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Role of CCL2/CCR2 axis in pulmonary fibrosis induced by respiratory viruses

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ABSTRACT

Respiratory virus infection is an important cause of both community acquired pneumonia and hospital-acquired pneumonia. Various respiratory viruses, including influenza virus, avian influenza virus, respiratory syncytial virus (RSV), SARS-CoV, MERS-CoV, and SARS-CoV-2, result in severe fibrosis sequelae after the acute phase. Since the COVID-19 pandemic, respiratory virus infection, as an important cause of pulmonary fibrosis, has attracted increasing attention around the world. Respiratory virus infection usually triggers robust inflammation responses, leading to large amounts of proinflammatory mediator production, such as chemokine (C-C motif) ligand 2 (CCL2), a critical chemokine involved in the recruitment of various inflammatory cells. Moreover, CCL2 plays a pivotal role in the pathogenesis of fibrosis progression, through regulating recruitment of bone marrow-derived monocytes and increasing the expression of extracellular matrix proteins. This review provided a concise overview of the common fibrosis sequelae after virus infection. Then we discussed the elevated levels of CCL2 in various respiratory virus infection, underscoring its potent profibrotic role. Targeting the CCL2/CCR2 axis holds promise for alleviating fibrosis sequelae post-acute virus infection and warrants further investigation.

1. Introduction

Acute viral infections of the lower respiratory tract can lead to substantial morbidity and mortality worldwide, bring a huge challenge to the global health care system. With the wide application of PCR for virus detection, increasing studies revealed the importance of respiratory virus infection in community acquired pneumonia (CAP).[1,2] Recent researches using PCR reported that approximate 30 % of adult CAP cases were due to virus infection.[2] A multi-site case-control study, which enrolled 4232 pediatric patients aged 1–59 months with severe pneumonia, found that about 61.4 % of cases were caused by respiratory viruses, including respiratory syncytial virus (RSV), influenza virus, parainfluenza virus, human metapneumovirus (HMPV) and so on.[3] In addition, respiratory viruses contribute to 15 %–30 % of hospital-acquired pneumonia (HAP) in adults and about 50 %–60 % of HAP in children.[4] The common clinical symptoms of respiratory virus infection include cough, fever, chill, fatigue, runny or stuffy nose, muscle pain, wheezing, headache and so on. Ground-glass opacity (GGO), patchy consolidations, centrilobular nodules or branching centrilobular nodules are the common manifestations on CT images of multiple kinds of respiratory virus infection.[5]

Besides the radiological manifestations mentioned above, it is worth noting that fibrotic changes can develop after the acute phase of virus infection. Viruses such as cytomegalovirus (CMV), avian influenza virus (AIV), and coronavirus (SARS-CoV, MERS-CoV, and SARS-CoV-2), can bring persistent damage to the lung and promote occurrence of fibrosis post-acute infection.[6] Increasing studies have reported fibrosis sequelae after SARS-CoV-2 infection.[7–10] Multiple factors are related to increased risk of fibrosis occurrence secondary to COVID-19, such as male, older, active smoking, diabetes, severity of acute infection, use of high flow oxygen or mechanical ventilation.[11] In spite of intense research into the molecular mechanisms of fibrosis sequelae induced by respiratory virus infection, pathogenesis of fibrosis progression remains elusive and therapeutic strategies are still limited. Among those increased pro-inflammatory mediators in respiratory virus infection, C-C motif ligand 2 (CCL2) is of great significance.

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CCL2, also named monocyte chemoattractant protein-1 (MCP-1), is a 13 kDa protein consisting of 76 amino acid residues, encoded by the *CCL2* gene which is located on human chromosome 17 (chr.17, q11.2), with three exons and two introns.[12,13] The biological activity of CCL2 is mainly associated with two important regions: amino acids 10 to 13 and amino acids 34 to 35. Mutation in the former region can reduce biological activity, while mutation in the latter region causes complete inactivation of CCL2.[13] The secondary structure of CCL2 includes four β-sheet sections (β0: residues 9–11; β1: residues 27–31; β2: residues 40–45; and β3: residues 51–54), a short N-terminal loop, and a C-terminal α-helix.[14,15] N-terminus is necessary for conformational structure and receptor activation. Furthermore, missing critical amino acid residues at the N-terminal, such as Asn6, Ala7, Val9, Tyr13, Asn14, Phe15, and Thr16, can result in activity loss of CCL2.[15,16] CCL2 belongs to the CC chemokine superfamily, primarily produced by various immune cells, such as monocytes/macrophages, T lymphocytes, and natural killer (NK) cells.[17–19] Besides, several other cell types, including astrocytes, microglia, mesangial cells, smooth muscle cells, endothelial cells, epithelial cells, and fibroblasts can also express CCL2 (Fig. 1).[15,17,20–23] The expression of CCL2 can be either persistent or inducible. A variety of factors can induce CCL2 expression, such as oxidative stress, oxidized low-density lipoprotein (oxLDL), cytokines (IL-1, IL-4, IL-6, TNF-α, and IFN-γ), or various growth factors (GM-CSF, M-CSF, PDGF, VEGF) (Fig. 1).[21,24–27]

