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Review

Chemokines and chemokine receptors during COVID-19 infection

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ABSTRACT

Chemokines are crucial inflammatory mediators needed during an immune response to clear pathogens. However, their excessive release is the main cause of hyperinflammation. In the recent COVID-19 outbreak, chemokines may be the direct cause of acute respiratory disease syndrome, a major complication leading to death in about 40% of severe cases. Several clinical investigations revealed that chemokines are directly involved in the different stages of SARS-CoV-2 infection. Here, we review the role of chemokines and their receptors in COVID-19 pathogenesis to better understand the disease immunopathology which may aid in developing possible therapeutic targets for the infection.

Contents

Abbreviations: AECs, airway epithelial cells; AP-1, Activator Protein 1; ARDS, acute respiratory disease syndrome; BALF, bronchial alveolar lavage fluid; CAP, community acquired pneumonia; CRS, cytokine releasing syndrome; DCs, dendritic cells; ECM, extracellular matrix; GAGs, glycosaminoglycans; HIV, human immunodeficiency virus; HRSV, human respiratory syncytial virus; IFN, interferon; IMM, inflammatory monocytes and macrophages; IP-10, IFN-γ-inducible protein 10; IRF, interferon regulatory factor; MERS-CoV, Middle East respiratory syndrome coronavirus; NETs, neutrophil extracellular traps; NF-κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells; NK cells, natural killer cells; PBMCs, peripheral blood mononuclear cells; PRR, pattern recognition receptors; RSV, rous sarcoma virus; SARS-CoV, severe acute respiratory syndrome coronavirus; TLR, toll like receptor; TRIF, TIR-domain-containing adapter-inducing interferon-β.

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1. Introduction

In 2020, the global pandemic COVID-19 infection caused many researchers to focus on the role of the immune system in fighting viral infections. The novel coronavirus, SARS-CoV-2, was found to be the causative of the acute respiratory disease syndrome (ARDS) which is similar to that caused by severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) [1,2]. Upon infection, some patients show mild symptoms such as fatigue and cough, whereas others develop severe symptoms such as bilateral infiltrates and pneumonia [3].

In COVID-19 patients, lymphopenia affecting natural killer (NK) and T cells ($CD4^+$ Th1, Tregs, and $CD8^+$), was more pronounced in severe cases [4,5]. Lymphopenia is also associated with neutrophilia and monocytopenia particularly in severely infected individuals [6]. Additionally, circulating $CD8^+$ T and NK cells displayed abnormal function and exhaustion, where a negative correlation between perforin content and serum cytokine levels was detected [5,7]. Despite the low count of $CD4^+$ T cells in COVID-19, these cells seem to be more activated as observed by CD69, CD38, CD44, and HLA-DR expression [5]. However, one of the main mechanisms associated with the pathophysiology of COVID-19 is the recruitment of inflammatory immune cells towards infected lungs and the subsequent hyperinflammatory state or the so-called cytokine releasing syndrome (CRS) [8–10]. These inflammatory mediators include TNF-α, interleukins such as IL-1β and IL-6 as well as chemokines.

2. Role of chemokines in viral infections

Chemokines play a critical role in fighting viral infections by recruiting innate and adaptive immune cells to sites of infection, and by enhancing their cytotoxic function and their ability to produce antiviral mediators [11]. On the other hand, some viruses manage to escape the immune system via chemokines. For instance, some large DNA viruses such as herpesviruses produce molecules that mimic the chemokines which dysregulate the signaling and immune response, thus leading to viral propagation and persistence [12].

There are different mechanisms through which chemokines exert their anti-viral effects. The role of chemokines and their receptors in NK cells have been previously described [13–16]. In this regard, chemokines have been reported to activate NK cells to kill virally-infected cells such as that observed in vaccinia virus and cytomegalovirus infections [17], as well as their ability to enhance NK cell lysis of tumor cells [18]. Additionally, chemokines and T cells were linked and investigated in viral infections such as hepatitis and HIV [17]. Further, viruses induce the production of inflammatory chemokines that promote a Th1- polarized immune response possibly by a cytokine-to-chemokine-to-cytokine signaling cascade that links innate and adaptive immune responses. Several viruses stimulate dendritic cells (DCs) to produce interferon leading to CCL3 (MIP-1α) production [19,20], and resulting in NK cell recruitment to perform direct killing of virally-infected cells as well as releasing IFN-γ. Reciprocally, this may lead to macrophage activation and CXCL9 production, thus recruiting Th1-polarized $CD4^+$ $CXCR3^+$ cells [21]. Additionally, other cytokines such as IL-1 and TNF-α, could induce the expression of chemokines such as CCL2, CCL3, CCL4, CCL5 and CXCL8 which are linked to viral infections [11].

Interferons along with interferon-inducible chemokines are also known to be involved in the host anti-viral response by promoting viral elimination until the adaptive immune system is activated [22]. IFN-γ-inducible protein 10 (IP-10 or CXCL10) is one of the main players in the anti-viral responses, especially in respiratory tract infections [23]. In several viral infections, CXCL10 was found to be elevated in the plasma and bronchial alveolar lavage fluid (BALF), and is correlated with disease severity [23–25]. Another key chemokine is CXCL8 that acts as a trafficking mediator for neutrophils. This chemokine is highly involved in inflammatory processes especially those associated with viral infections. CXCL8 level in the nasal fluid was found to be correlated with the severity of acute respiratory tract infections [26].

CCL2 and CXCL10 were highly expressed in the cerebrospinal fluid (CSF) of patients with viral meningitis, possibly in order to stimulate the migration of immune cells towards sites of infection [27]. Also, CXCL10 has been reported to act as a marker in hepatitis B and HIV infections [28,29]. This was supported by a study where CXCL10 levels were found to be elevated in untreated HIV-infected patients and would be restored to normal upon receiving antiretroviral therapy [30]. Other CC or CXC chemokines such as CCL3, CCL5 or CXCL10 were also involved in viral infections such as influenza and human respiratory syncytial virus (HRSV) [11,31,32]. Furthermore, CCL5 and CXCL9 (MIG) are involved in the inflammatory state of patients with chronic hepatitis C infection [33]. Whereas mice deficient in CCL3 exhibit delayed viral clearance when infected with influenza virus, or murine cytomegalovirus [34,35]. In patients infected with HIV, expression of CCL3, CCL4, and CCL5 was correlated with a Th1 immune response [36]. Also, CXCR4 and CCR5 were found to be co-receptors for HIV entry, while their ligands CXCL12 and CCL5 inhibited HIV infection [37,38].

