent [105]. Interestingly, studies have shown that after inducing Aspergillus fumigatus infection, CCR6 receptor-deficient mice had significantly fewer pulmonary dendritic cells (DCs) and monocytes/macrophages. These mice developed more severe infections and exhibited higher mortality rates compared to wild-type mice [106]. In contrast to previous findings, the CCL20-CCR6 axis appears to play a protective role in invasive pulmonary aspergillosis [106, 107]. Murdock et al. exposed immunocompromised mice to Aspergillus fumigatus spores and observed that it elicited Th1, Th2, and Th17-type immune responses. The CCR6 receptor, on the surface of Th17 cells, regulates their migration to the site of lungs infection by binding to the chemokine CCL20 [108]. A recent study found that when a human small airway epithelial cell line (HSAEC1-KT) was infected with Aspergillus fumigatus, it resulted in decreased levels of CCL20 in the culture supernatant [109]. This finding suggests that Aspergillus fumigatus infection depletes CCL20, thereby suppressing the host's innate immune response and exacerbating the infection. These results underscore the importance of the CCL20-CCR6 axis as a critical host defense mechanism in Aspergillus fumigatus infection.

Progress of CCL20-CCR6 in Viral Infectious Pneumonia

Influenza viruses are common respiratory pathogens responsible for seasonal infectious pneumonia [110]. The virulence of a particular influenza strain largely depends on its ability to elicit an immune response in the host [111]. In influenza A virus (IAV)-induced pneumonia, the H1N1 strain exacerbates lung inflammation by disrupting the Th17/Treg cell balance and reducing the ability of $CD8^+$ T cells to clear the virus, which is associated with increased expression of CCL20 and CCR6 [112]. Conversely, inhibition of CCL20-CCR6 expression affects dendritic cell (DC) recruitment, reduces the body's ability to respond to the virus, and improves viral clearance efficiency in a model of RSV-infected pneumonia [113]. These findings suggest that targeting CCL20 and

CCR6 may help attenuate pulmonary infection in viral pneumonia.

COVID-19, caused by a single-stranded RNA beta coronavirus, has been associated with severe cellular inflammatory responses and elevated chemokine levels. Studies have indicated that CCL20 is a key factor in the progression of severe COVID-19 [114–116]. High levels of CCL20 have been detected in the blood and lung tissues of critically ill patients, who are at increased risk for complications such as acute respiratory distress syndrome (ARDS) and multi-organ failure, often resulting in poor therapeutic outcomes and high mortality rates [117–119]. These findings suggest that CCL20 may have prognostic relevance in COVID-19 infection. However, the mechanisms involved are still not fully understood, and further research is needed to determine whether anti-CCL20 therapy could provide prognostic benefits for infected patients.

In this section, we will present the aforementioned information in a tabular format, as follows: (Table 1)

CCL20 and CCR6 inhibitors

Inhibition of the CCL20-CCR6 axis encompasses the use of CCL20 inhibitors and CCR6 inhibitors. CCL20 and its corresponding monoclonal antibodies have demonstrated the ability to inhibit CCL20 chemotaxis and the activation of the CCL20/CCR6 pathway across a range of diseases [43]. These inhibitors have exhibited promising therapeutic effects in models of respiratory diseases, neuroinflammatory disorders, rheumatoid arthritis, breast cancer, and other conditions [65, 120, 121]. In the context of immunoinflammatory diseases, CCL20-neutralizing monoclonal antibodies effectively neutralize CCL20 chemokines, thereby preventing the recruitment of inflammation-related factors and reducing the disease's inflammatory immune response [122]. Park et al. discovered that CCL20 regulated airway hyperresponsiveness and bronchial airway remodeling, while CCL20 inhibitors and monoclonal antibodies could ameliorate airway hyperresponsiveness, airway inflammation, and airway remodeling induced by CCL20 [65]. In further studies, anti-CCL20 therapy has been shown to alleviate smoking-induced airway inflammation and emphysema in a rat model [90]. Additionally, the application of related biologics, such as infliximab and tocilizumab, has been explored in related clinical treatments [4, 123]. Consequently, anti-CCL20 therapy has a positive impact on mitigating airway inflammation and lung tissue structural alterations.