As an important inflammatory chemoattractant, CCL2 can recruit multiple immune cells during inflammation process, including monocytes, dendritic cells (DCs), memory T lymphocytes, and NK cells by binding to its receptor, CC chemokine receptor type 2 (CCR2) (Fig. 1).[28–30] CCR2 is a G-protein coupled receptors (GPCRs), having two alternatively spliced variants with a different number of amino acids in human, CCR2A and CCR2B.[31] CCR2B is mainly expressed on the surface of different cell types, while CCR2A is primarily localized in the cytoplasm.[32] The extracellular sites of CCR2 are critical for the high-affinity binding to specific ligands and activating following signal transduction.[33,34] In addition to CCL2, CCR2 can also bind to several other ligands, such as CCL7, CCL8, CCL12, CCL13, and CCL16.[35] Multiple cell populations, including monocytes, macrophages, endothelial cells, dendritic, and T cells can all express CCR2, which interacts with CCL2 and transduce extracellular signals into the cell.[36] The activation of CCL2/CCR2 axis plays an important role in the pathogenesis of various disease, such as tumor, atherosclerosis, lupus nephritis, especially lung fibrosis.[37–41]

CCL2 plays an important role in leukocyte recruitment and is related to lung fibrosis (Fig. 1).[42,43] Researches have reported elevated CCL2 expression in both pulmonary alveolar epithelial cells (AECs) and fibroblasts of IPF patients.[43–45] Inhibition CCL2 signaling in lung epithelial cell of bleomycin (BLM)-induced fibrosis murine model can reduce severity of fibrosis.[43] The primary mechanisms of CCL2's pro-fibrotic role include monocyte chemotaxis and upregulation of excessive extracellular matrix (ECM) proteins.[46] Additionally, elevated CCL2 expression can be observed in multiple respiratory virus infection, including influenza, avian influenza, RSV, SARS-CoV, MERS-CoV, SARS-CoV-2, and has positive association with inflammation injury, illness severity, and ultimate mortality.[47–51]

In this review, we briefly summarized the fibrosis sequelae after multiple respiratory virus infection, then elaborating the profibrotic role of CCL2/CCR2 axis and its involvement in the immunopathogenesis of virus infection, finally highlighting the rationale of inhibiting CCL2/CCR2 signaling for the treatment of pulmonary fibrosis induced by multiple respiratory virus (Fig. 2).

2. Fibrosis-induced by multiple respiratory viruses

Multiple respiratory viruses, including influenza virus, avian influenza virus, RSV, measles virus, SARS-CoV, MERS-CoV, and SARS-CoV-2, can induce pulmonary fibrosis after the acute phase of virus infection. Serial high-resolution CT (HRCT) scans of H1N1 patients showed ground-glass opacities with or without consolidation in the first week, which then tended to resolve into fibrosis.[52] Autopsy specimens from H1N1 patients also demonstrated remarkable pulmonary fibrosis, involving both lung interstitium and alveolar spaces.[53] In the recovering period of H7N9 infection, fibrosis and traction bronchiectasis were the main features on chest CT.[54] Pathology of autopsy samples from H5N1 patients exhibited remarkable organizing diffuse alveolar damage with interstitial fibrosis.[55] H5N1-infected mice developed fibrosis of different severity at restoration stage, accompanied by dramatically elevated hydroxyproline levels and deposition of collagen.[56] One patient suffering from severe measles infection developed chronic respiratory

