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Journal
Expert Review of Clinical Immunology, 18(1)

ISSN
1744-666X

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Publication Date
2022-01-02

DOI
10.1080/1744666x.2022.2017282

Peer reviewed

HHS Public Access

Author manuscript

Expert Rev Clin Immunol. Author manuscript; available in PMC 2023 January 03.

Published in final edited form as:

Expert Rev Clin Immunol. 2022 January ; 18(1): 57–66. doi:10.1080/1744666X.2022.2017282.

Evaluating the role of chemokines and chemokine receptors involved in coronavirus infection

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Abstract

Introduction: Coronaviruses are a large family of positive-stranded non-segmented RNA viruses with genomes of 26–32 kilobases in length. Human coronaviruses are commonly associated with mild respiratory illness; however, the past three decades have seen the emergence of severe acute respiratory coronavirus (SARS-CoV), middle eastern respiratory coronavirus (MERS-CoV), and SARS-CoV-2 which is the etiologic agent for COVID-19. Severe forms of COVID-19 include acute respiratory distress syndrome (ARDS) associated with cytokine release syndrome that can culminate in multiorgan failure and death. Among the proinflammatory factors associated with severe COVID-19 are the chemokines CCL2, CCL3, CXCL8 and CXCL10. Infection of susceptible mice with murine coronaviruses, such as mouse hepatitis virus (MHV), elicits a similar chemokine response profile as observed in COVID-19 patients and these *in vivo* models have been informative and show that targeting chemokines reduces the severity of inflammation in target organs.

Areas covered: PubMed was used using keywords: Chemokines and coronaviruses; Chemokines and mouse hepatitis virus; Chemokines and COVID-19. Clinicaltrials.gov was used using keywords: COVID-19 and chemokines; COVID-19 and cytokines; COVID-19 and neutrophil

Expert opinion: Chemokines and chemokine receptors are clinically relevant therapeutic targets for reducing coronavirus-induced inflammation.

Keywords

Coronavirus; chemokines; chemokine receptors; inflammation; clinical targets

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Declaration of interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

1. Introduction

Coronaviruses are classified based on several fundamental characteristics, including nucleic acid type, a lipid envelope, and their distinctive morphology [1–3]. All members have characteristic petal-shaped proteins extending from the virion surface. Coronaviruses infect numerous vertebrate hosts including humans, chickens, pigs, and mice, causing a wide variety of disorders involving several different organ systems; however, there are specific tropisms for the central nervous system (CNS), lungs, gastrointestinal tract, and liver [1–3]. Coronavirus genomes are single-stranded positive-polarity RNA molecules, larger than the size of any other known stable RNA, ranging from 27 kb for the avian infectious bronchitis virus, to 31 kb for murine coronaviruses [4]. Genomic RNA is infectious, contains a cap structure at the 5′-end and poly(A) at the 3′-end. The genome is organized into seven or eight genes, each containing one or more open reading frames (ORF) separated by intergenic sequences that contain the signals for the initiation of transcription of the sub-genomic viral messenger (m)RNA species. Upon entry, the viral RNA encodes an RNA polymerase that transcribes the genome into a negative-stranded RNA [4]. The latter serves as templates for positive-sensed genomic RNA and sub-genomic mRNAs. Important viral structural proteins include membrane (M), nucleocapsid (N), envelope (E), and the spike (S) that binds to receptors expressed on the surface of target cells [1–3]. Analysis of monoclonal antibody neutralization escape variants demonstrated that the viral S protein controls cellular tropism in vivo and the role of the S protein in tropism has recently been confirmed using stable recombinant viruses in which all genes except the S protein gene were held constant [5, 6].

To date, seven different coronaviruses have been identified that infect humans (HCoV's) and these include HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, severe acute respiratory syndrome (SARS)-CoV, Middle East respiratory syndrome (MERS)-CoV, and SARS-CoV-2. Of these, the four commonly circulating endemic HCoV's are 229E, OC43, NL63, and HKU1, are often referred to as the common cold coronaviruses, are known to account for 15–20% of seasonal colds, and are associated with mild to moderate infections of the upper respiratory tract [1–3]. Comparatively, SARS-CoV-1, MERS-CoV, and SARS-CoV-2, have been associated with severe respiratory disease and have prompted public health emergencies. Despite primarily infecting respiratory and gastrointestinal tracts, neurological symptoms that vary in severity are commonly associated with SARS-CoV-2. Approximately 20% of SARS-CoV-2-infected individuals develop post-acute sequelae of COVID-19 [7].