However, massive recruitment of cells towards infected sites along with the enhanced antiviral and cytotoxic responses, could lead to hyperinflammation and tissue damage. Therefore, inflammatory chemokines could have beneficial or harmful roles during viral infections, and their blockage could provide a therapeutic approach against certain viruses [17]. Several molecules and antagonists targeting chemokines or their receptors, have been developed for the treatment of various diseases [39]. For instance, CCR4 blocker, Mogamulizumab, and anti-CXCR4 were utilized in treatment of leukemias and lymphomas [39–41]. The absence of the CCR5 receptor was suggested to provide resistance against HIV transmission. This was the case in HIV "Berlin patient" who went into remission due to the transplantation of bone marrow from a CCR5 Δ32 homozygous donor whose CCR5 gene had a 32-bp deletion and a non-functional CCR5 receptor [42]. Another possible therapeutic mechanism to block virus entry using CCR5 antagonists such as Maraviroc and Cenicriviroc was suggested in the treatment of HIV [43–45]. Similarly, several CXCR4 antagonists such as AMD3100, AMD3465, and AMD070 demonstrated efficacy for combating HIV [43]. The proinflammatory chemokine CCL2 was elevated during HIV infection, and was found to stimulate HIV production, promoting viral propagation and persistence. Thus, neutralization of CCL2 might be a therapeutic modality to fight HIV infection [46–47].

3. Role of chemokines in coronavirus infections

Before discussing the chemokine profile in COVID-19 and their roles in disease pathogenesis, it is important to highlight the chemokine signature of SARS and MERS since they share structural features and clinical presentation with COVID-19. However, studies have shown notable differences among the three viruses such as the receptors used to infect host cells, susceptibility to type I IFN, and the cytokines and chemokines involved in the immunopathology of the lungs. Like other viral infections, the production of chemokines is an important anti-viral response responsible for infiltrating immune cells towards infected lungs as part of

the immune response against corona viruses. Although chemokines are vital to attract immune cells to clear the virus, exacerbated expression leads to excessive inflammation and consequently ARDS, a common complication for SARS, MERS and COVID-19 [48–50]. Accordingly, controlling chemokines and their inflammatory effects are crucial for disease management. In addition, studying the chemokine profile in a temporal manner in COVID-19 patients may improve our understanding of the immunopathological processes of SARS-CoV-2 infection and may serve as an important prognostic marker for disease progression and outcome.

3.1. Chemokine profile in SARS-CoV and MERS-CoV patients

Post SARS-CoV infection, two waves of cell types occur. First, a rapid recruitment of monocytes and macrophages into the lungs occurred early after infection as determined by high-density oligonucleotide array analysis of gene expression changes in PBMCs of heathy donors inoculated with SARS-CoV [51,52]. The second wave results in T cells infiltration into the lungs where they initiate a specific response to clear the virus [53]. Both waves are controlled by chemokine gradients recruiting these cell types

In both SARS and MERS, CXCL10 and CCL2 are released as early as 2 to 3 days when the virus peaks in the lungs and persist in infected individuals [53–58]. CXCL10 and CCL2 suppress the proliferation of myeloid progenitor cells leading to lymphopenia in both SARS and MERS patients [58–60]. Other studies supported the increase in CXCL10 transcription in fibroblasts and macrophages infected with SARS-CoV, but CCL5 transcripts are absent in SARS-CoV infected tissue cells [61–63]. Contradictory data revealed that SARS-CoV infected DCs and airway epithelial cells (AECs) significantly up-regulated CCL5 [61,64,65]. Interestingly, Interferon regulatory factor 3 (IRF-3) responsible for IFN induction is reduced in SARS patients and IRF-3 contributes as well to the transactivation of CCL5 and CXCL10 genes [66]. However, the increase in CXCL10 and the decrease in CCL5 in some studies post SARS-CoV infection reflect that CXCL10 transcription might be less dependent on IRF3 and is rather more induced by other transcription factors such as IRF5 and NF-κB [67–69]. Furthermore, in a SARS mouse model, the lack of detectable IFN-γ which tightly controls the expression of CXCL9 and CXCL10, suggests the role of other factors in inducing these chemokines [70]. Accordingly, CXCL10 is less responsive to coronavirus inhibition mechanism by the IFNs [71].

Regarding CCL2, it was shown by ex vivo measurement of chemokines produced by inflammatory monocytes and macrophages (IMM) that CCL2 is released predominantly to amplify these cells activation [72]. IMMs can be either protective or pathogenic depending on the infecting pathogen. In the context of SARS-CoV, macrophages are prominent immune cells in the infected lungs and are a major source of inflammatory cytokines and chemokines where they contribute significantly to disease pathogenesis [73,74]. In BALB/c mice, the number of $Ly6C^{hi}CD11b^{+}$ cells increased dramatically in the lungs three days post SARS-CoV infection and it was shown that the recruitment and activation of IMM are dependent on IFN-α signaling [72]. Phenotypic examination of pulmonary IMM revealed the expression of CCR2, the receptor for CCL2, CCL7 and CCL12 [72,75]. Moreover, postmortem examination of SARS patients as well as patients with persistent ARDS showed elevated levels of CCL2 in BAL fluid and this correlated positively with the presence of alveolar macrophages [74,76–78]. Besides, CCL2 and CXCL2 play crucial roles in the migration of macrophages, monocytes and neutrophils. Interestingly, CCL2 and CXCL2 have the ability to clear SARS-CoV in the absence of $CD4^{+}$, $CD8^{+}$ T cells or neutralizing antibodies post 12 days of infection. This reflects their importance in activating the innate anti-viral immune response by recruiting neutrophils, mononuclear phagocytes and monocytes towards the site of infection [79,80]. In addition to CCL2, it is worth mentioning that although SARS-CoV is unable to induce potent IFN-α and IFN-β response in human macrophages, other chemokines such CXCL10, CCL3, CCL7, and CCL8 are released and contribute to SARS pathogenesis [81,82]. Collectively, these chemokines further increase the accumulation of pathogenic IMMs which in turn produce pro-inflammatory cytokines such as TNF-α, IL-6, or IL-1β leading to T cell apoptosis and impeding virus clearance [72,83]. Similarly, MERS-CoV infection of the monocytic cell line THP1, and of human peripheral blood monocyte-derived macrophages and dendritic cells induced elevated levels of CCL2 and CCL3 [58].

Another important chemokine that serves as a prognostic marker for SARS and MERS severity is CXCL8. The levels of CXCL8 were shown to be elevated in both the blood and alveolar spaces in SARS-CoV patients early after disease onset [84]. Such elevation of CXCL8 level could be due to a direct effect of the virus at the cellular level or could be associated with superimposed bacterial infection during SARS [69,85]. Similarly, MERS-CoV infected patients exhibited significant increase in CXCL8, and its expression level was correlated with fatality rate [48]. This could be due to increased numbers of neutrophils in BAL fluid where they secrete myeloperoxidase and elastase that could cause acute lung injury and progress to pneumonia and ARDS [86–89]. Another effect of CXCL8 in MERS infection is the ability to upregulate CD4 molecules and to enhance T helper cell function [90].