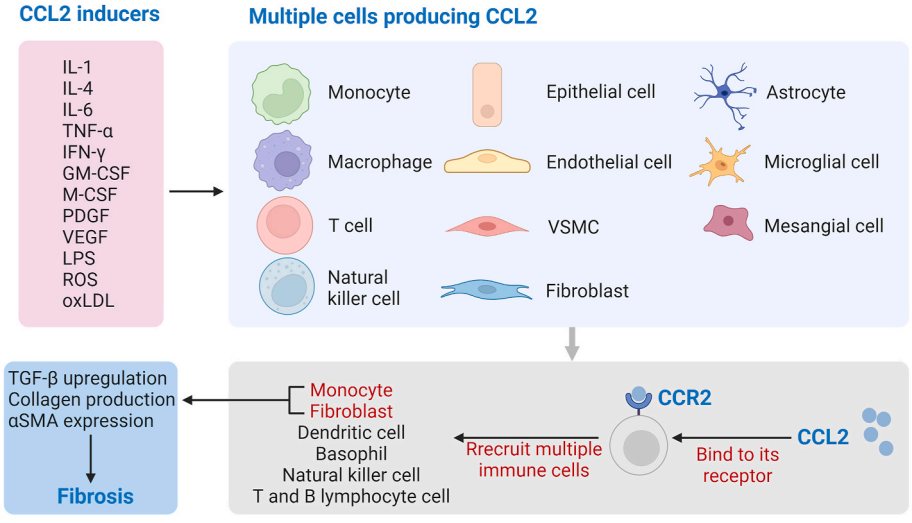

Fig. 1. CCL2 production and its main role of cell recruitment. Multiple cells can produce CCL2, of which monocytes and macrophages are particularly important. The expression of CCL2 can be either persistent or inducible. Multiple inducers can induce CCL2 expression, including IL-1, IL-4, IL-6, FNF-α, IFN-γ, ROS, oxLDL, and several growth factors. CCR2 is the receptor of CCL2, through which CCL2 can recruit various cells, such as monocytes, fibroblast, dendritic cell, basophil and so on. Recruited monocytes and fibroblasts can contribute to fibrosis progression through multiple mechanisms, such as TGF-β upregulation, collagen production, and αSMA expression. Abbreviation: VSMC, vascular smooth muscle cell; GM-CSF: granulocyte–macrophage colony stimulating Factor; M-CSF: macrophage colony stimulating factor; PDGF: platelet-derived growth factor; VEGF: vascular endothelial growth factor; LPS: lipopolysaccharides; ROS: reactive oxygen species; oxLDL: oxidized low-density lipoprotein.

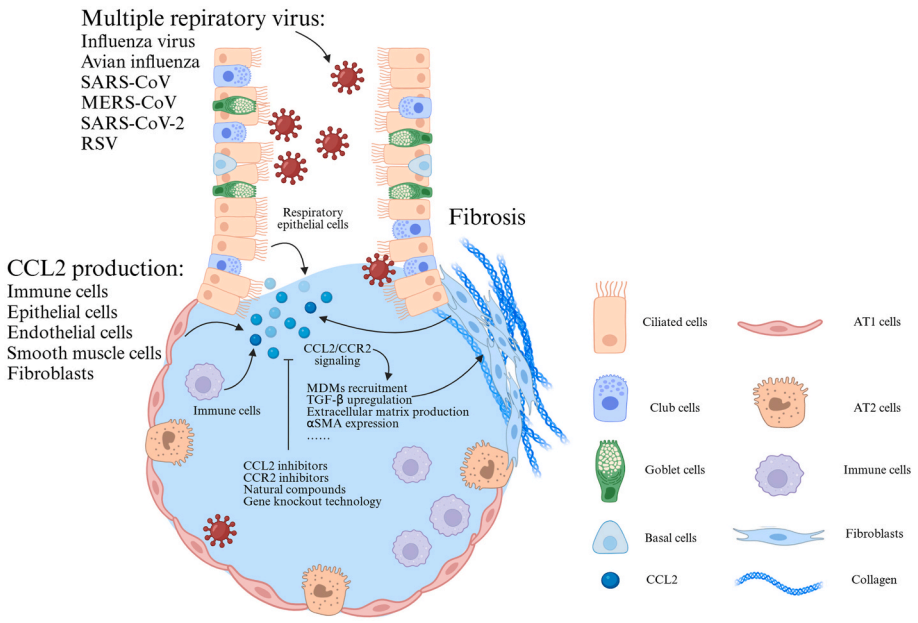

Fig. 2. The pro-fibrotic role of CCL2/CCR2 axis in respiratory virus-induced fibrosis. Multiple respiratory viruses, including influenza, avian influenza, SARS-CoV, MERS-CoV, SARS-CoV-2, and RSV, contribute to enhanced CCL2/CCR2 signaling after infection. Various cell types are able to produce CCL2 during infection, such as immune cell, both airway and alveolar epithelial cells, endothelial cells, smooth muscle cells, and fibroblasts. Increased CCL2 promotes fibrosis progression through MDMs recruitment, TGF-β upregulation, extracellular matrix production, and αSMA expression. CCL2 inhibitors, CCR2 inhibitors, several natural compounds, and gene knockout technology can effectively suppress CCL2/CCR2 axis signaling, serving as potential therapeutic choice for virus-induced fibrosis treatment.