2. Chemokine and chemokine receptors

Chemokines represent a family of low molecular weight (7–17kDa) proinflammatory cytokines that are divided into four subfamilies based on structural and functional criteria [8–10]. The two major subfamilies are the CXC and CC chemokines. The CXC subfamily is structurally characterized by two conserved cysteine residues that are separated by an amino acid, while theCC subfamily is structurally characterized by conserved cysteine residues adjacent to one another. Chemokines function by binding to seven-transmembrane-spanning G protein-coupled receptors. These receptors are divided into those that preferentially bind CXC or CC chemokines, and are capable of binding more than one CC or CXC chemokine,

respectively. The CX3C chemokine, fractalkine, is unique in that it is expressed on the surface of cells as well as secreted into the surrounding environment [11]. Chemokines have been shown to selectively attract distinct leukocyte populations during periods of inflammation in various disease models. The CXC chemokines function primarily in attracting neutrophils, yet have a limited effect on T lymphocytes and monocytes [8–10]. However, there are exceptions to this rule in that CXC chemokines that lack the glutamic acid-leucine-arginine (ELR) motif on the amino terminus are chemotactic for T cells. For example, the non-ELR chemokine CXCL10 is a potent chemoattractant for activated T cells and NK cells and functions by binding to CXCR3 expressed on the surface of these cells [12–14]. The CC chemokines are thought to attract T cells, monocytes, and macrophages but not neutrophils. The CC chemokine ligand 5 (CCL5) can attract both T cells and macrophages by binding to one of several CC chemokine receptors including CCR1 and CCR5. Furthermore, there is increasing evidence that chemokines, such as CCL3, influence other immune system activities including T cell polarization and T cell proliferation.

3. Chemokine responses following murine coronavirus infection

Coronaviruses elicit a chemokine response following infection of susceptible hosts. Many of the early studies that focused on defining the functional role of chemokines in host defense and disease following viral infection were performed in a CNS model of infection using intracranial inoculation of mice with the neuroadapted John Howard Mueller (JHM) strain of mouse hepatitis virus (JHMV). Like SARS-CoV-1, MERS-CoV, and SARS-CoV-2, JHMV is a beta coronavirus and elicits an orchestrated secretion chemokines from host-infected tissue in response to infection [3]. In brief, intracranial inoculation of mice with JHMV results in widespread replication within astrocytes, microglia, and oligodendrocytes with relative sparing of neurons. Both innate and adaptive immune responses are rapidly mobilized in response to infection which are required to control viral replication. Chemokine mRNA transcripts are rapidly expressed in response to JHMV infection, with resident CNS cells including astrocytes and microglia being prominent cellular sources for expression of various chemokines that help orchestrate the corresponding immune response [15]. Among the chemokines that are expressed early post-infection are the ELR-positive chemokines CXCL1 and CXCL2, which in mice are chemoattractant for neutrophils expressing the cognate chemokine receptor CXCR2. CXCL1 and CXCL2 are up-regulated early within the brain and spinal cord of JHMV-infected mice with CXCL1 protein expression appearing to colocalize with reactive astrocytes [16]. Treatment of JHMV-infected mice with anti-CXCR2 blocking antibody dramatically reduced neutrophil trafficking into the CNS and this correlated with reduced MMP-9 activity resulting in a reduction in the breakdown of the blood-brain-barrier (BBB). Correspondingly, CXCR2 neutralization resulted in diminished infiltration of virus-specific T cells, an associated inability to control viral replication within the brain and increased mortality. Importantly, blocking CXCR2 signaling did not impair the generation of virus-specific T cells indicating that CXCR2 signaling is not required to generate anti-viral T cell responses. More recently, transgenic mice have been generated in which expression of the neutrophil chemoattractant, chemokine CXCL1, is under the control of a tetracycline-inducible promoter active within GFAP-positive astrocytes. This has allowed for a selective increase in CNS expression of CXCL1 in response to

JHMV infection of the CNS to further evaluate the effects chronic CXCL1 production on neuroinflammation, control of viral replication, and demyelination [17]. Sustained CXCL1 expression within the CNS of JHMV-infected mice results in increased neutrophil infiltration, diminished numbers of mature oligodendrocytes, and an increase in the severity of demyelination. Neutrophil ablation in CXCL1-transgenic mice reduced the severity of demyelination, highlighting an important role for these cells in amplifying the severity of white matter damage [17]. These studies highlight that in response to JHMV infection of the CNS, the CXCL1/2-CXCR2 axis is important in attracting neutrophils to the CNS that aid in host defense by contributing to the breakdown of endothelial barriers allowing enhanced access of inflammatory leukocytes into the parenchyma.