The chemokine receptors CCR1, CCR2, and CCR5 were shown to be protective in a mouse model infected with MA15-SARS-CoV, and in human DCs infected with SARS-CoV. The deficiencies of these receptors were associated with severe disease and mortality due to the reduction in the recruitment of immune cells into the lungs [89]. In MERS infected patients, CCR2 and CXCR3 were upregulated in a study investigating pulmonary Th1 and Th2 responses [92]. Studies on other respiratory viruses confirm the protective role of the aforementioned chemokine receptors in SARS and MERS. For instance, CXCR3 is crucial for cell-mediated clearance of west Nile virus (WNV) infection [93]. Moreover, CCR2 and CXCR3 were reported to be upregulated in RSV, which was correlated with disease severity [94]. Further, antagonizing CCR2 during influenza A (H1N1) infection and blocking CXCR3 during respiratory virus infections reduced pulmonary immunopathology [95,96].

Despite sharing similar chemokine profiles, comparative studies between SARS and MERS showed that MERS-CoV-infected monocytes and dendritic cells induce higher levels of CXCL10 for a prolonged interval of time compared to SARS-CoV. This may explain the systemic dissemination, the hyperactive inflammation and higher fatality of MERS compared to SARS patients [58,97].

3.2. Chemokine profile in COVID-19 patients

SARS-CoV-2 shares structural and viral features with SARS-CoV and MERS-CoV. Therefore, it is expected that the chemokine profile of COVID-19 patients will have common inflammatory mediators as well as some differences that account for the high transmissibility and low mortality rate of SARS-CoV-2 compared to SARS and MERS. Also, the hyperinflammation that occurs during other respiratory viruses such as influenza H1N1, avian H5N1 or Rous Sarcoma Virus (RSV) may help in revealing immune molecules that might be involved in the inflammation process post SARS-CoV-2 infection [23,98,99]. Hence, identifying the chemokine signature of SARS-CoV-2 and differentiating it from non-COVID-19 bacterial or viral ARDS will help in developing interventional strategies to prevent complications and reduce mortality. Fig. 1 illustrates the chemokine profile in asymptomatic, symptomatic and severe COVID-19 patients.

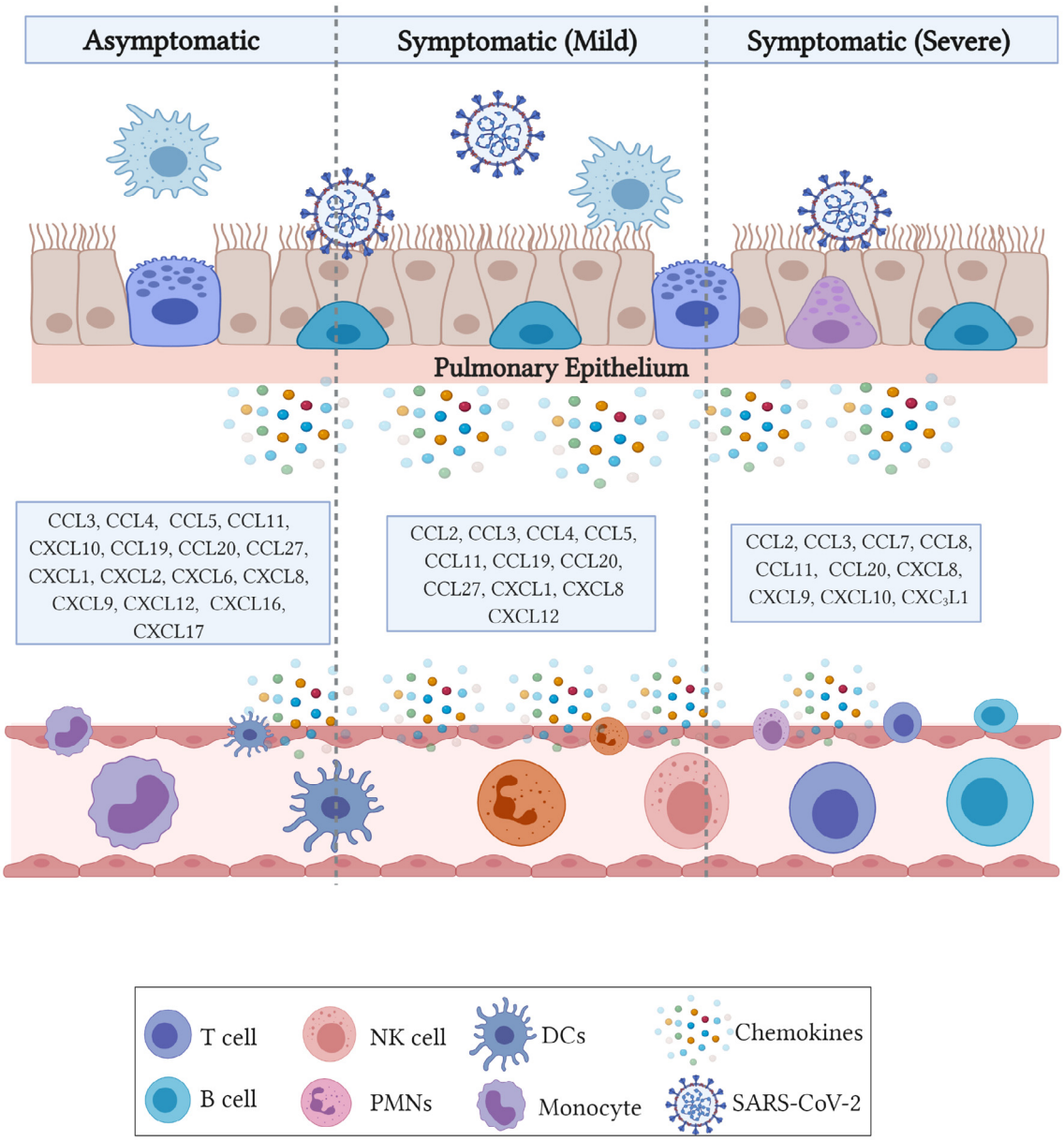

Fig. 1. The chemokine profile in COVID-19 patients. Chemokines are involved during all stages of SARS-CoV-2 infection and contribute differently to disease pathogenesis by recruiting immune cells to the pulmonary microenvironment. The upregulation of chemokines as determined by transcriptomic analysis and kinetic studies revealed a chemokine signature of asymptomatic, mildly infected, and severely infected patients. Upregulated chemokines in severely infected patients such as CCL2, CXCL8 and CXCL10 may be used as plausible biomarkers for disease outcome.

