CXCL10 Chemokine: A Critical Player in RNA and DNA Viral Infections

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Abstract: Chemokines constitute a group of small, secreted proteins that regulate leukocyte migration and contribute to their activation. Chemokines are crucial inflammatory mediators that play a key role in managing viral infections, during which the profile of chemokine expression helps shape the immune response and regulate viral clearance, improving clinical outcome. In particular, the chemokine ligand CXCL10 and its receptor CXCR3 were explored in a plethora of RNA and DNA viral infections. In this review, we highlight the expression profile and role of the CXCL10/CXCR3 axis in the host defense against a variety of RNA and DNA viral infections. We also discuss the interactions among viruses and host cells that trigger CXCL10 expression, as well as the signaling cascades induced in CXCR3 positive cells.

Keywords: chemokines; RNA viruses; DNA viruses; CXCL10

1. Role of Chemokines during Viral Infections

Chemokines are small, secreted molecules that enhance cell interaction via G-protein-coupled receptors [1]. The chemokine-encoding genes in humans are located on chromosomes 4 and 17 [2]. In addition to being active as monomers, during an immune response, chemokines form homodimers and heterodimers, which result in a robust immunological response [3,4]. A general classification of chemokines is based on the structure of the two cysteine residues closest to the N terminus, which can be juxtaposed (CC) or separated by a single amino acid (CXC) or by three amino acids (CX3C). Chemokines that lack the first cysteine residue are known as XC chemokines [5,6]. Others classified chemokines into two primary categories according to their functions: those engaged in homeostasis and those involved in inflammation. Chemokine biological effects include many processes, such as angiogenesis regulation, tumor development, and invasion [7].

Further, chemokine receptors can be categorized into conventional (cCKRs) and atypical [8]. Conventional receptors can heterodimerize with other cCKRs, membrane proteins, and atypical chemokine receptors in addition to existing as homodimers and oligomers [9,10]. It should be noted that chemokines may also operate as natural antagonists rather than inducing activating signals when they attach to their appropriate receptors [11]. On the other hand, atypical chemokine receptors (ACKRs) are structurally linked to cCKRs when they bind to chemokines with a high affinity. However, because the intracellular signaling motifs are absent or altered, they do not activate the same signaling pathways as cCKRs [12,13]. In other words, the perturbation of ACKRs does not activate the G-protein signaling pathway but instead internalizes the chemokines to be degraded through the recruitment of β-arrestins [8]. Functionally, atypical chemokine receptors are known to regulate the localization, distribution, and abundance of chemokines and are considered proficient scavengers, thus modulating chemokine concentrations and...
bioavailability [14]. Moreover, ACKRs prevent unnecessary desensitization upon excessive exposure to chemokine ligands [15–18].

Several physiological processes, including cell proliferation and angiogenesis, as well as pathological conditions, including inflammation, neoplasia, autoimmunity, and infections (viral, bacterial, or parasitic), are controlled by binding chemokines to their cognate receptors [19]. During viral infections, chemokines are released as a result of a series of events [20], connecting several components [21] that boost the innate and adaptive immune systems which promote cell migration towards the sites of infection [22]. Nevertheless, viruses attempt to elude the immune system by molecular mimicry [23].