Following JHMV infection, inflammatory monocytes/macrophages migrate into the CNS in response to expression of chemokines CCL2 and CCL5 [18–21]. Through use of germline knockout *Ccr2*$^{-/-}$ and *Ccr5* $^{-/-}$ mice, it was determined that in absence of either of these receptors, inflammatory monocyte/macrophage infiltration in response to JHMV infection was reduced, highlighting that these respond to expression of ligands for these receptors *e.g.* CCL2, CCL3, CCL4 and CCL5 [19, 20]. In addition to resident glial cells, inflammatory monocytes/macrophages also express transcripts for these chemokines following infection, which enables the accumulation of additional monocytes/macrophages [22]. During acute disease, these cells express transcripts for major histocompatibility complex (MHC) class I and II which greatly aid in controlling viral replication and limiting the severity of acute disease [22, 23].

The ability to survive MHV infection appears to be predominantly due to an effective T cell-mediated response [24]. Recent data have confirmed that cell-mediated immunity is critical during acute infection [25–29]; however, the ability to prevent viral recrudescence is associated with the continued presence of plasma cells in the CNS secreting neutralizing antibody [30, 31]. Control of JHMV replication within the CNS is primarily mediated by inflammatory virus- specific CD4+ and CD8+ T cells that undergo expansion within draining cervical lymph nodes and subsequently migrate to the CNS [28, 32, 33]. Early studies demonstrated an important role for CCL3 signaling in tailoring T cell responses that allowed for efficient egress out of draining cervical lymph nodes and trafficking into the CNS [34]. Although generation of antigen-specific CD8+ T cells was not impaired following JHMV infection of *Ccl3*$^{-/-}$ mice, a significant percentage of CD8+ T cells retained expression of lymph-node homing receptors CD62L (L-selectin) and the CC chemokine receptor 7 (CCR7) [34]. Additionally, these did not display a dramatic increase in mRNA transcripts encoding CXCR3 or CCR5, two receptors which are important in allowing JHMV-specific T cell migration to the CNS [34]. Analysis of antiviral effector functions also revealed that CD8+ T cells derived from *Ccl3*$^{-/-}$ mice displayed overall muted cytolytic activity as well as muted expression of interferon (IFN)-γ when compared to CD8+ T cells from *Ccl3*$^{+/+}$ mice [34]. Subsequent studies revealed a role for CCL3 in dendritic cell maturation that correlated with enhanced activation of JHMV-specific T cells, further highlighting how CCL3 impacts antiviral T cell function in response to JHMV infection [35]. Collectively, these studies highlight that, in addition to chemotactic function, chemokines influence specific lymphocyte responses and ultimately effector functions that are required for optimal host defense against microbial pathogens.

Control of JHMV replication within the CNS is mediated, in part, by lysis of virally-infected cells via cytotoxic CD8+ T lymphocytes (CTLs) as well secretion of IFN-γ by both CD4+ and CD8+ T cells [29]. CD4+ T cells also enhance antiviral activity of CD8+ T cells via secretion of IL-21 [36]. Cytotoxic activity by virus-specific CTLs is thought to control JHMV replication in microglia/macrophages and astrocytes whereas IFN-γ is important in dampening replication in oligodendrocytes [29, 37]. The demonstration that CD8+ CTLs suppress JHMV replication by these two separate effector mechanisms, which function within the CNS in a cell type-specific manner, is an important concept that has contributed to our understanding of how T cells participate in host defense following CNS viral infection. T cells respond to several different chemokines to access the CNS of JHMV-infected mice following expansion in draining cervical lymph nodes. Among the first chemokines expressed following JHMV infection are the non-ELR chemokines CXCL9 and CXCL10 [15] which are mostly likely produced in response to secreted type I interferons [38]. Early following infection, astrocytes, microglia, monocytes/macrophages, and dendritic cells express transcripts for CXCL9 and CXCL10 [15, 22, 39]. While neither CXCL9 or CXCL10 exert a direct effect on JHMV replication [15], these are potent chemoattractants for activated CD4+ and CD8+ T cells that express the signaling receptor CXCR3 [9]. Confirmation of the importance of both CXCL9 and CXCL10 in recruiting activated T cells into the CNS of JHMV-infected mice was initially provided by administration of blocking antibodies specific for each chemokine that resulted in a dramatic reduction in T cell infiltration into the CNS and was accompanied by impaired control of viral replication and increased mortality [39, 40]. Moreover, JHMV infection of *Cxcl10*$^{-/-}$ mice replicated findings using anti-CXCL10 blocking antibodies [41]. Further support for the importance of CXCL9 and CXCL10 was derived using JHMV infection of *Cxcr3*$^{-/-}$ mice which also resulted in altered CNS T cell infiltration, increased viral titers and mortality [42]. CXCL10 signaling does not aid in enhancing anti-viral T cell responses (e.g. IFN-γ secretion and cytolytic activity) in JHMV-infected mice, arguing it functions to specifically attract virus-specific T cells [43].