Before discussing the chemokine profile of the different status of COVID-19 patients (mild, severe or fatal), it is worth highlighting the differences in the chemokines involved in SARS-CoV-2 ARDS versus those involved in non-COVID-19 bacterial or viral ARDS. Generally, CCL3, CXCL10, CCL5, and CCL20 were shown to be upregulated in COVID-19 patients compared to the non-COVID-19 counterparts and the concentration of the chemokines released by $CD14^{+}CD16^{+}$ inflammatory monocytes such as CCL19, CCL20 and CCL5 remained stable over time [5,49]. Interestingly, CXCL10 is lower in bacterial ARDS upon comparing to non-COVID-19 viral ARDS, indicating that this chemokine may be used as a viral biomarker [49]. Furthermore, the initial innate immune response elicited by SARS-CoV-2 is explained by the upregulation of CXCL17 (VCC-1) that is responsible for attracting DCs and monocytes towards infected lungs. This is considered specific to COVID-19 infection as it is absent in community acquired pneumonia (CAP) cases [100]. These findings implicate that the population of immune cells in infected organs of COVID-19 patients is different when compared to patients with bacterial or non-COVID-19 ARDS, and accordingly the mechanisms driving the course of COVID-19 and its subsequent complications may be different. Also, this confirms that the chemokine profile is an important diagnostic tool for intervention and treatment post SARS-CoV-2 infection.

The chemokine signature of SARS-CoV-2 infected patients can vary depending on the medical status of individuals ranging from being asymptomatic, symptomatic, severely infected or recovering from the disease. However, despite the level of disease severity, there is a general chemokine profile shared by all COVID-19 patients. In the presence or absence of symptoms and in recovering patients, CCL3, CCL4 and CCL5 were detected in a similar fashion [101]. Moreover, serum analysis of SARS-CoV-2 in cohort positive patient revealed a generalized inflammation defined by a signifi-

cant increase of CXCL2, CXCL8, CXCL9 and CXCL16 levels [102]. Collectively, T and NK cells recruited by CXCL9 and CXCL16 respectively, monocytes and macrophages recruited by CCL8 and CCL2, and neutrophils recruited by CXCL8 and CXCL2, constitute the main immune cells infiltrating the lungs of COVID-19 patients [103,104]. In turn, recruited macrophages initially expressed high amounts of CCL2, CCL7 and CCL8, whereas in advanced disease stages and increased severity, the levels of CXCL10 and CCL3 were elevated [105]. Symptomatic patients showed higher levels of CXCL10, CCL2 and CXCL9 compared to convalescent cases [101]. It is worth noting that CXCL10 is absent in healthy individuals, while it increases with disease severity, suggesting that CXCL10 may help in early diagnosis and could be a potential predictive marker of disease outcome [101]. Further, CXCL10 can help in controlling new outbreaks given it is a crucial detection marker for asymptomatic patients. Moreover, genome-wide RNA-sequencing showed that other chemokines are elevated in the BALF samples of patients infected with SARS-CoV-2 compared to healthy individuals and these include CXCL1, CXCL6, CCL3 and CCL4 [106]. The same study detected an increase in the transcription of CCR2 and CCR5 and reflected the activation of their signaling pathways. The deficiency of these receptors in mice infected with mouse-adapted SARS-CoV virus aggravated the disease and increased the mortality due to defect in directing immune cells into the sites of viral infection [91,106].

Most studies investigating the role of cytokines and chemokines in the pathogenesis of COVID-19 revealed a broad array of elevated inflammatory mediators during the cytokine storm without specifying the exact time points of their increase during the infection. Therefore, it is crucial to analyze the temporal changes of chemokines over the course of the disease in order to catch the window of treatment when designing drugs that target critical immune molecules. Recently, simultaneous detection of 48 cytokines, chemokines and growth factors was performed using multiplex system on mild, severe and fatal COVID-19 group of patients in order to investigate the kinetic changes of chemokines. The levels of CCL4 and CCL5 were shown to be upregulated in all three groups of patients, but negatively correlated with disease severity, as the expression of these chemokines was significantly higher in mild cases. This suggests that CCL4 and CCL5 are likely to be associated with recovery and resolution of inflammation possibly through the activation of cytotoxic T cells and release of CCL5 upon antigen presentation [1,107]. Furthermore, elevated CCL5 levels remained consistently high during the 4-week follow up period [107]. However, contradictory data exist regarding CCL5, as some studies showed the presence of this chemokine in severe patients as well as its close association with disease progression [108].

Although increased by several folds, CXCL1, CXCL12, CCL11 and CCL27 did not show significant differences among the three groups of patients and remained steady over the different tested time points. This suggests that these chemokines contribute to the common pulmonary inflammation and respiratory symptoms in all COVID-19 patients [1]. On the other hand, patients dying from SARS-CoV-2 infection showed significantly higher plasma levels of CXCL8, CXCL9, CXCL10, CCL2, CCL3, CCL7, CCL20, and CX_3CL1 compared to severe and/or mild COVID-19 patients [1,49]. Another study confirmed the use of CXCL10 and CCL7 as independent predictors for COVID-19 progression since they were highly correlated with the ARDS group including critically ill and severe cases [109]. Further, transcriptional studies on post-mortem lung samples of COVID-19 patients showed significant upregulation of genes coding for CCL2, CCL8 and CCL11 [102]. The upregulation of these chemokines was associated with an intense, unresolved inflammation during the early stage of the infection and with a prolonged duration of ICU stay [110,111].

Notably, the serum concentration for CXCL10 showed differences between patients who died post ARDS complications versus those who remained alive [49]. These observations were in line with another clinical investigation on samples of COVID-19 patients requiring ICU admission exhibiting higher levels of CXCL10, CCL2, CCL3 and CCL7 compared to mildly infected patients [3,109]. It is worth noting that among the chemokines significantly elevated in fatal COVID-19 cases, CXCL8, CCL2 and CCL3 were increased similarly in mild and severe cases during early stages of infection and remained at steady levels afterwards in mild cases. However, these molecules were further increased during the late stages of the infection as reported in fatal cases [1]. On the other hand, the levels of CXCL9, CXCL10 and CCL7 did not change during late stages of the disease and their significant upregulation to higher levels in fatal patients make them important predictors of COVID-19 severity [1]. Based on the above, the chemokine profile is an important tool that aids in stratifying patients and identifying those at higher risk to develop complications in severe cases.