failure associated with lung fibrosis 6 months following infection, manifested as fibrosing interstitial pneumonia with thickened interlobular septa.[57] Histopathologically, the lungs of SARS patients exhibited interstitial and airspace fibrosis after ~10–14 days. The extent of fibrosis of the lung tissues is positively related to the disease duration.[58] A follow-up study using chest radiographs demonstrated that approximate 33 % of patients developed lung fibrosis after recovery from acute MERS-CoV infection.[59] Follow-up (23 days after symptom onset) chest CT scans of a 30-year-old male with Middle East respiratory syndrome (MERS) infection showed remarkable decreased extent of previous detected lesions, and developed traction bronchiectasis, which indicated fibrosis.[60] Multiple case reports have described post-COVID-19 pulmonary fibrosis on chest CT.[61–63] For example, a COVID-19 patient showed remarkable fibrotic changes, such as architectural distortion, traction bronchiectasis, and interlobar septal thickening on chest CT 3 weeks post virus infection.[63] Pathology of lung tissues from deceased COVID-19 patients found marked fibrotic lung parenchymal remodeling, fibroblast proliferation, and micro-honey-combing.[64] The potential mechanisms underlying fibrosis sequelae after virus infection include enhanced TGF-β/Smad signaling, possible epithelial-mesenchymal transformation,[65] impaired alveolar epithelium regeneration,[66] and recruitment of profibrotic macrophages.[67] CCL-2, as a profibrotic chemokine, is implicated in the pathogenesis of various respiratory viruses. The detailed association between CCL-2 and fibrosis sequelae would be discussed below.

3. CCL2/CCR2 axis as drivers of pulmonary fibrosis

Recently, a growing body of researches have demonstrated the close relationship between CCL2/CCR2 axis and fibrosis pathophysiology, such as pulmonary fibrosis and liver fibrosis.[41,68] This section will primarily talk about the cellular source of CCL2, elevated CCL2/CCR2 signaling in both animal and human pulmonary fibrosis studies, the potential profibrotic mechanisms of CCL2/CCR2 axis, and possible strategies in fibrosis treatment.

3.1. The source of CCL2

The elevated CCL2 observed in fibrosis process can derive from multiple cell types, such as epithelial cells, immune cells, and fibroblasts.[44,69–71] Lung epithelial cells may be the major source of CCL2 production in the fibrotic lung.[44,69] Lung epithelial cells from IPF patients strongly expressed CCL2, while epithelial cells from non-IPF patients did not express CCL2.[44] Proteinase-activated receptor-1 (PAR(1)) is the receptor of thrombin. Activation of PAR(1) in lung epithelial cells contribute to increased local CCL2 release.[69] Thus, targeting PAR(1) of epithelial cells may be a potential therapeutic strategy for pulmonary fibrosis.[69] Apart from epithelial cells, CCL2 from macrophage can also exacerbated IPF phenotype. Nuclear factor of activated T cells cytoplasmic member 3 (NFATc3) contributes to pulmonary inflammation and fibrosis through modulating the gene expression of CCL2 in macrophage.[71] Macrophage colony-stimulating factor (M-CSF) induced CCL2 production in human and mouse macrophages, contributing to the pathogenesis of pulmonary fibrosis in mice and IPF patients.[72]

3.2. CCL2/CCR2 axis in animal fibrosis studies

CCR2 signaling plays a critical role in the initiation and progression of pulmonary fibrosis through multiple mechanisms, including regulating recruitment of bone marrow-derived monocytes and upregulation of extracellular matrix proteins (Fig. 2).[45,46] In both fluorescein Isothiocyanate (FITC) and bleomycin-induced fibrosis model, CCL2 was up-regulated in lung homogenates.[73,74] Besides CCL2, another murine CCR2 ligand, MCP-5 (CCL12) was induced ~2 fold at day 7 post-FITC administration.[73] Overexpression of IL-10 in mice can induce fibrosis, in part, through fibrocyte recruitment and M2 macrophage activation in a CCL2/CCR2 dependent manner.[75] CCL2 can stimulate isolated rat lung fibroblast collagen expression via endogenous up-regulation of TGF-β in a dose-dependent manner.[45]

3.3. CCL2/CCR2 axis in human fibrosis studies

Several studies have also reported increased CCL2 levels in pulmonary fibrosis patients, which may be characteristic for IPF.[41] CCL2 levels were significantly elevated in BALF and serum of patients with IPF, and monitoring of serum CCL2 may help to predict the clinical course of interstitial lung diseases.[76] Higher concentration of CCL2 in BALF was also observed in sulfur mustard (SM) gas-induced pulmonary fibrosis and CCL2 level correlated not only with the percentage but also with the absolute number of lymphocytes of BALF in patients with pulmonary fibrosis.[77] Furthermore, a study including both patients with acute exacerbation of IPF (AE-IPF) and patients with stable IPF (S-IPF) showed that CCL2 is associated with macrophage activation and may impair the overall survival of IPF patients.[78]

Fibroblasts from IPF patients were hyperresponsive to TGFbeta1, IL-13 and CCL2. Besides, these three factors feedback on each other, enhancing the fibrotic response.[70] CCL2 stimulation directly induced increase in alpha-smooth muscle actin (αSMA) and procollagen III expression in fibroblasts from both IPF patients and non-fibrotic fibroblasts.[70]