These findings were further confirmed through use of a recombinant mouse hepatitis virus (MHV) expressing the T cell-chemoattractant CXCL10 (MHV-CXCL10) [44]. Instillation of MHV-CXCL10 into the CNS of *Cxcl10*$^{-/-}$ mice resulted in viral infection and replication in both brain and liver [45]. Expression of virally encoded CXCL10 within the brain protected mice from death and correlated with increased infiltration of T lymphocytes and accelerated viral clearance when compared with mice infected with an isogenic control virus. Similarly, viral clearance from the livers of MHV-CXCL10-infected mice was accelerated in comparison to MHV-infected mice and allowed for protection from severe hepatitis as evidenced by reduced pathology and serum alanine aminotransferase levels. Treatment of MHV-CXCL10-infected *Cxcl10*$^{-/-}$ mice with an anti-CXCL10 blocking antibody resulted in increased clinical disease, correlating with enhanced viral recovery from the brain and liver as well as increased serum alanine aminotransferase levels. These studies further highlight that CXCL10 expression promotes protection from coronavirus-induced disease in the CNS, and functions in a similar capacity in other peripheral organs such as the liver.

Antibody and B cells have a critical role in preventing viral recrudescence in persistently infected mice [31, 46, 47]. Given the importance of antibody secreting cells (ASC) in suppressing re-emergence of virus, understanding how these cells migrate into the CNS is important with regards to understanding host defense mechanisms associated with viral persistence within the CNS. Bergmann and colleagues [48, 49] have shown that ASC express CXCR3, arguing for directed migration and accumulation within the CNS of JHMV-infected mice in response to ligands CXCL9 and CXCL10 expressed in areas of viral replication. Phares et. al. [50] clearly showed that ASC recruitment to the CNS of infected *Cxcl10*$^{-/-}$ mice, but not *Cxcl9*$^{-/-}$ mice, was dramatically impaired thus highlighting that CXCL10 is critical for ASC recruitment. In addition to attracting ASC's to the CNS, CXCL10 was also required for entry of these cells into the parenchyma of JHMV-infected mice [50].

Although virus-specific T cells are effective in controlling JHMV replication in the CNS, sterile immunity is not achieved and virus persists in white matter tracts resulting in a chronic demyelinating disease where foci of demyelination are associated with areas of viral RNA/antigen [51]. Both CXCL10 and CCL5 are the prominent chemokines expressed in mice persistently infected with JHMV with established demyelination, suggesting these chemokines may contribute to this pathological white matter damage through attraction of inflammatory T cells and monocyte/macrophages [15, 18, 25]. Anti-CXCL10 neutralizing antibody treatment in mice with established demyelination and paralysis resulted in a significant reduction of CD4+—but not CD8+—T cells present within the CNS, which correlated with a reduction in the severity of demyelination and improved motor skills [52]. Moreover, the dramatic regain of movement in anti-CXCL10-treated mice corresponded with more than 80% of previously demyelinated axons undergoing remyelination, indicating that removal of CXCL10 promoted an environment capable of remyelination. In addition to reduced numbers of CD4+ T cells within the CNS, there was a paucity of macrophage infiltration into the CNS of anti-CXCL10-treated mice that correlated with a dramatic reduction in the levels of the macrophage-chemoattractant CCL5. These data were consistent with previous studies indicating that CD4+ T cells were the major source for CCL5 in MHV-infected mice undergoing demyelination [25, 52]. These studies highlighted the pleiotropic nature of chemokines like CXCL10 and CCL5 and their importance in contributing to both control of viral replication during acute infection and development of pathology during chronic disease.