2. Structure and Function of CXCL10

Three chemokines are known to be interferon (IFN)-induced angiostatic CXC chemokines. These include monokine induced by interferon (MIG/CXCL9), interferon gamma-induced protein 10 (IP-10/CXCL10), and interferon-inducible T-cell chemoattractant (I-TAC/CXCL11). The chemokine CXCL10 binds CXCR3, which is present in T helper lymphocytes, natural killer (NK) cells, dendritic cells (DCs), macrophages, and B cells [24–27]. CXCR3 has two different isoforms, CXCR3-A and CXCR3-B, that possess several functions. For example, upon the binding of CXCL10 to isoform A, chemotaxis and proliferation are induced [28,29], while binding to the B isoform results in inhibiting cell migration and proliferation [29,30]. The atypical chemokine receptor ACKR2 is known to bind most inflammatory CC chemokine members [31] and is activated by the agonist CXCL10. Chevigné et al. described a novel aspect of CXCL10 regulation [32]. In an inflammatory status, CXCL10 could be secreted by various immune cells such as neutrophils, eosinophils, and monocytes, as well as epithelial cells, endothelial cells, and fibroblasts upon IFN-γ triggering [33–35]. Consequently, activated Th1 lymphocytes, monocytes, and NK cells would migrate towards the sites of inflammation in order to trigger the release of pro-inflammatory cytokines and chemokines. CXCL10 does not have the structural domain ELR “Glu-Leu-Arg” tripeptide motif, which is present in certain CXC chemokines and which might have anti-angiogenic along with anti-tumor properties [30,36–39]. The gene coding for CXCL10 is localized on chromosome 4 at band q21, and its translation produces a 12 kDa protein that has 2 internal disulfide cross-bridges [34]. Upon cleavage, a 10 kDa protein is generated and secreted with 4 conserved cysteine residues in the N-terminal [34]. The structure of CXCL10 exhibits a typical chemokine fold consisting of a three-stranded β sheet overlaid by an α helix with a number of the receptor binding residues located in the associated loops stabilized by the disulfide bonds [40]. The transcription of CXCL10 is regulated by various external stimuli, including cytokines such as IFN-γ and bacterial components such as lipopolysaccharides (LPS).

CXCL10 possesses an upstream regulatory sequence that contains several critical regulatory elements for nuclear factor-κB (NF-κB) and interferon-stimulated response element (ISRE), as well as sites for the binding of proteins such as heat shock (HS) factors [41]. Cytokines such as tumor necrosis factor (TNF-α) and IFN-γ induce the expression of CXCL10 through NF-κB and ISRE present in the promoter of CXCL10 [42–44]. This could lead to the activation of protein kinase C and increase the intracellular Ca²⁺ mobilization [45,46]. Since it is an inflammatory chemokine, CXCL10 was associated with multiple disorders, including infectious diseases, autoimmune diseases, and cancer [18,47–50]. Furthermore, it exacerbates inflammation, causing tissue damage [47]. Moreover, CXCL10 was expressed within tissues following viral infections, suggesting an essential role for this chemokine in host defense by contributing to the lymphocyte activation, migration, and infiltration of specific T cell subsets within the sites of infection [51].

3. Role of CXCL10 in RNA Viral Infections

CXCL10 could be protective or pathogenic in viral infections depending on the host’s immune status and the type of viral infection [52]. CXCL10 has been implicated in multiple RNA viral infections, including rhinovirus, respiratory syncytial virus (RSV), coxsackie virus, hepatitis C virus (HCV), Ebola, dengue, and equine infectious anemia
viruses [33,53–60]. It is also involved in various models of respiratory viral infection, including Sendai, influenza, corona, and adenoviruses, as well as neurogenic viral reactions where the expression and role of CXCL10 have been reported [61–66]. This highlights the significance of CXCL10 expression in multiple viral infections that could aid in viral clearance or contribute to disease pathogenesis.

The absence of CXCL10 using antibodies or knockout mouse models resulted in increased viral titers and reduced T cell infiltration within the brains of mice infected with a murine hepatitis virus (MHV), leading to increased mortality [67,68]. CXCL10 also affects the migration of CD8+ T cells in the liver of adenovirus-infected mice [69,70]. These studies indicate that CXCL10 is crucial in host defense and the development of a protective T cell response during viral infections. Furthermore, CXCL10 has been shown to induce the migration of T cells and NK cells following viral infections [71–74], where it attracts NK cells into the CNS post MHV infection [51]. Moreover, CXCL10 limits the spread of infection, contributing to early host defense and associated with a direct anti-viral effect against several RNA viruses [75,76]. For instance, CXCL10 blocked the entry and replication of the dengue virus by inhibiting its binding to the cell surface receptors [77]. Additionally, NK cell activation and migration caused an increase in IFN-γ production, which stimulates CXCL10 expression in cardiomyocytes and other resident myocardial cells in coxsackievirus B3 viral infection. This led to an inhibition of viral replication at an early stage in order to prevent cardiomyocyte damage and improve cardiac function [78].