3.4. Measures aimed at reducing CCL2 in fibrosis

Several researches demonstrated that measures reducing CCL2 level can alleviate the severity of pulmonary fibrosis.[79–81] $CD4^{+}CD25+FoxP3+$ regulatory T cells (Tregs) adoptive transfer attenuated BLM-induced murine pulmonary fibrosis, accompanied by reduced CCL2 production in lung homogenates and fewer bone-marrow derived fibrocytes accumulation.[81] Amniotic fluid stem cell (AFSC) treatment significantly reduced CCL2 expression in bleomycin-injured BALF, inhibiting collagen deposition and fibrosis progression.[80] CCL12 is a murine homolog of human CCL2. Deletion of CCL12 within alveolar epithelial cells led to decreased recruitment of macrophages in bleomycin-induced fibrosis mice. Consequently, mice with lung epithelial specific deletion of CCL12 were protected from fibrosis and the expression levels of CCL2 and CCL7 were similar to that of control mice treated with bleomycin.[43] Nintedanib (NTD), which is approved for IPF therapy, can reduce CCL2 production in human monocyte-derived macrophages.[79]

Nevertheless, the correlation between CCL2/CCR2 axis and pulmonary fibrosis is extremely intricate, due to the complex sources of CCL2 and the existence of multiple ligands for CCR2.[43,82] Measures aimed at reducing CCL2 level may promote the production of other CCR2 ligands, leading to failure in fibrosis therapy. For instance, in bleomycin-induced fibrosis model, complete deletion of CCL12 showed markedly increased concentrations of other CCR2 ligands and no protection from fibrosis after bleomycin injury.[43] Similar phenomenon was observed in a phase 2 clinical trial. Carlumab is a human IgG1kappa monoclonal antibody with high affinity and specificity for human CCL2. In a phase 2 trial of carlumab, CCL2 inhibition showed no therapeutic response in IPF patients, perhaps due to a marked compensatory upregulation of CCL2 production.[82]

4. CCL2/CCR2 in the pathogenesis of respiratory virus infection

4.1. Influenza virus and avian influenza virus infection

Multiple researches demonstrated that CCL2/CCR2 signaling are significantly enhanced in respiratory influenza virus and avian influenza virus infection, including H1N1, H7N9, and H5N1. Serum CCL2 level was markedly elevated in confirmed human cases of H7N9 and H5N1 acute infection (Table 1).[47] Similarly, increased CCL2 levels were also detected in BALF and lung tissue of H7N9-infected mice. More importantly, CCL2-deficient mice exhibited attenuated severity of H7N9 induced acute lung injury, manifested as less weight loss, improved lung edema, ameliorated histopathological changes, and especially a lower

Table 1
Researches related to CCL2/CCR2 axis in important respiratory virus infection.

Virus	Species	Sample	Notes	Refs
H7N9	Human	serum	In acute serum sample of H7N9-infected patients, increased CCL2 was detected.	47
H7N9	Mouse	BALF and lung tissue	CCL2 was elevated in BALF and lung tissue of H7N9-infected wild-type mice. CCL2-deficient mice exhibited ameliorated acute lung injury.	48
Influenza A	Mouse	lung tissue	Lung RNA expression of CCL2 increased at day 2 postinfection. CCR2-deficirnt mice showed defects in macrophage recruitment and were protected from influenza A infection.	83
RSV	Human	epithelial cells of the lower respiratory tract	RSV induced dose- and time-dependent CCL2 production in epithelial cells of the lower respiratory tract in vitro.	84
RSV	Human	airway epithelial cells and monocytes	Coculture of monocytes with RSV-infected airway epithelial cells resulted in the production of CCL2.	85
RSV	Mouse	lung tissue	CCL2 was induced in RSV-induced mouse model shortly after infection.	87
RSV	Human	BALF	BALF samples of infants with RSV bronchiolitis showed remarkable up-regulation of CCL2 expression.	88
RSV	Human	NPS	CCL2 concentrations of nasopharyngeal secretions were positively related to the degree of hypoxia in infants with RSV infection.	89
RSV	Human	NP wash samples	Both moderate and severe RSV-infected patients had significantly higher CCL2 concentrations in nasopharyngeal wash sample, compared with mild patients.	90
SARS-CoV	Human	blood	There was a significant elevation of CCL2 in the plasma of SARS patients, and corticosteroid can reduce CCL2 significantly.	50
SARS-CoV	Human	blood and lung tissue	The level of CCL2 was increased in the blood and lung tissues of the patients with superinfection, indicating a high risk of death.	91
SARS-CoV	Human	macrophage	SARS-CoV can induce human macrophages to produce high level of CCL2 in the first few hours post infection in vitro.	93
SARS-CoV	Rat	lung tissue	CCL2 was drastically elevated at 24 h post-infection and remained high level at 48 h post-infection.	92
SARS-CoV	Mouse	lung tissue	CCL2 was induced in a biphasic pattern in SARS-CoV-infected mice, and can sustain even after viral clearance.	96

(continued on next page)

Table 1 (*continued*)