To determine the functional role of CCL5 in JHMV-induced immune-mediated demyelination, infected mice were treated with anti-CCL5 monoclonal antibody (mAb) following onset of clinical disease and demyelination. Such treatment resulted in reduced severity of clinical disease compared to mice treated with an isotype-matched antibody [19]. Upon removal of anti-CCL5 treatment, clinical disease returned to mice such that there was no difference between the two experimental groups of mice. Immunophenotyping the cellular infiltrate of mice treated with anti-CCL5 revealed reduced T cell and macrophage infiltration into the CNS that is consistent with our earlier studies, indicating that CCL5 attracts these cells into the CNS of mice with chronic demyelination. Further, analysis of the severity of demyelination in experimental groups of mice indicated that anti-CCL5 treatment

resulted in a significant ($p<0.05$) reduction in the severity of demyelination compared to control-treated mice.

These findings illustrate that infection of susceptible mice with JHMV results in an orchestrated expression of chemokines dictated by the stage of disease that serve to attract targeted populations of leukocytes to sites of infection. Early following infection, chemokine synthesis serves to link innate and adaptive immune responses that contribute to T cell-mediated control of JHMV replication within the CNS. Nonetheless, virus persists in white matter tracts within the brains and spinal cords leading to chronic expression of chemokines that ultimately participate in demyelination and immune-mediated pathology through recruitment and retention of activated T cells and inflammatory monocytes/macrophages. This highlights the delicate balance that occurs with regards to beneficial and detrimental effects of chemokine expression in response to viral infection.

4. Chemokine responses following human coronavirus infection

A dysregulated immune response, highlighted in part by elevated chemokine expression, has been implicated in the prognosis of all the recently emerging highly pathogenic HCoV's (hpHCoVs) SARS-CoV, MERS-CoV, and SARS-CoV-2 [53, 54]. While the majority of cases are confined to an upper-respiratory infection resulting in a mild illness with flu-like symptoms such as fever, cough, and sore throat, a percentage of infections extend to the lower respiratory airways leading to acute lung injury (ALI), ARDS and fatal pneumonia. Notably, although the pathogenic mechanisms involved in the development of severe hpHCoVs remain to be fully elucidated, they all are characterized by rapid viral replication, low interferon response, upregulated pro-inflammatory cytokine and chemokine profiles, and extensive immune cell infiltration [54–58].

With regards to SARS-CoV-2, the causative agent for the current global pandemic termed coronavirus disease 2019 (COVID-19), approximately 20% of infections result in hospitalization, of which a third progress to ARDS and ~16% result in fatality [59]. Clinical reports of COVID-19 patients cite increased plasma concentrations of pro-inflammatory chemokines CXCL8, CCL2, CCL3, CCL5, and CXCL10 that correlate with disease severity [60–62]. Therefore, pharmacological targeting of pro-inflammatory chemokines and their respective receptors provide a viable opportunity for successful treatment intervention, reduction in disease progression and enhanced recovery.

Similar to CXCL1's role in attracting neutrophils to the CNS of JHMV infected mice [17], the human analog, CXCL8, is important in recruitment and activation of neutrophils into the lungs in response to SARS-CoV-2 infection [63]. Following lung infiltration, neutrophils amplify the innate immune response via secretion of soluble factors and cytokines including S100A8/A9, S100A12, IL-1ß and expression of pro-inflammatory chemokines CCL3, CCL4, and CXCL8 [64, 65]. Neutrophil release of decondensed chromatin (neutrophil extracellular traps - NETs) and cytotoxic oxidative degranulation assist in limiting the spread of microbial pathogens but can also contribute to tissue pathology [66]. Progression from mild to severe COVID-19 diagnosis has been correlated with significant increases in plasma CXCL8, CXCR2 transcripts, an excess of neutrophil infiltration in the lungs, and

consequent hyperactivated NET formation leading to neutrophil-mediated pathology [55, 60, 65, 67]. Histopathological analysis by Nicolai et al. highlighted the involvement of neutrophils and NETs in the creation of microvascular thrombi, a pathological hallmark of multi-organ failure, found in the lungs, kidneys, and heart of severe and critical COVID-19 patients [67]. Indeed, early elevation of neutrophil levels precede critical illness and elevated neutrophil-to-lymphocyte ratios (NLR) have been found to be predictive of COVID-19 severity and mortality [68–70]. Therefore, blocking neutrophil hyperactivation early on in hospitalization may help prevent disease progression. Monoclonal antibodies against CXCL8, such as BMS-986253, as well as Reparixin, an oral inhibitor of CXCR1/2, have both been shown to effectively reduce neutrophil degranulation and NET formation *in vitro* [63]. Additionally, Reparaxin, which has proved to significantly reduce lung micro-thrombosis and SARS-CoV-2-related immunopathology *in vivo,* is currently in phase 3 clinical trials in the U.S. for treatment of COVID-19-related pneumonia [63]. Similarly, BMS-986253 is currently in phase 2 clinical trials in the U.S. for treatment of hospitalized COVID-19 patients (NCT04347226) (Table 1). Lastly, several drugs targeting different aspects behind the mechanism of NET-formation are also currently undergoing clinical trials (internationally and domestically) including the DNase enzyme Dornase Alfa, histone-neutralizing drug STC3141, and small-molecule inhibitor Alvelestat (NCT04445285, NCT04880694, NCT04539795) (Table 1).