Regarding chemokine receptors, SARS-CoV-2 upregulated CCR1, CCR2 and CCR5 on the human thoracic dorsal root ganglion indicating the impact of inflammatory mediators on activating the sensory neurons of the lungs. This could possibly suggest that pharmacological inhibition of these receptors might suppress the hyperinflammation in critical COVID-19 patients [112]. Moreover, host genomic factors are important elements that can impact the infection and mortality rate due to SARS-CoV-2. For instance, the frequency of CCR5 Δ32 showed significant positive correlation with COVID-19 infection and mortality rate/million especially in an African population, yet the mechanism through which this polymorphism increases patients predisposition to SARS-CoV-2 infection and death is still unknown [113,114]. Other polymorphisms such as ORF wt/Δ32, −2459G/A, and rs1015164G/A that regulate the expression of CCR5 should be considered in the treatment outcome analysis of COVID-19 patients [112].

Furthermore, a *meta*-analysis showed that CXCR6 and CCR9 located at chromosome 3p21.31 were also associated with genome-wide significance with the respiratory failure of Italian and Spanish COVID-19 patients. In this case CXCR6 regulates the localization of lung-resident memory $CD8^+$ T cells in response to airway pathogens such as influenza viruses [112,115]. Further, an increase in the expression of CCR7 receptor, which has a crucial role in adaptive immunity particularly during T cell activation and tolerance, was detected on naïve and central memory Tregs in COVID-19 patients. The same study reported a lower expression of CCR6 and CXCR3 on $CD8^+$ T cells of patients [116]. This supports the decrease in the number of $CD8^+$ T cells and an increase in the number of different types of Tregs in the peripheral blood of infected patients, thus explaining the suppressed immunity during SARS-CoV-2 infection [116]. In addition, CXCR4 was shown to be higher in severe COVID-19 cases along with an elevation in the $CD10^{Low}CD101^-$ immature neutrophils in the blood. This could probably be due to the premature release of neutrophils from the bone marrow to infiltrate the lungs of severely infected patients [117]. On the other hand, an increase of CXCR5, a lymph node homing receptor used to define peripheral T follicular helper (pTfh), is seen in convalescent COVID-19 patients [118]. This finding supported another study which reported an increase in total pTfh during acute infection with SARS-CoV-2 [119]. During SARS-CoV-2 infection, the increase in antigen specific pTfh population was correlated with neutralizing antibodies against the membrane (M), nucleocapsid (N) and spike (S) proteins of the virus, with the highest correlation observed against the S protein [118]. Therefore, focusing research on pTfh cells in the context of COVID-19 is of high importance to better understand the humoral response, considering that T cells are crucial contributors to the formation of neutralizing antibodies which can optimize vaccine design.

Upon comparing the chemokine profile of SARS-CoV-2 to SARS-CoV and MERS-CoV, it can be concluded that CXCL8, CXCL10 and CCL2 are crucial contributors to pulmonary pathogenesis in all three corona viruses. However, the differences in the virus behavior of SARS-CoV-2 and SARS-CoV in ex vivo human lung tissue explants particularly in relation to the higher infection and replication capacity of SARS-CoV-2 and the lower ability to trigger antiviral IFN release, suggest that the two viruses modulate the production of cytokines and chemokines differently [69]. For instance, SARS-CoV upregulated 11 out of the 13 pro-inflammatory factors evaluated, whereas SARS-CoV-2 upregulated CXCL10, IL-6, CCL2, CXCL1 and CXCL5. Specifically, CXCL10 was significantly more induced by SARS-CoV-2 than SARS-CoV [120]. Discrepancies among different studies regarding the expression level of chemokines cannot only be attributed to the differences in viral load among the three β-CoVs but also due to the inconsistencies in the temporal studies and detection tools used. After discussing the role of chemokines in viral infections in general and their involvement in the pathogenesis in SARS, MERS and COVID-19 (Fig. 2), we will discuss in the following section the role of the invariably upregulated chemokines that are correlated with disease severity such CCL2, CCL5, CXCL8 and CXCL10, which are culprits in increasing the mortality rate in COVID-19 patients [121]. Also, we will address the possible mechanisms for targeting these chemokines.

However, it is crucial to mention beforehand that besides the specific therapeutic options available or under clinical investigations, there are possible ways to target the signaling pathways that lead to the release of important chemokines implicated in COVID-19 pathogenesis such as CCL2 and CXCL8. NF-κB/TNFα and the sphingosine-1-phosphate (S1P) receptor 1 pathways are among the most important pathways that induce cytokine and chemokine production leading to pulmonary inflammation post infection with respiratory viruses including SARS-CoV and influenza [122,123].

Generally, corticosteroids inhibit NF-κB and AP-1 activation and ma consequently, reduce the levels of chemokines that contribute directly to SARS-CoV-2 pathogenesis such as CXCL8 and CXCL10, in a similar effective way as in SARS-CoV infection [124]. Accordingly, glucocorticoids such as dexamethasone are being proposed by clinicians to reduce the excessive inflammation in severe COVID-19 patients [125,126]. Yet, corticosteroids ought to be used with care to avoid undesired immunosuppressive effects especially during early disease stages, where they might lead to disseminated fungal disease or even increase mortality [127,128]. Furthermore, the specific pharmacological inhibition of NF-κB using caffeic acid phenethyl ester (CAPE), Bay 11–7082, and Parthenolide, suppressed the mRNA expression of TNF-α, CXCL2, and CCL2 in the lungs of mice, enhancing their survival post SARS-CoV infection [122]. Regarding SIP agonists, Fingolimod, an approved drug for multiple sclerosis, is currently used in a non-randomized phase II clinical trial to establish its efficacy in the treatment of COVID-19 (NCT04280588) [129].

3.3. Role of chemokines in COVID-19 pathogenesis

3.3.1. CXCL8lCXCR1, CXCR2 axis

CXCL8 is released by monocytes/macrophages and alveolar epithelial cells. Its synthesis is induced by IL-17A and IL-17F secreted by IL-6-dependent Th17 cells whose numbers are ele-