Previous studies reported a synergy among double-stranded RNA (dsRNA) and IFN-γ-induced signaling in regulating CXCL10 production. As mentioned earlier, pro-inflammatory mediators and IFN-γ increased CXCL10 expression by a number of cell types, including keratinocytes, macrophages, endothelial cells, smooth muscle cells, and epithelial cell fibroblasts and astrocytes [79–88]. Majumder et al. reported that IFN-γ and TNF-α could promote CXCL10 production in human fibrosarcoma cell lines via binding the p48 complexes and the signal transducer and activator of transcription 1 (STAT-1) to ISRE site in CXCL10 promoter [89]. In another study, Oslund et al. determined that IFN-γ and influenza virus were able to synergistically induce CXCL10 in human airway epithelial cells through dsRNA-induced signaling both in vitro and in vivo [90]. Furthermore, the 735 bp proximal region of the CXCL10 promoter was the cause of this induction as it contains ISRE and NF-κB transcription factor binding sites. Following influenza virus infection, CD8+ T cell and NK cell migration towards the airway epithelial milieu was significantly affected by the ability of the airway epithelial cells to dramatically upregulate CXCL10 [90]. Other dsRNA-mediated pathways have also been identified in the upregulation of CXCL10, including retinoic acid-inducible gene I (RIG-I) and protein kinase R (PKR), which further augment the anti-viral signal by the activation of type I IFN production [91–93].

CXCL10 was found to have a protective function during certain RNA viral infections such as the severe acute respiratory syndrome coronavirus (SARS-CoV) and Epstein-Barr virus (EBV) [94–96]. On the other hand, CXCL10 was found to promote the infection caused by the human immunodeficiency virus (HIV) by stimulating the virus replication in macrophages and lymphocytes [97]. In short, the expression of CXCL10 was differentially associated with clinical symptoms in multiple infections. For example, a high expression of CXCL10 occurred before the development of clinical symptoms during HIV infection and murine retroviruses [98], and CXCL10 levels were positively correlated with organ damage and pathogen burden in HCV and HIV infections [99,100]. Moreover, persistent high levels of CXCL10 were linked to the failure of highly active antiretroviral therapy (HAART) in HIV-infected patients [101], as anti-retroviral treatment decreased the plasma levels of CXCL10, indicating its vital role in disease pathogenesis [97]. Additionally, the elevation of CXCL10 levels was reported for at least two weeks after disease onset, while corticosteroid therapy caused a reduction in the plasma CXCL10 levels, during SARS infection [102,103]. The chemokine receptor CXCR3 was highly expressed on viral-specific stem-like CD8+ T cells. CXCL10 regulates the persistence and heterogeneity of CD8+ T cells in the spleens of mice infected with lymphocytic choriomeningitis virus (LCMV). Moreover, functional
CD8+ T cell responses were found to be greater in Cxcl10−/− mice and were associated with a lower viral count [104].

Among various chemokines, CXCR3 has been studied in viral hepatitis as it plays a significant role in the recruitment of T cells into the peripheral inflammatory sites [105, 106]. The RNA virus, hepatitis A virus (HAV), is known to cause severe liver injury accompanied by the release of inflammatory mediators. HAV-infected hepatocytes produced multiple chemokines, including CXCL10. Moreover, CXCL10 levels were significantly increased in the serum of patients infected with HAV [107]. The CXCL10 production was reduced subsequent to inhibiting the signaling molecules associated with RIG-I-like receptor (RLR), such as mitochondrial antiviral signaling protein and interferon regulatory factor 3 (IRF3), in HAV-infected cells [107]. Similar to HAV, HCV-infected cells produced CXCL10 independent of type I or III IFNs [108], regulated by the expression of interferon regulatory factor 3 (IRF3) and NF-κB [109]. Additionally, CXCR3 is involved in the recruitment of effector CD8+ T cells and CD4+ T helper cells into HCV-infected livers [110–112], and the expression of CXCR3 in the liver or the peripheral blood is correlated with the severity of hepatic inflammation in HCV infection [113–116]. Similarly, the Kernow-p6 hepatitis E virus (HEV) strain was reported to stimulate the release of CXCL10 in enterocytes and infected hepatocytes [117–120]. Further, patients with HEV genotype three infections (clade efg) suffer from severe clinical representations, accompanied by higher CXCL10 serum levels and liver necro-inflammatory activity [121].