Neutrophil accumulation in the lungs of COVID-19 patients is accompanied by increased infiltration of monocytes/macrophages and increased plasma levels of corresponding chemoattractants CCL2, CCL3 and CCL5 [60, 71]. CCL5 upregulation, which in the JHMV model recruits both activated virus-specific CD4+ and CD8+ T cells as well as monocytes/macrophages [18, 19, 72, 73], has correlated with mild disease, the presence of clonally expanded virus-specific CD8+ T-cells, and resolution of infection [71]. Conversely, progression to severe disease is often accompanied by decreased CCL5 expression, lymphopenia, and increased plasma levels of CCL2 and CCL3 [60, 74]. Single-cell RNA-sequencing of bronchoalveolar lavage fluid (BALF) from severe COVID-19 patients reveal distinct subsets of activated macrophages as key sources of pro-inflammatory mediators CCL2, CCL3, CXCL8, and CXCL10 as well as upregulation of corresponding receptors CCR2 and CCR5 [58]. Therefore, blocking of either CCR2 and CCR5 signaling or of their corresponding chemokine ligands could ameliorate macrophage accumulation within the lungs and the exuberant macrophage response, similar to what was reported with the use of germline knockouts *Ccr2*$^{-/-}$ and *Ccr5* $^{-/-}$ in the JHMV model of infection. In a case study of ten terminally ill COVID-19 patients, emergency use administration (EUA) of CCR5-blocking antibody Leronlimab was found to reduce plasma levels of pro-inflammatory cytokine IL-6, increase CD8+ T-cells, and decrease plasma viremia [75]. Leronlimab is currently in phase 2 clinical trials in the U.S. for treatment of mild, moderate, and severe COVID-19 (NCT04343651, NCT04347239) (Table 1). Additionally, Maraviroc and Cenicriviroc, originally developed for blocking HIV infection, are potent antagonists of CCR5 and CCR2/CCR5, respectively, that have been successfully repurposed for treatment of liver inflammation in non-alcoholic steatohepatitis (NASH) [76, 77]. Both have been proven to reduce monocyte infiltration and inflammation of the liver in mouse models of NASH and have been suggested as therapeutic anti-inflammatories in COVID-19 patients

[78]. Maraviroc, which is FDA approved, is currently in phase 1 of clinical trials for treatment of moderate and severe COVID-19, while Cenicriviroc has advanced to phase 3 in the U.S (NCT04435522, NCT04593940).

CXCL10 expression in COVID-19 patients has been reported to be predictive of disease severity and mortality, with CXCL10 plasma levels increasing markedly in severe disease as compared to development of mild/moderate disease [79–82]. In both JHMV infection of the CNS and in animal models of viral and non-viral-induced ARDS, the CXCL10-CXCR3 signaling axis has proven to be important in the amplification of a inflammatory response, with CXCL10 attracting CXCR3-expressing neutrophils and activated Th1-polarized CD4+ T cells to sites of infection and tissue damage [40, 52, 83]. More specifically, in the JHMV model of neurologic disease, CXCL10 aids in host defense during acute disease by attracting activated virus-specific CD4+ and CD8+ lymphocytes to the CNS yet chronic expression amplifies disease through continued attraction of activated CD4+ T cells that enable a proinflammatory feedback loop [40, 52, 84]. Similarly, in other viral infections such as hepatitis C (HCV), CXCL10 has been noted to correlate with viral presence in hepatocytes, the recruitment of T cells, corresponding histological tissue damage, and lobular inflammation, suggesting involvement of an over-exuberant Th1 response in pathology [85–87]. Furthermore, in autoimmune disorders such as autoimmune thyroiditis (AT) and Graves disease (GD), CXCL10 has also been associated with initiation of disease and disease relapse [88] arguing that CXCL10 may be a clinical target for reducing clinical disease severity in these autoimmune diseases. Secretion of IFN-γ and TNF-α by damaged cells recruits Th1 lymphocytes, prompting secretion of CXCL10 by both, Th1 lymphocytes and target cells that leads to a pro-inflammatory feedback loop linked to increases in disease severity [89]. Therefore, CXCR3 and its corresponding ligands have been suggested as potential therapeutic targets to ameliorate pathology induced by upregulation of CXCL10 and other Th1 chemokines. In SARS-CoV-2, Callahan et al. [90] demonstrated that following in vitro infection, human lung epithelial cells highly upregulate production of CXCL9, CXCL10, and CXCL11. Transcriptomic sequencing of BALF and peripheral blood mononuclear cells (PBMC's) from severe COVID-19 patients indicated increased expression of CXCL10 as compared to those with mild disease, pointing to a robust Th1 response as a potential mediator of disease severity [58].