Virus	Species	Sample	Notes	Refs
MERS-CoV	Mouse	lung tissue	In C57B6/hDPP4 mice infected with MERS-CoV, CCL2 expression was dramatically upregulated at 2, 4, and 7 days post-infection.	49
MERS-CoV	Alpaca	lung tissue	In MERS-CoV infected alpacas, upregulation of CCL2 expression is correlated with a transient accumulation of mononuclear leukocyte in the alveoli.	97
SARS-CoV-2	Human	blood	SARS-CoV-2 infection caused significant elevation of CCL2 in blood, and concentrations of CCL2 had positive associations with disease severity.	51, 98–100
SARS-CoV-2	Human	lung tissue	Transcriptional profiling revealed robust CCL2 levels in lung samples from deceased COVID-19 patients.	100
SARS-CoV-2	Human	BALF	scRNA-seq of BALF samples from COVID-19 patients indicated upregulation of CCL2, facilitating migration of immune cells to the infective site.	101, 102
SARS-CoV-2	Human	BALF	Multiplex cytokine assays and scRNA-seq of BALF samples from COVID-19 patients exhibited the positive association between the level of CCL2 and the severity of radiographic fibrosis.	103
SARS-CoV-2	Ferret	nasal wash	Nasal wash of SARS-CoV-2-infected ferrets showed increased CCL2 expression on day 7 post-infection.	100

Abbreviation: BALF, bronchoalveolar lavage fluid; Nasopharyngeal, NP; NPS, nasopharyngeal secretions.

mortality rate (Table 1).[48] In high pathogenicity virus infection, accumulating CCR2^{+} inflammatory monocytes contributes to excessive production of inflammatory innate immune responses, and leads to the fatal outcomes. CCR2-deficient mice were protected from influenza A infection due to defect in inflammatory monocyte recruitment, though increased expression CCL2 was observed in this gene knockout animal model (Table 1).[83]

4.2. Respiratory syncytial virus (RSV)

Multiple studies have observed enhanced CCL2 expression in RSV infection. Respiratory epithelial cells, alveolar macrophages, and monocytes can all produce CCL2 after RSV infection in vitro (Table 1).[84–86] CCL2, CCL7, and CCL12, which were all ligands for CCR2, were induced in RSV-infected mouse model shortly after infection.[87] BALF samples of infants with RSV bronchiolitis showed remarkable up-regulation of CCL2 expression.[88] Besides, another study reported that the CCL2 concentrations of nasopharyngeal secretions were positively related to the degree of hypoxia in infants with RSV infection.[89] Both moderate and severe RSV-infected patients had significantly higher CCL2 concentrations in nasopharyngeal wash sample, compared with mild patients.[90]

4.3. SARS-CoV

Early study has indicated that increased amount of CCL2 was associated with pulmonary inflammation and extensive lung injury in SARS patients. Plasma CCL2 concentration had positive correlation with disease severity of SARS patients. Besides, corticosteroid treatment can significantly suppress the elevated CCL2, subsequently mitigate the inflammation responses in SARS (Table 1).[50] Another study demonstrated that the levels of IL-6, IL-8, and CCL2 were markedly upregulated in the SARS patients at the end stage of their illness, suggesting that these cytokines/chemokines can serve as vital markers for identifying SARS patients at high risk of death (Table 1).[91] Both in vivo and in vitro studies indicate that SARS-CoV can promote CCL2 production. In the lung tissues of SARS-CoV infected mice, the levels of CCL2 were drastically elevated at 24 h post-infection and remained high level at 48 h post-infection (Table 1).[92] SARS-CoV can induce human macrophages to produce high level of CCL2 in the first few hours post infection, confirmed by real-time quantitative RT-PCR of macrophages and ELISA of culture supernatant (Table 1).[93]

Several researched reported that CCL2 level was related to virus replication.[94,95] Kinetic studies of protein expression revealed that CCL2 protein could be detected in lung of C57BL/6 mice during a very narrow time window around 3 days after SARS infection, which is the time of peak viral load.[95] In the lung lavage of SARS-CoV-infected mice, increased IL-6 and CCL2 were observed at 2 days and 3 days after infection, and the high levels of the two mediators were closely related to the virus replication and disease severity.[94] In SARS-CoV-infected aged mice, multiple genes, including Il6, Tnfa, Ccl10, Ccl3, Ccl2, and Ifng, were induced in a biphasic pattern that associated with peak viral replication and following influx of lymphocytes. The upregulated CCL2 can sustain even after viral clearance, indicating that this heightened immune response is not required for viral clearance and may be responsible for the observed severe histopathologic changes (Table 1).[96]

4.4. MERS-CoV

In C57B6/hDPP4 mice infected with 2.5×10^4 PFU MERS-CoV, RNA-seq of lung tissues suggested that CCL2 expression was dramatically upregulated at 2, 4, and 7 days post-infection compared to mock-infected controls (Table 1).[49] In MERS-CoV infected alpacas, upregulation of CCL2 expression is correlated with a transient accumulation of mononuclear leukocyte in the alveoli (Table 1).[97]