In chronic HCV infection, CXCL10 contributed to the development of necroinflammation and liver fibrosis. Moreover, the intrahepatic production of IFN-γ promoted CXCL10 expression by sinusoidal endothelium and hepatocytes, thereby triggering the recruitment of CXCR3+ T cells. CXCL10 plasma levels were significantly higher in HCV-infected patients with advanced fibrosis [122]. Additionally, CXCL10 levels were associated with the extrahepatic manifestations observed with this viral infection. For instance, CXCL10 levels were much higher in patients with HCV-associated cryoglobulinemia compared with those patients with autoimmune thyroiditis [122]. Additionally, high CXCL10 levels present in cases of HCV-associated cryoglobulinemia were associated with the presence of another extrahepatic manifestation, i.e., active vasculitis. Therefore, targeting CXCL10 and its receptor CXCR3 was suggested for treating HCV patients. Examples of such an approach include antibodies blocking the interaction between CXCR3 and its ligands, which reduced chronic liver inflammation and damage via the impairment of the infiltration of the nonspecific T cells [123]. This therapeutic strategy could be evaluated primarily for the non-responders to current anti-HCV therapy. This and other studies highlighted the potential use of CXCL10 as a prognostic marker of HCV clearance and successful therapy [122].

CXCL10 is also known to play a critical role in the host defense against infection caused by the John Howard Mueller (JHM) strain of mouse hepatitis virus (JHMV). Early expression of CXCL10 was observed to promote the attraction of CXCR3+ T cells into the central nervous system, which subsequently aids in limiting viral replication [124]. On the other hand, chronic CXCL10 expression contributed to the neuroinflammation and demyelination associated with JHMV infection. This was attributed to the attraction of CD4+ T cells that amplify neuroinflammation through the IFN induction of chemokine release. Therefore, the CXCL10/CXCR3 signaling pathway may influence glial biology and may repair virally induced neurologic diseases [124].

CXCL10 is a key player in respiratory syndromes. Its level was higher in the plasma and bronchial alveolar lavage fluid (BALF), which correlated with the disease severity [125–127]. Elevated CXCL10 levels were reported in patients with SARS or Middle East respiratory syndrome (MERS) as early as 2–3 days post-infection [61, 103, 128–131]. This increase was found to reduce the proliferation of myeloid progenitor cells, triggering lymphopenia as observed in coronavirus disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [131]. Additionally, CXCL10 was reported to trigger T cells apoptosis and lymphopenia seen in SARS-CoV-, MERS-, and SARS-CoV-2-infected patients, leading to T lymphocyte malfunction and worsening clinical outcome [132]. Previous
studies using ex vivo human lung tissue explants demonstrated that the inoculation of SARS-CoV and SARS-CoV-2 induced the expression of various chemokines and cytokines, particularly CXCL10 [133].

Similar to other respiratory diseases, high CXCL10 levels in COVID-19 patients showed a strong correlation with disease severity [134,135]. As mentioned earlier, CXCL10 levels were increased in SARS-CoV-2 infected patients, especially those with acute respiratory distress syndrome (ARDS) [136,137]. Consequently, the use of CXCL10 as an independent predictor for COVID-19 progression was suggested since it was correlated with ARDS in critically ill patients and severe cases [132,138,139]. This was further supported in COVID-19 patients requiring intensive care unit (ICU) admission, who exhibited higher levels of CXCL10 than patients with mild infection [138,140–143]. Furthermore, higher mortality was reported in COVID-19 patients with a dramatic increase in CXCL10 levels compared with severe and mild COVID-19 patients [136,144–146]. In this regard, symptomatic COVID-19 patients showed higher levels of CXCL10 compared with convalescent cases [134]. Interestingly, CXCL10 levels were reported to be significantly reduced upon improving clinical outcomes in hospitalized COVID-19 patients [137]. Consequently, several studies reported CXCL10 as an excellent predictive biomarker of patient outcomes in COVID-19 [137,141]. CXCL10 was also identified to be a potential biomarker to predict left ventricular dysfunction in multisystem inflammatory syndrome (MIS-C) patients, occurring post-exposure to COVID-19 infection [147].