The development of CCR6 antagonists presents a greater challenge compared to the application of various CCL20 antagonists. Sara et al. have developed a monoclonal antibody, 1C6, which targets the human CCR6 receptor (hCCR6). This antibody reduces the migration

Table 1 Summary table of CCL20-CCR6 in the respiratory system

Name	frequency	Action mechanism	Effector cell	Phenotype	Reference
Asthma	↑	The secretion of CCL20 by airway epithelium is stimulated by MAPK and AKT pathways under the stimulation of related inflammatory factors.	DCs, Treg	Harmful	[5, 65]
NSCLC	↑	NSCLC cells promote CCL20 production and induce lung cancer cell migration through MAPK, Wnt, and PI3K pathways.	Th17, Treg, ILC3s	Harmful	[73]
COPD	↑	Activation and activation of TGF-β induced by integrin avβ8 enhances CCL20 transcription and exacerbates airway fibrosis.	DCs	Harmful	[88, 89]
Pulmonary tuberculosis	↑	Induces T lymphocytes to migrate to the site of inflammation.	$CD4^+$ T, $CD8^+$T	Harmful	[95]
Pulmonary nodular disease	↑	Stimulate the activation of the PI3k/Akt pathway, causing Th17/Treg imbalance; Activate the TGF-β/Smad pathway.	Treg, Th1, Th17	Harmful	[103, 104]
Pulmonary aspergillosis	↓	By depleting CCL20, the innate immune response of the host is suppressed.	Th1, Th2, Th17	Protective	[109]
Viral Infectious Pneumonia	↑	The imbalance of Th17/Treg cells and the decreased ability of $CD8^+$T cells to clear the virus aggravate lung inflammation.	Treg, Th17	Harmful	[112]

The ↑ symbol indicates an increase in expression levels, the ↓symbol indicates a decrease in expression levels

of HCCR6 to CCL20 and may potentially inhibit the recruitment of Th17 cells to inflammatory tissue [124]. However, 1C6 remains at the preclinical stage and lacks clinical validation data. ChemoCentryx has made progress in this field by developing a small molecule antagonist, CCX2553, that targets CCR6 (U.S. Patent Application No. 15/353,889) [125]. It works in a mouse model of psoriasis by preventing the accumulation of γδT17 cells in psoriatic skin. Another novel CCR6 antagonist, PF-07054894, has shown promising inhibition of T lymphocyte migration in both mice and monkeys and is currently in Phase I clinical trials [126].

Despite achieving relatively promising research outcomes in numerous studies, unfortunately, no CCR6 inhibitors have been approved for clinical use to date. However, there has been recent progress in this area with the development of the small molecule CCR6 antagonist IDOR-1117–2520, also referred to as compound 45, by Actelion-Idorsia [127]. Following a comprehensive series of experiments and model validations, IDOR-1117–2520 has demonstrated favorable activity and in vivo efficacy, suggesting its potential for future clinical application (Table 2).

Discussion

In this paper, we demonstrate the comprehensive involvement of the CCL20-CCR6 axis in immune mechanism responses and elucidate the efficacy of anti-CCL20 and anti-CCR6 treatments in alleviating disease progression to a certain extent. This discovery is pivotal for indicating that CCL20-CCR6 may serve as a promising therapeutic target for a wide range of conditions, including inflammation, autoimmune diseases, and cancer. Our findings identify CCL20-CCR6 as a potential therapeutic target, highlighting its significant potential for transformation and development.

In the respiratory system, previous studies on the CCL20-CCR6 axis have primarily concentrated on cancer and asthma. However, our research has revealed that CCL20-CCR6 is also implicated in the pathogenesis of additional respiratory diseases, including COPD, tuberculosis, and pulmonary sarcoidosis. This review explores the role of the CCL20-CCR6 axis in the respiratory tract. In diseases such as asthma, COPD, and pneumonia, CCL20-CCR6 is related to the recruitment and activation of T lymphocytes, particularly Th17 cells. Once activated, these Th17 cells release pro-inflammatory cytokines into damaged tissues, exacerbating the inflammatory response. Furthermore, in lung cancer, the interaction between CCL20 and CCR6 can activate downstream cancer signaling pathways, induce resistance to apoptosis, and promote cancer cell proliferation and migration.

Despite the promising progress in CCL20-CCR6 research, which indicates its feasibility as an immunosuppressive target, it is crucial to acknowledge several potential limitations. For example, in studies investigating the CCL20-CCR6 axis, the absence of CCL20 knockout ($CCL20^{-/-}$) mice has often led researchers to rely on CCR6 knockout ($CCR6^{-/-}$) mouse models or the application of CCL20-targeting monoclonal antibodies to block