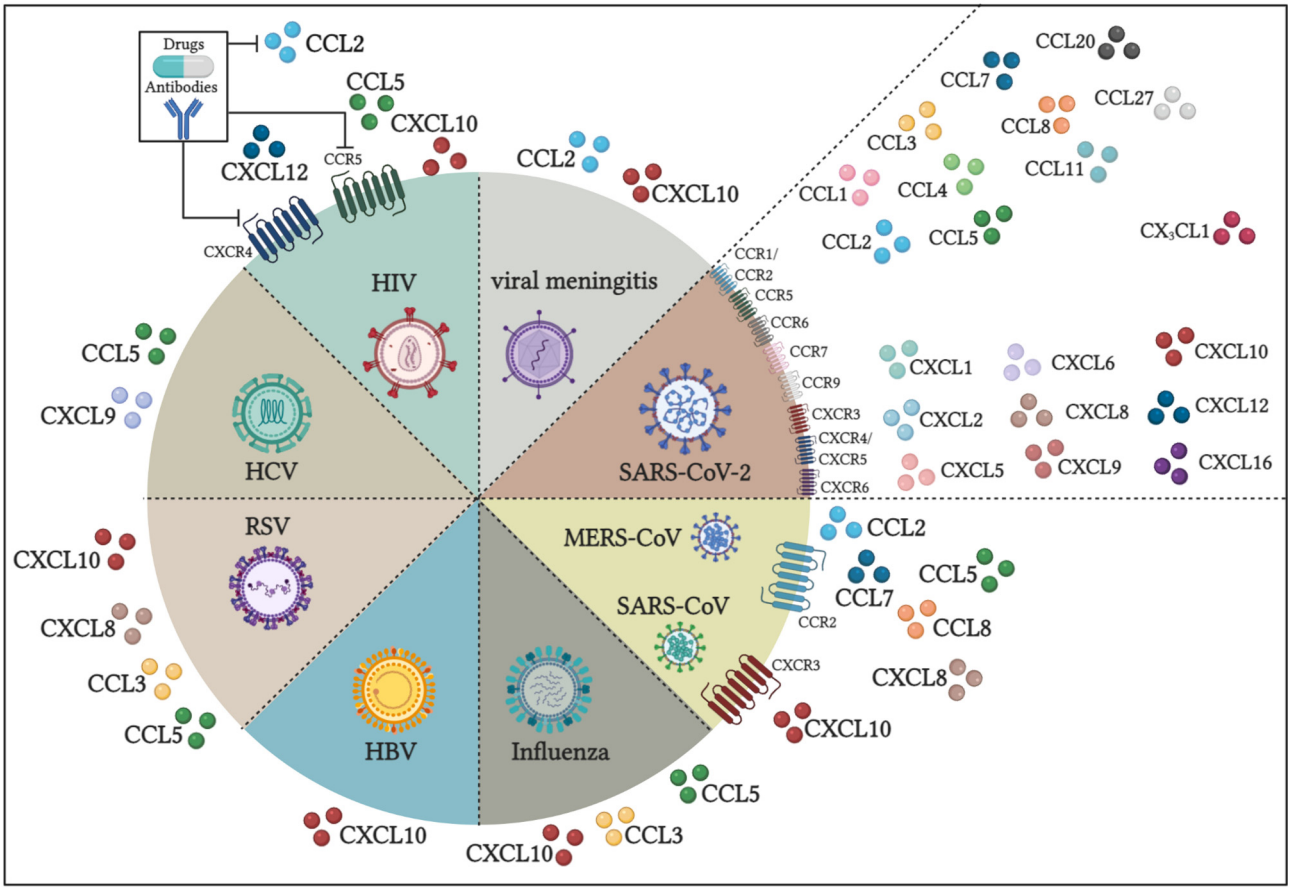

Fig. 2. Involvement of chemokines in viral infections including SARS, MERS and SARS-CoV-2. Several chemokines are involved in various viral infections such as human immunodeficiency virus (HIV), influenza, hepatitis B virus (HBV), respiratory syncytial virus (RSV), viral meningitis, and hepatitis C virus (HCV) as well as coronaviruses including SARS-CoV, MERS-CoV and SARS-CoV-2.

vated in the peripheral blood of COVID-19 patients [104,130]. The activity of CXCL8 is strongly dependent on the transcription factor AP-1 and is linked to the viral spike and nucleocapsid proteins of SARS-CoV which is shared with SARS-CoV-2 [131,132]. CXCL8 is known to directly inhibit IFN induction by viral proteins leading to reduction in the antiviral effect of IFN especially during early stages of SARS-CoV infection [71,133]. Functionally, CXCL8 is responsible for the recruitment, activation and accumulation of neutrophils. Also, CXCL8 induces the formation of the highly immunogenic and toxic neutrophil extracellular traps (NETs) that lead to inflammation and epithelial/endothelial cell death [134–137]. This is attributed to the ability of CXCL8 to stimulate exocytosis and oxidative burst of superoxide and hydrogen peroxides from neutrophils [138]. In turn, lung NETs release more CXCL8 which further recruits more neutrophils, and prevents their apoptosis [135,136,139]. Moreover, CXCL8 stimulates the airway epithelium and induces its contraction which allows for further recruitment of other inflammatory cells in the infected lungs [140]. Collectively, the above functions of CXCL8 explain how it may contribute to COVID-19 pathogenesis and disease severity. This was further confirmed in a study which used single cell RNA sequencing analysis (scRNA-seq analysis) to compare the immunological response of severe and mild COVID-19 patients. The increase in CXCL8 release from myeloid cells was more pronounced in severe cases and was associated with an increase in neutrophil recruitment to the lungs along with an elevation in the number of neutrophils in the blood [141]. Moreover, higher expression of secretion-related molecules, lysosome-associated molecules, and NETosis features were observed in the neutrophils of severe patients [141]. These findings corroborated with the elevated NETs in the sera of COVID-19 patients when compared to healthy controls [142]. Importantly, scRNA-sequence analysis showed that although NETosis genes were elevated in severe cases, they are considered abnormal when it comes to their antiviral effect. However, the same data revealed one mechanism through which neutrophil NETs might aggravate COVID-19 pathogenesis through epithelial damage [141].

As neutrophils contribute significantly to SARS-CoV-2 immunopathology, reducing their numbers by targeting the CXCL8-CXCR1/2 axis can also be of clinical benefit to COVID-19 patients. For instance, the CXCR2 antagonists Reparixin, a non-competitive CXCR1 and CXCR2 dual inhibitor, the humanized mAb against CXCL8, the neutralizing antibodies against CXCR1/2, the miRNAs against CXCL8 mRNA expression, or the inhibitors of CXCL8, are considered possible therapeutic modalities [143–150]. Currently, an ongoing phase 2 clinical trial (NCT04347226) is testing the efficacy of anti-CXCL8 on SARS-CoV-2 patients [141].