4.5. SARS-CoV-2

Elevated CCL2 level was observed in both blood and lung samples of COVID-19 patients, and severe cases had higher CCL2 level when compared with mild cases (Table 1).[51,98–100] Plasma CCL2 concentration was upregulated in both ICU patients and non-ICU patients after SARS-CoV-2 infection, compared to the healthy adults. In addition, further comparison showed that CCL2 plasma concentration was higher in ICU patients than non-ICU patients.[98] Another study reported similar phenomenon. Non-survival COVID-19 patients had higher serum level of CCL2 as compared to the survival group, and CCL2 remained elevated in non-survivors at 7 days post SARS-CoV-2 infection. These results suggested that CCL2 may be a potential molecule related to COVID-19 heterogeneity, and has an important role in disease severity prediction.[99] Single-cell RNA sequencing (scRNA-seq) of BALF samples from COVID-19 patients reveled upregulation of both CCL2 and the corresponding receptor CCR2, which facilitate the migration of immune cells to the infection site, underlining the significant correlation between COVID-19 pathogenesis and excessive cytokine generation.[101] Another study using scRNA-seq data of BALF samples showed that CCL2 expression was much higher in lung macrophages of severe COVID-19 patients (Table 1).[102] Similarly, a recent study utilizing multiplex cytokine assays and scRNA-seq reported that, in COVID-19 patients with

post-acute sequelae of COVID-19 and radiographic abnormalities, the level of CCL2 in BALF had positive correlation with the severity of radiographic fibrosis.[103]

4.6. Targeting CCL2/CCR2 axis in respiratory virus infection

Multiple strategies, such as various inhibitors and gene knockout technology, can suppress the CCL2/CCR2 axis signaling and may be candidate treatment choices for virus infection.[15] The CCL2/CCR2 axis has various of inhibitors, including CCL2 inhibitors (carlumab, Bindarit, etanercept and adalimumab), CCR2 inhibitors (BMS-813160 and BMS-687681, PF-04178903, cenicriviroc), and several natural compounds (Lippia sidoides and Terminalia glabrescens extracts, curcumin, Shufeng Jiedu capsule, and progesterone) (Fig. 1).[15,82,104–110]

Pharmacologically blocking CCR2 using a small molecule inhibitor (PF-04178903) can lead to reduction in BALF total protein, albumin, and lactose dehydrogenase activity, accompanied by increased influenza nucleoprotein-specific cytotoxic T cell activity and finally decreased mortality after H1N1A/Puerto Rico/8/34 infection.[107] Shufeng Jiedu capsule (SFJDC) is usually used to control symptoms of upper respiratory infection, such as fever, headaches, coughing, sore throat, and runny nose.[111] CCL2 is one of the main targets of SFJDC.[15] SFJDC can significantly reduce the viral load and promote IFN-γ production in mice infected with H1N1 virus strain FM1 or PR8.[111] Inhibition CCL2/CCR2 axis may also have the potential to attenuate inflammation and fibrosis responses in COVID-19.[108] Progesterone is reported to inhibit the production of pro-inflammatory mediators, such as CCL2,[112] and is likely to effectively treat moderate to severe COVID-19 in male patients.[15,113] Inhibiting CCL2 with anti-CCL2 antibody can reduce virus-induced weight loss and delay mortality in mice infected with the β variant of SARS-CoV-2.[114]

However, several researches using other CCL2/CCR2 axis inhibitors failed to observe remarkable therapeutic effect in respiratory virus infection.[115–117] Treatment with Bindarit, a potent inhibitor of CCL2 synthesis, did not protect mice from lethal avian IAV H7N9 infection.[117] Cenicriviroc, a CCR2/CCR5 antagonist, showed no obvious benefit in COVID-19 pneumonia treatment compared with placebo in the I-SPY COVID trial.[115,116] Thus, the effect of inhibiting CCL2/CCR2 axis in respiratory virus infection can be discrepant due to the different types of inhibitors used and viruses infected. Selecting appropriate inhibitors for specific virus may be the key to obtaining significant curative effect.

Besides inhibitors of CCL2/CCR2 axis, gene knockout technology was also used to explore its potential regulative role in respiratory virus infection.[118,119] CCR2-deficient mice displayed remarkable reduced inflammatory cell recruitment, weight loss, lung injury, and mortality in influenza infection.[118] CCR2-deficient H1N1 IAV-infected mice, which lacked CCR2+ inflammatory monocyte recruitment, showed decreased leukocyte infiltration, multiple cytokines production, and increased survival rate after H1N1 infection.[119] Nevertheless, these researches rarely paid attention to the anti-fibrotic role of inhibiting CCL2/CCR2 axis, which deserves further study in the future.