Table 2 CCL20 and CCR6-related inhibitors

	Name of Inhibitor	Mechanism of inhibitor	Type of Inhibitor	References
1	GSK3050002	Aggregates containing complement proteins can serve as substrates for complement activation	Humanized IgG1κ monoclonal antibody targeting CCL20	[128]
2	Di-S-IdoA	Humanized IgG1κ monoclonal antibody targeting CCL20	Small-molecule carbohydrates	[30]
3	NCT01984047	Neutralization of monoclonal antibodies (mAbs) with the chemokine ligand CCL20	A humanized anti-CCL20 monoclonal antibody (mAb)	[129]
4	CCX9664	Targeting CCR6 reduces T lymphocyte infiltration	A small-molecule antagonist of CCR6	[124]
5	Infliximab	TNF-induced upregulation of CCL20 is inhibited by the NF-κB pathway	Monoclonal antibody	[4, 123]
6	etanercept	Anti-TNF-α modified fusion protein	Monoclonal antibody	[4, 123]
7	Tocilizumab	Block $CD4^+$ T lymphocyte differentiation into Th17 cells	Antibodies targeting the interleukin-6 receptor (IL-6R) production	[4, 123]
8	CO339589	Inhibition of CCL20-mediated chemotaxis and binding in human natural killer (NK) cells and CCR6-rich peripheral blood mononuclear cells (PBMCs)	A small-molecule antagonist effective against CCR6 in both humans and mice	[4]
9	WO2017011559A1	Competitive inhibition of CCR6 binding to CCL20	Anti-CCL20 antibody	[130]
10	IDOR-1117–2520	Migration of CCR6 to the bronchus and alveoli is inhibited	A highly effective small-molecule antagonist of CCR6	[127]
11	PF-07054894	Blocking CCR6-mediated chemotaxis and the binding of CCL20 to CCR6	A selective small-molecule antagonist of CCR6	[126]

CCL20 expression [123]. Currently, most CCL20-CCR6 blockers available on the market are neutralizing monoclonal antibodies, such as infliximab, tocilizumab, and etanercept [4]. Although satisfactory results are often achieved in experimental studies, the extent to which CCR6-deficient mice accurately represent CCL20 expression remains questionable. Notably, human β-defensin 2, which is structurally similar to CCL20, and its immediate homolog, murine β-defensin 4, both have the ability to bind to CCR6 and competitively inhibit CCL20 [36]. Furthermore, it is worth noting that the atypical chemokine receptor ACKR4 can also serve as a receptor for CCL20, albeit with a lower affinity compared to the CCL20-CCR6 axis [34]. This competition raises concerns about whether the interaction between CCR6 and CCL20 is fully representative in these models. Indeed, despite the presence of interfering factors, including ACKR4 and beta-defensins, it is solely the binding of CCL20 to CCR6 that initiates the classical G-protein signaling pathway. From this perspective, although small-molecule chemokine receptor antagonists have failed to demonstrate clinical efficacy in the treatment of inflammatory diseases, CCL20-CCR6 remains an attractive target for drug development research due to its specificity and potential therapeutic benefits. Consequently, while CCL20-CCR6 blockers hold promise, their application on a large scale in clinical settings remains limited, highlighting the need for further research and development to explore these new therapeutic options.

Furthermore, this paper acknowledges additional limitations. Given that CCL20-CCR6 research within the respiratory system is still an emerging field, the available literature for review is limited. Additionally, some studies date back several years, and their results may not accurately reflect the current research progress due to potential lags in publication and advancements in the field. Therefore, these findings should be interpreted with caution and considered in the context of ongoing research developments.

Conclusion

In conclusion, while the significance of the CCL20-CCR6 axis in the respiratory system is increasingly recognized, there remain substantial gaps in understanding its mechanisms of action. Further research is needed to deepen our knowledge and explore potential therapeutic applications.

Abbreviations

CCL	C–C motif chemokine ligand
CCR	C–C motif chemokine receptor
CXCR	C-X-C motif chemokine receptor
COVID-19	Coronavirus Disease 2019
IL	Interleukin
TNF-a	Tumour necrosis factor-a
GAGs	Glycosaminoglycans
HBD	Human beta-defensin
DCs	Dendritic cells
NSCLC	Non-small cell lung cancer
NNK	Nicotine-derived nitrosamines
AC	Adenocarcinoma
SCC	Squamous cell carcinoma
EMT	Epithelial-mesenchymal transition
CAR-T	Chimeric antigen receptor
COPD	Chronic obstructive pulmonary disease
MMPs	Matrix metalloproteinases
TGF-β	Transforming growth factor-β
BALF	Bronchoalveolar lavage fluid
ARDS	Acute respiratory distress syndrome

Authors' contributions

Yong Wang and Ya-Jing Li designed the study. Ya-Jing Li wrote most of the manuscript. Wan-Li Geng, Chen-Chen Li, Jia-Hao Wu, and Fei Gao performed the study and contributed to the collection of data and analysis. The authors declare no conflicts of interest.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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