Several clinical studies have suggested evaluating serum levels of CXCL10 as a relevant biomarker for severity of disease as well as a target for therapeutic intervention in SARS-CoV-2 infection [82, 91]. In support of this, a clinical trial was recently completed using measurement of CXCL10 in a Clinical Decision Support Protocol in COVID-19 patients, which positively correlated CXCL10 levels with mortality and was determined to be a potentially actionable measure in managing disease [92] (NCT04389645). Additionally, TNFα-antagonist therapy in hospitalized adults with hypoxic respiratory failure and COVID-19 pneumonia resulted in improved outcome associated with dramatic decrease in CXCL10 as well as CXCL9 serum levels and this strongly correlated with reversal of lymphopenia [81]. Animal models of COVID-19 have also implicated an important role for CXCL10 in contributing to disease progression. Administration of an inhibitor of integrin α5β1 with a small peptide in SARS-CoV-2 infected K18-hACE2 mice resulted in reduced viral load in the lungs and improved lung histology that correlated with reduced expression

of CXCL10 [93]. To our knowledge, there are no clinical trials in progress for testing anti-CXCL10 treatment or CXCR3-antagonists for reducing clinical disease severity in COVID-19 patients. Considering CXCL10's role as a potential driver of hyperinflammation in COVID-19, it could prove of clinical significance to further explore how targeting CXCL10 signaling impacts clinical outcome in COVID-19 patients with severe disease.

5. Conclusion

Coronavirus infection of mammalian hosts results in a regulated expression of chemokines depending upon disease stage and serves to attract targeted populations of immune cells that contribute to both control of viral replication but also enhance immune-mediated tissue damage. Dysregulated immune responses are often associated with severe COVID-19 patients in comparison to those patients with moderate to mild disease and this is often associated with elevated expression of specific chemokines. Preclinical models of infection of susceptible strains of mice with murine coronaviruses such as JHMV argue that blocking chemokine signaling offers an effective method for reducing immune cell recruitment to target tissue and reducing the severity of immune-mediated damage. Collectively, these findings argue for pursuing select chemokine pathways in reducing disease severity in response to infection with human coronaviruses including SARS-CoV-2.

6. Expert Opinion

Severe cases of COVID-19 are associated with dampened expression of both type I and III interferon responses that is often associated with impaired control of viral replication and cytokine release syndrome associated with acute respiratory distress syndrome [53, 94]. In addition to exacerbated cytokine responses, chemokine expression is also dysregulated, and this contributes to sustained cellular infiltration into the lungs of infected individuals. Collectively, these findings argue that therapeutic targeting of both cytokines and chemokines offers an approach to effectively limit immune cell infiltration into the lungs of patients with severe COVID-19 and increase recovery and survival. This is further supported from pre-clinical mouse models following infection with either murine coronaviruses or SARS-CoV-2 demonstrating that reducing cytokine/chemokine signaling reduces immune cell infiltration into target tissues. Indeed, numerous clinical trials are now ongoing that are either directly targeting cytokines e.g. IL-6, TNF, IL-1β and GM-CSF or cytokine receptors including IL-6 receptor and IL-1 receptor through administration of monoclonal antibodies [94]. Alternate approaches being employed for dampening inflammation in COVID-19 patients include targeting NF-κB, P38 MAPK and JAK/STAT as well as administering recombinant IFN-α, IFN-β and IFN-λ [94]. In addition, ongoing clinical trials are now underway that are specifically targeting select chemokines in an attempt to limit inflammatory responses in COVID-19 patients and dampen disease severity (Table 1). Many of these approaches employ monoclonal antibodies targeting selected chemokines and cytokines as these have proven successful for other human inflammatory diseases and are highly specific and well-tolerated. One additional potential chemokine target is CXCL10, whose expression has been associated with increased disease severity in COVID-19 patients [81, 82, 91, 92]. A human monoclonal antibody for CXCL10 has been developed and has been shown to be effective in limiting inflammatory responses on patients

with ulcerative colitis and rheumatoid arthritis [95, 96]. Blocking CXCL10 signaling has been shown to be effective in limiting T cell accumulation within the CNS in mice infected with JHMV yet this did result in increased disease severity as this approach restricted virus-specific T cells from gaining access to infected tissues [40, 43, 45, 84]. Therefore, targeting CXCL10 may increase disease severity in acute COVID-19 cases by blocking virus-specific T cells accumulating in lungs and other infected tissues and this should be considered if pursuing this therapeutic option.