Intriguingly, across all three coronaviruses (SARS-CoV, MERS-CoV, and SARS-CoV-2), CXCL10 was identified as a crucial contributor to pulmonary pathogenesis. CXCL10 was associated with lung injury and the activation of the toll-like receptor 4 (TLR4) signaling pathway [148,149]. Although not an ELR chemokine, CXCL10 induced neutrophil infiltration into the lungs, triggering further production of this chemokine, coupled with the release of oxidative burst by neutrophils. Eventually, this worsens the inflammatory lung state, causing progression to ARDS [150,151]. Therefore, antibodies against CXCL10 could be a potential and promising therapeutic approach in ARDS, as previously described in the influenza A virus subtype (H1N1) mouse model [150,152]. Furthermore, corticosteroids, the anti-inflammatory agents used in COVID-19 infection, were found to reduce the levels of multiple chemokines, including CXCL10, along with stimulating the NF-κB and activator protein-1 (AP-1) signaling pathways [153].

IL-6 is one of the cytokines released during COVID-19-mediated cytokine storm [154,155]. During this storm, high IL-6 levels act on lung endothelial cells, causing an increase in their permeability for serum proteins and the infiltration of inflammatory cells. This leads to an uncontrolled excessive immune response, such as in severe COVID-19 cases [154,155]. In addition, CXCL10 was recognized as a fundamental chemokine acting as a chemoattractant for monocytes, macrophages, and dendritic cells, as well as NK and T cells during COVID-19 infection. Upon the entry of SARS-CoV-2 into the lung epithelium, it triggers cytokine and chemokine production, which include IL-6 and CXCL10. One of the causes for the increased production of CXCL10 is IL-6, which also leads to an increase in the infiltration of CXCR3+ macrophages, the main producers of IL-6. These observations highlight the vicious cycle between CXCL10, IL-6, and macrophages in the lungs of COVID-19 patients, which could regulate the onset, maintenance, and progression of cytokine storms during COVID-19 infection [156].

As in respiratory coronavirus infections, CXCL10 showed a significant increase during measles virus (MeV) infection, which may distinguish MeV from other diseases such as rubella virus (RuV), parvovirus B19 (B19V), human herpesvirus 6 (HHV6), EBV, and human cytomegalovirus (HCMV). Another common factor was the high level of CXCL10 in hospitalized MeV patients compared with non-hospitalized ones, and higher CXCL10 level was observed in cases of primary infection compared with re-infected cases [157,158]. This demonstrates persistent inflammation and robust viral replication that might aggravate the clinical course of primary infection [159,160]. Interestingly, CXCL10 levels were associated with the serological stages of MeV infection. For instance, CXCL10 production was in-
creased early after infection and reached its peak with the appearance of MeV-specific IgM antibodies, which later declined [157]. Another interesting finding during MeV infection is the association between mortality due to MeV infection and high CXCL10 levels in children. This further supports the link between CXCL10 and the clinical severity of MeV infection. CXCL10 and CCL5 were highly expressed in vitro and in vivo during RSV infection. However, CXCL10 was found to have a protective role by decreasing viral load and disease pathogenesis [161]. This was mediated via the promotion of leukocyte recruitment and the trafficking of dendritic cells (DCs). Furthermore, CXCL10 is stimulated by type I IFN in CXCR3+ DCs, triggering myeloid DC maturation [161]. 

CXCL10 expression was higher in Zika virus (ZIKV)-infected individuals. This expression could be mediated through the induction of IFN-γ signaling pathway by the ZIKV NS5 protein. Previously, CXCL10 was discovered to be a biomarker of several bacterial infections [162]. Similarly, CXCL10 was identified as a biomarker of acute ZIKV infection and a predictor of disease severity [163]. A summary of the role of CXCL10 in RNA viral infections is shown in Figure 1.