3.3.2. CXCL10/CXCR3 and CXCL11/CXCR3 axis

CXCL10 is considered a key chemokine downstream the common TLR4-TRIF signaling pathway implicated in the pathogenesis of lung injury [151,152]. In response to infection, CXCL10 is produced at high concentrations by activated bronchial and alveolar epithelial cells and consequently, activates CXCR3 cascade involved in the etiology of various pulmonary conditions such as pulmonary fibrosis [153,154]. CXCL10 attracts monocytes, NK cells [16], Th1 cells expressing CXCR3, and activates cell-mediated immune response [85]. Furthermore, CXCL10 might be implicated in T cells apoptosis and lymphopenia seen in SARS, MERS and COVID-19 patients which results in impairing T lymphocyte function to clear the virus [85]. Importantly, although CXCL10 is a non-ELR chemokine (lacking Glu-Leu-Arg tripeptide adjacent to CXC motif), it was reported to play a crucial role in pulmonary neutrophil infiltration, which in turn releases significant amounts of CXCL10 [155,156]. Moreover, CXCL10/CXCR3 axis acts in an autocrine manner on the recruited neutrophils and elicits the oxidative burst which contributes to exacerbating lung inflammation and progression to ARDS [155]. This may explain the importance of CXCL10 as a prognostic and predictive marker for SARS-CoV-2 outcome. Accordingly, antibodies targeting CXCL10 may stand to be a potential and promising therapeutic option in treating the acute phase of ARDS as reported previously in H1N1 mouse model [155,157].

It is worth mentioning that aside from CXCL10, CXCL11 is also the ligand with high affinity for CXCR3 [158]. The CXCL11/CXCR3 axis is induced following IFN-γ and IFN-β production, and is likely related to activated Th1 response [159,160]. Moreover, the CXCL11/CXCR3 pair has a role in coordinating the distribution of circulating Tfh cells into infected tissues to form resident memory cells capable of responding faster to viral antigens at the level of the bronchus-associated lymphoid tissue and assisting other local resident memory B and $CD8^+$ T cells [161–165]. This was further supported by single-cell analysis which revealed the presence of infiltrated Tfh cells in the airway of COVID-19 patients [166].

3.3.3. CCL2/CCR2 axis

Monocytes and macrophages are important immune cells in COVID-19 pathogenesis where resident alveolar macrophages play a protective role during the early phase of the disease. Infiltrating monocytes constitute the majority of leukocytes migrating into the infected lungs, contributing significantly to the severe lung inflammation in SARS-CoV-2 patients, possibly due to the excessively released cytokines and chemokines [73,74,167]. This is corroborated with the upregulation of monocytes-attractant chemokines such as CXCL6, CXCL11, CCL2, CCL3, CCL4, CCL7, CCL8 and CCL20, which are detected in the BALF samples of COVID-19 patients [168]. In turn, high numbers of macrophages specifically the M1 phenotype, present in severely and moderately infected COVID-19 patients, induce the release of CXCL9, CXCL10 and CXCL11 which are responsible for the recruitment of inflammatory cells towards infected lungs, and which are positively associated with intra-alveolar hemorrhage by compromising the integrity of the endothelium [169,170]. Although several chemoattractant molecules are utilized for migration of monocytes, CCL2 and CCL7 are usually rapidly produced by both stromal cells and immune cells upon activation of pattern recognition receptors (PRR) or cytokines [171]. As indicated above, CCL2 is the prominent chemokine linked to COVID-19 severity, is upregulated during the early phase of infection and is increased further during late stages of fatal cases [1,76]. In the lungs, CCL2 is mainly produced by alveolar macrophages, T cells and endothelial cells and its cognate receptor CCR2, is mainly expressed on monocytes and T cells [172]. Upon binding to CCR2, CCL2 dimerizes, binds to ECM GAGs and induces the recruitment of monocytes into infected lungs where they elicit calcium influx, producing oxygen radicals and superoxide as well as upregulating integrin expression [171,173,174]. CCL2/CCR2 axis was also demonstrated to recruit mast cell progenitors during pulmonary inflammation as observed in freshly isolated bone marrow in vitro and in allergic airway models in vivo [175]. Together, histamine and leukotrienes released from mast cells enhance Th2 polarization [176].

Furthermore, the presences of CCR2 bearing blood monocytes enhance the accumulation of neutrophils drastically reflecting the cooperativity and coordination between monocytes and neutrophils in leukocyte efflux during lung inflammation [177]. Additionally, CCL2 was reported to increase procollagen synthesis by fibroblasts [176,178]. Collectively, these functions of CCL2 may lead to fibroproliferative complications in ARDS [176]. Hence, the prophylactic use of CCL2 antagonists tends to reduce the pulmonary immunopathology and significantly improve the survival of infected mice [95,179]. Moreover, blocking the CCL2/CCR2 axis by CCR2 antagonist was shown to inhibit inflammatory monocytes

Table 1
Chemokines and chemokine receptors implicated during COVID-19 infection.

Chemokine	Receptor	Role in Immunity	Expression and Role in COVID-19
CCL2 (MCP-1)	CCR2	Migration of inflammatory monocytes	- Produced by alveolar macrophages, T cells and endothelial cells - Demonstrated to recruit mast cell progenitors - Enhances the accumulation of neutrophils - Increases procollagen synthesis by fibroblasts - Upregulated early post SARS-CoV-2 infection - Higher levels detected in mildly symptomatic and severe cases compared to asymptomatic
CCL3 (MIP-1α)	CCR1 and CCR5	Migration of macrophages and NK cells T cell/DCs interaction	- Upregulated early post SARS-CoV-2 infection - Higher levels detected in mildly symptomatic and severe cases compared to asymptomatic
CCL4 (MIP-1β)	CCR5	Migration of macrophages and NK cellsT cell/DCs interaction	- Upregulated early post SARS-CoV-2 infection
CCL5 (RANTES)	CCR1, CCR3, CCR5	Migration of macrophages and NK cells T cell/DCs interaction	- Ability to cause acute renal failure and liver toxicity - Upregulated early post SARS-CoV-2 infection
CCL7 (MCP-3)	CCR2 and CCR3	Migration of monocytes	- Higher levels detected in mildly symptomatic and severe cases compared to asymptomatic - Independent predictor for COVID-19 progression
CCL8 (MCP-2)	CCR1, CCR2, CCR3 and CCR5	Th2 response	- Detected in post-mortem lung samples and associated with disease severity
CCL11 (Eotaxin-1)	CCR3	Migration of eosinophil and basophil	- Upregulated early and remained steady post SARS-CoV-2 infection - Detected in post-mortem lung samples and associated with disease severity
CCL19 (MIP-3β)	CCR7	T cell and DC homing to lymph node	- Upregulated and its level remained steady post SARS-CoV-2 infection
CCL20 (MIP- 3α)	CCR6	Th17 responses B cell, and DC homing to gut-associated lymphoid tissue	- Higher levels detected in mildly symptomatic and severe cases compared to asymptomatic
CCL27 (CTAK)	CCR10	T cell homing to skin	- Upregulated early and remained steady during SARS-CoV-2 infection
CXCL1 (GRO-α)	CXCR2	Migration of neutrophils	- Upregulated and remained steady during SARS-CoV-2 infection
CXCL2 (GRO-β, MIP-2α)	CXCR2	Migration of neutrophils	- Upregulated and remained steady during SARS-CoV-2 infection
CXCL6 (GCP-2)	CXCR1, CXCR2	Migration of neutrophils	- Upregulated post SARS-CoV-2 infection
CXCL8 (IL-8)	CXCR1 and CXCR2	Migration of neutrophils	- Released by monocytes/macrophages and alveolar epithelial cells. - Induced by IL-17A and IL-17F secreted by IL-6-dependent Th17 cells - Inhibits IFN induction by viral proteins. - Stimulates exocytosis and oxidative burst of superoxide and hydrogen peroxides from neutrophils - Induces the formation of the highly immunogenic and toxic neutrophil extracellular traps (NETs) that lead to inflammation and epithelial/endothelial cell death - Stimulates the airway epithelium and induces its contraction and recruitment of more inflammatory cells - Upregulated early post SARS-CoV-2 infection - Higher levels detected in mildly symptomatic and severe cases compared to asymptomatic
CXCL9 (MIG)	CXCR3	Migration of Th1, CD8 and NK cells Th1 response	- Upregulated early post SARS-CoV-2 infection - Higher levels detected in mildly symptomatic and severe cases compared to asymptomatic
CXCL10 (IP-10)	CXCR3	Migration of Th1, CD8 and NK cells Th1 response	- Produced by activated bronchial and alveolar epithelial cells - Implicated in T cells apoptosis and lymphopenia - Plays a crucial role in pulmonary neutrophil infiltration - Upregulated early post SARS-CoV-2 infection - Levels increase with disease severity and death - Important marker for disease outcome
CXCL12 (SDF-1)	CXCR4	Bone marrow homing	- Upregulated and its level remained steady post SARS-CoV-2 infection
CXCL16	CXCR6	Migration and survival of NKT and ILC	- Upregulated early post SARS-CoV-2 infection
CXCL17	?	Migration of macrophages and DC	- Upregulated early post SARS-CoV-2 infection
CX_3CL1 (Fractalkine)	CX3CR1	Migration of NK cells, monocytes and T cells	- Higher levels detected in mildly symptomatic and severe cases compared to asymptomatic