Acknowledgments

Funding

This work was supported by funding from National Institutes of Health (NIH) research grants R01NS041249 and R35NS116835 and National Multiple Sclerosis Society Grant CA-1607-25040 to T Lane. G Olivarria was supported by (NIH) Immunology Research Training Grant 5T32AI060573-15. The authors declare no other financial interests

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Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

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Article Highlights

- Coronaviruses elicit an orchestrated expression of chemokines following infection and this is regulated, in part, by stage of disease.
- Coronavirus-induced expression of chemokines attracts targeted populations of leukocytes that aid in host defense or contribute to ongoing inflammation and disease pathology.
- Chemokines represent promising markers for evaluating disease severity in COVID-19 patients as circulating levels of specific chemokines have been associated with ARDS as well as other multi-organ failure.
- Ongoing clinical trials targeting chemokines may offer new therapeutic pathways in dampening tissue inflammation and improve clinical outcome.

Table 1:

Overview of clinical trials for COVID-19 targeting chemokines

Drug Name	Drug Target	Role of Target in COVID-19	Drug Type	Drug Mechanism of Action	Clinical Trial
BMS-986253	CXCL8	Proinflammatory; Chemoattractant for neutrophils & monocytes. Drives excess recruitment of both in ARDS.	Monoclonal antibody	Human monoclonal α-CXCL8 antibody neutralizes CXCL8 function.	NCT04347226
Reparixin	CXCR1 CXCR2	Proinflammatory; Primary receptors for CXCL8. Mobilize neutrophils & monocytes to lungs & sites of inflammation.	Allosteric receptor inhibitor	Prevents natural ligand CXCL8 from activating chemotaxis in neutrophils and monocytes.	NCT04878055
Dornase Alfa	NET formation	Limits viral spread; Enables antiviral protein release; Prothrombotic coagulation in critical/severe COVID-19 patients.	DNase enzyme	Hydrolyzes extracellular DNA released by neutrophils to reduce coagulation and viscosity produced by NET aggregation.	NCT04445285 NCT04488081
STC3141	NET formation	Limits viral spread; Enables antiviral protein release; Prothrombotic coagulation in critical/severe COVID-19 patients.	Small polyanion (SPA) cation neutralizer	Small polyanions interact electrostatically to neutralize decondensed chromatin histone cations present in NETs.	NCT04880694
Alvelestat	NET formation	Limits viral spread; Enables antiviral protein release; Prothrombotic coagulation in critical/severe COVID-19 patients.	Enzyme inhibitor	Inhibits neutrophil elastase (NE) function and prevents NE-activated chromatin decondensation.	NCT04539795
Leronlimab	CCR5	Proinflammatory; Receptor for CCL3, CCL4, and CCL5. Mobilizes T cells & macrophages to sites of inflammation. Enables excess recruitment of both in ARDS.	Competitive receptor inhibitor	Competitively binds to CCR5 and prevents natural ligands CCL3, CCL4, and CCL5 from activating chemotaxis in T cells and macrophages.	NCT04343651 NCT04347239
Maraviroc	CCR5	Proinflammatory; Receptor for CCL3, CCL4, and CCL5. Mobilizes T cells & macrophages to sites of inflammation. Drives excess recruitment of both in ARDS.	Allosteric receptor inhibitor	Prevents natural ligands CCL3, CCL4, and CCL5 from activating chemotaxis in T cells and macrophages.	NCT04435522
Cenicriviroc	CCR2/CCR5	Proinflammatory; Receptors for CCL2, CCL3, CCL4, and CCL5. Mobilize T cells & macrophages to sites of inflammation. Drive excess recruitment of both in ARDS.	Receptor Inhibitor	Prevents natural ligands CCL2, CCL3, CCL4, and CCL5 from activating chemotaxis in T cells and macrophages.	NCT04593940

Expert Rev Clin Immunol. Author manuscript; available in PMC 2023 January 03.