![Diagram of CXCL10 in viral infections](image)

**Figure 1.** Role of CXCL10 during RNA viral infections. ARDS: acute respiratory distress syndrome, CNS: central nervous system, HAV: hepatitis A virus, HCV: hepatitis C virus, HIV: human immunodeficiency virus, LCMV: lymphocytic choriomeningitis virus, MERS-CoV: middle east respiratory syndrome coronavirus, MeV: measles virus, MHV: murine hepatitis virus, RSV: respiratory syncytial virus, SARS-CoV: severe acute respiratory syndrome coronavirus, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

### 4. Effects of CXCL10 during DNA Viral Infections

As illustrated in Figure 2, CXCL10 is implicated in various DNA viral infections. For instance, CXCL10 was found to be a critical player in the innate defense against vaccinia virus infection by recruiting and activating NK cells [75]. In varicella-zoster virus (VZV) infection, upregulated CXCL10 expression was demonstrated along with the infiltration of CXCR3+ cells towards the infected dorsal root ganglia. Consequently, CXCL10 could
be a distinct chemokine that attracts inflammatory cells, specifically CXCR3+ cells causing ganglionitis [164].

![Diagram](image)

**Figure 2.** Role of CXCL10 during DNA viral infections. HBV: hepatitis B virus, HSV: herpes simplex virus, VZV: varicella-zoster virus.

According to several studies, CXCL10 is implicated in hepatitis B virus (HBV) infection, including a study where the polymorphism G-201A in the promoter of the CXCL10 gene predicted susceptibility to chronic HBV infection [52]. During chronic infection, serum and intrahepatic levels of CXCL10 were elevated and correlated with HBV DNA and alanine aminotransferase (ALT) enzyme levels, coupled with progressive liver disease [165,166]. Other studies confirmed that CXCR3 ligands such as CXCL9, CXCL10, and CXCL11 are highly increased along with ALT in acute hepatitis patients, resulting from the release of IFN-α and IFN-γ by plasmacytoid DCs and NK cells, respectively, in response to HBV infection [167,168]. Furthermore, these three chemokines were decreased with reduced HBV DNA during acute infection [169]. In contrast, high CXCL10/IP-10 and CXCL9/Mig levels during HBV infection were correlated with severe liver disease. Subsequently, their neutralization was linked to the preservation of antiviral effects including less tissue damage [170]. Zhou et al. demonstrated that the upregulation of CXCL10 was dose-dependent through the activation of NF-κB, thereby enhancing the infiltration of peripheral leukocytes into the liver of HBV infection [171]. Consequently, blocking CXCL10 could reduce the recruitment of lymphocytes and improve the disease severity [71,172]. In HIV and HBV co-infected patients, mRNA levels for CXCL10 and CXCL3 were correlated with liver fibrosis. It has been suggested that the HIV infection of hepatocytes in the presence of HBV could promote inflammation and flux of CXCL10 production, thus promoting the recruitment of activated CXCR3+ cells towards the liver that could cause liver fibrosis [173].

CXCL10 is crucial in host defense against multiple neurotropic viruses, including herpes simplex virus-1 (HSV-1) [174]. It was previously reported that lack of either CXCL10 or its receptor CXCR3 could impair the mobilization of functional CD8+ effector memory (TEM) and CD8+ residual memory (TRM) cells within latently infected trigeminal ganglia following HSV-1 reactivation [175]. In contrast, increasing the levels of CXCL10 in latently HSV-1 infected CXCL10-deficient mice significantly restored the number of local antiviral CD8+ TEM and CD8+ TRM cells associated with protection against recurrent ocular herpes. These findings demonstrate that CXCL10/CXCR3 axis is crucial for CD8+ T cell immunity, which protects against recurrent herpesvirus infection [175]. The chemokine receptor CXCR3 is highly expressed on activated CD4+, CD8+ T cells, and NK cells at the sites of HSV-1 replication [176–180]. Additionally, during HSV-1 infection, CXCL10 was one of the first and most abundantly expressed chemokines, indicating that it may be essential for the coordinated immune response against HSV-1. Further, HSV-1 viral burden was elevated in CXCR3-deficient (CXCR3−/−) and CXCL10-deficient (CXCL10−/−) animals compared with wild types [174,177]. In this regard, CXCL10−/− mice exhibited impaired
NK and HSV-1-specific CD8+ T cell activation, which increased their susceptibility to HSV-1 infection [174]. Unlike HSV-1, CXCL10 was found to promote the infection caused by stimulating virus replication in immune cells during herpes simplex virus type 2 (HSV-2) infection [181]. The expression of CXCL9 and CXCL10 was increased in the cervical tissues of mice infected with HSV-2 [182–184]. At the same time, other studies reported an upregulation of CXCL10 and CXCL11 during HSV-2 infection [182,185,186]. Moreover, the HSV-2 protein infected-cell polypeptide 4 (ICP4) was suggested to be the critical viral component that stimulated the production of CXCL9, CXCL10, and CXCL11 [186].