recruitment in a murine model of hepatocellular carcinoma where antagonizing CCR2 had an anti-tumor effect [180].

3.3.4. CCL5/CCR5 axis

CCL5 is a chemotactic cytokine for monocytes, DCs, granulocytes and leukocytes during acute viral infection and can activate T cells [181] and NK cells [18], as well as sustains the response of $CD8^+$ T cells during chronic viral infections. In SARS-CoV-2 infection, the effect of CCL5 is rather contradictory. For instance, in mildly infected patients, it is assumed that the main source of CCL5 during the early stage of the disease is the virus specific $CD8^+$ T cells. This is probably due to the higher number of lymphocytes in mild cases compared to severe cases [107]. Moreover, CCL5/CCR5 axis is important for preventing apoptosis of macro-

phages, the crucial immune cells in viral clearance. In a mouse model infected with parainfluenza or human influenza virus, the absence of CCL5 caused a delay in viral clearance, excessive airway inflammation and respiratory death [182]. The same study revealed the signal transduction downstream the activation of CCR5 where bilateral activation of Gαi/PI3K/AKT and Gαi/MEK/ERK pathways induce anti-apoptotic activity and rescue macrophages [182]. Based on the above, it is thought that CCL5 may have a protective anti-viral role in COVID-19 patients. However, other studies reported contradictory data where critically ill patients with liver and kidney injuries showed elevated levels of CCL5 compared to healthy controls or mildly and moderately SARS-CoV-2 infected patients [183]. This goes in parallel with the ability of high levels of CCL5 to cause acute renal failure and liver toxicity [184,185]. The discrepancy regarding the role of CCL5 in COVID-19 pathogenesis might be attributed to the differences in the populations studied, timing of chemokine measurement or the detection method. Therefore, CCL5 is not considered a clear predictive marker of COVID-19 outcome and more studies are needed to confirm its inflammatory or protective role. CCL5 was proven to exacerbate the status of COVID-19 patients, and thus a clinical trial targeting CCR5 (NCT04343651), may be beneficial [186]. Leroli-mab, an antibody used to block CCR5, prevents CCL5-induced calcium mobilization in $CCR5^{+}$ macrophages and T cells. This results in a rapid reduction of IL-6, a decline in myeloid cell clusters and plasma viremia, and restoration of CD4/CD8 ratio. Consequently, this may resolve the hyperinflammation and enhance anti-viral immunity in COVID-19 patients [112,183].

Table 1 illustrates the role of the different chemokines implicated in COVID-19 pathogenesis and clearly reflects the redundancy in the chemokine system which is attributed to two main reasons: (1) the promiscuity of chemokine receptors which allow various chemokines to bind to the same receptor and produce different functions, and (2) the overlapping spectrum of action through the ability of different chemokines to produce the same effect on specific immune cells. The redundancy in the chemokine system is not only important to produce a robust immune response to fight infection, but is also crucial to overcome genetic and epigenetic differences among individuals.

4. Summary and outlook

Chemokines and their receptors are vital players during an immune response, yet tight regulation of their functions is mandated to prevent excessive inflammation. In COVID-19 patients, chemokines serve various roles in the different phases of the disease. In this article, we identified a clear consensus among the various studies conducted regarding the chemokine profile in COVID-19 patients despite the differences in sample size and detection methods. Here, it is important to highlight the need for studies on larger groups of patients with different ethnic backgrounds and clinical history so as to reach a comprehensive conclusion about COVID-19 chemokine signature which could be used to predict disease outcome. In addition, we highlighted the most prominent chemokines correlated to COVID-19 progression which include CCL2, CXCL10 and CXCL8, and their importance as potential biomarkers. However, it is not only important to block inflammatory mediators, but it is also crucial to determine when to intervene so as not to compromise the protective role of chemokines in recruiting the immune cells needed for viral clearance. Further, we discussed the chemokine profiles pertaining to the different stages of SARS-CoV-2 infection and their importance in stratifying patients at risk to develop complications. This will aid in identifying the right protocols to target chemokines in order to avoid complications and reduce mortality. Finally, we shed some light on the available targeted therapies against chemokines or their receptor in the ongoing related clinical trials. Based on the predictive and prognostic values of the chemokine profile, it ought to be included in the routine clinical tests of COVID-19 patients. Analysis of chemokines and their receptors during the infection stages will help in identifying the possible outcome of the disease and the likelihood of complications development.

CRediT authorship contribution statement

Bariaa A. Khalil: Conceptualization, Writing - original draft, Writing - review & editing. **Noha M. Elemam:** Conceptualization, Writing - original draft, Writing - review & editing. **Azzam A. Maghazachi:** Conceptualization, Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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