5. Discussion and future prospects

This review delved into the intricate relationship between the CCL2/CCR2 axis and pulmonary fibrosis induced by respiratory viruses. Fibrosis sequelae after respiratory virus infection is a common phenomenon as discussed comprehensively by Huang WJ et al. in their review paper.[6] Large numbers of animal and human researches reported the elevated CCL2 in respiratory virus infection (Table 1). This elevation correlates with disease severity and clinical outcomes (Table 1). The profibrotic role of CCL2/CCR2 axis has also been well demonstrated in previous researches.[41,70,73,74] However, few studies noticed the potential profibrotic role of CCL2/CCR2 axis in respiratory virus infection. Based on these previous study, this review linked these findings, underscoring the significant profibrotic role of CCL2/CCR2 axis in respiratory virus infection.

Since the COVID-19 pandemic, respiratory virus infection, as an important cause of pulmonary fibrosis, has attracted increasing attention around the world. The exact mechanisms of pulmonary fibrosis post various acute virus infection are still incompletely understood, perhaps relevant to enhanced TGF-β signal,[120] apoptosis of epithelial cells,[121] hyperexpression of profibrotic growth factor (FGF, FGFR, EGF, and EGFR),[122] imbalance between extracellular matrix degradation and synthesis,[123] alternatively activated macrophages, Th2 bias,[124,125] aberrant AT2 cell differentiation and impaired lung regeneration.[66,126] In this review, we emphasized the long-neglected profibrotic role of CCL2/CCR2 after virus infection. Enhanced CCL2/CCR2 signaling facilitates bone marrow-derived monocytes recruitment,[43] TGF-β upregulation and extracellular matrix proteins production,[45,70] thus promoting fibrosis progression.

Treatment targeting inhibiting the CCL2/CCR2 signaling may serve as a potential choice for fibrosis sequelae induced by respiratory virus infection. Measures focused on reducing CCL2 level showed exact antifibrotic effect in BLM-induced murine pulmonary fibrosis.[80,81] Though in a phase 2 clinical trial of Carlumab, a monoclonal antibody of CCL2, inhibition CCL2 did not exhibited evident therapeutic effect in IPF patients due to compensatory upregulation of CCL2,[82] other strategies, such as CCR2 antagonist or inhibitor of CCL2/CCR2 pathway downstream targets, are still of great potential in fibrosis treatment and merit further investigation.

Apart from CCL2, several other chemokines of the CC family also participate in modulating the fibrosis process. For instance, chemokine CCL1 promotes myofibroblast differentiation and fibrosis progression through binding to autocrine motility factor receptor (AMFR)[127]; CCL3 interacts with CCR5 and promotes BLM-induced fibrosis development in mice[128]; CCL5 contributes to accumulation of inflammatory cell in PF[46]; the expression levels of CCL7 is significantly higher in usual interstitial pneumonia (UIP) lung biopsies compared to other interstitial lung diseases (ILDs); CCL17, CCL22, and their shared receptor CCR4, also involve in pathogenesis of fibrosis[46]; elevated CCL18 expression was observed in both serum and BALF samples of IPF patients, and CCL18 can induce pro-fibrotic M2 macrophage polarization[129,130]; CCL21-CCR7 axis can regulate fibroblast activation in IPF and is a possible strategy for IPF therapy[131]; CCL24 stimulates human fibroblast proliferation and collagen production, thus exerting pro-fibrotic effects.[132] Whether these chemokines of the CC family besides CCL2 can contribute to the fibrosis sequelae or serve as therapeutic targets in respiratory virus infection warrants further investigation.

6. Limitations

The present review aimed to elucidate the potential linkages between CCL2/CCR2 axis and pulmonary fibrosis induced by respiratory viruses. We acknowledge that there are several limitations in this review. Firstly, even though we endeavored to conduct a comprehensive literature search, due to the rapid development of research and the vast amount of available literatures, there may be unintentional omission of some relevant studies. Additionally, while this review mainly concentrated on several common respiratory viruses, CCL2/CCR2 axis may also be implicated in regulation of fibrosis sequelae caused by other viruses. Lastly, although we explored the therapeutic potential of CCL2/CCR2 axis in virus-induced fibrosis, further studies are essential to validate the clinical efficacy and safety of these treatments.

7. Conclusion

Briefly, multiple respiratory viruses can cause fibrosis sequelae of varying severity after the acute phase. The elevated CCL2 in respiratory infection participates in regulation the immunopathogenesis of disease severity, and is likely to facilitate the fibrosis sequelae development. Targeting the CCL2/CCR2 axis using appropriate inhibitors may serve as

a new choice for the treatment of fibrosis sequelae, and further researches are needed to validate the efficacy and safety of these therapeutic measures in virus infection.

CRediT authorship contribution statement

Shuangyan Li: Writing – review & editing, Writing – original draft, Conceptualization. **Mingming Pan:** Writing – review & editing. **Hui Zhao:** Writing – review & editing. **Yanming Li:** Conceptualization.

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Declaration of competing Interest

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