5. Role of CXCL10 in Oncolytic Viruses

Multiple strains of oncolytic viruses such as vesicular stomatitis virus (VSV), HSV-2, maraba virus, chikungunya virus, and reolysin have been reported to drive the high expression of chemokines in infected tumors [187–190]. For instance, the intratumoral administration of oncolytic HSV-2 was associated with high CXCL10 expression, promoting the attraction of adoptively transferred T cells towards treated lesions [190]. Among many other cytokines and chemokines, CXCL10 was tested as an immune stimulant in the genomes of oncolytic viruses, to enhance the anti-tumor activity in several cancer studies [187]. Moreover, VSV was identified in promoting inflammatory tumor cell killing via the release of chemokines, including CXCL10, which trigger the infiltration of T effector cells into the tumor growth sites [191]. Another example was the oncolytic adenovirus with an inserted CXCL10 gene (Adv-CXCL10), which enhanced the recruitment of CXCR3+ T cells into the colon tumor microenvironment corroborated with increasing the efficacy of PD-1 antibody [192]. These results were translated into a clinical trial using an oncolytic adenovirus (NG-641) expressing CXCL9, CXCL10, and IFN-α, which is currently under investigation (NCT04053283) [193,194].

6. Conclusions

An impaired immune response is a critical hallmark in the development and progression of viral infections. Notably, the role of chemokines during viral infections has been explored and analyzed during the context of many RNA and DNA viral infections. CXCL10 was found to mediate its inflammatory activity through CXCR3, which is mainly expressed on T cells, NK cells, macrophages, and dendritic cells. Several studies report the significance of CXCL10 and its chemokine receptor CXCR3 in host defense and viral clearance, while other reports demonstrate its role in disease pathogenesis. Moreover, CXCL10 was suggested to be a potential diagnostic and prognostic marker in several viral infections such as COVID-19. Further, CXCL10 has a potential role as an anti-tumor agent mediated by oncolytic viruses. Therefore, targeting CXCL10 could be a possible therapeutic modality against many viral infections, as well as against tumor development. Further in-depth understanding of the chemokine system may allow the development of such therapeutics against viral infections, which could be beneficial in preventing opportunistic microbes.

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References
1. Maghazachi, A.M.A.; Al-Aoukaty, A. Chemokines activate natural killer cells through heterotrimeric G-proteins: Implications for the treatment of AIDS and cancer. *FASEB J.* 1998, 12, 913–924. [CrossRef] [PubMed]
2. Nomiyama, H.; Osada, N.; Yoshie, O. The evolution of mammalian chemokine genes. *Cytokine Growth Factor Rev.* 2010, 21, 253–262. [CrossRef] [PubMed]
3. Proudfoot, A.E.; Ugucioni, M. Modulation of Chemokine Responses: Synergy and Cooperativity. *Front. Immunol.* **2016**, 7, 183. [CrossRef]

4. Mellado, M.; Rodríguez-Fraide, J.M.; Vila-Coro, A.J.; Fernández, S.; Martín de Ana, A.; Jones, D.R.; Torán, J.L.; Martínez, A.C. Chemokine receptor homo- or heterodimerization activates distinct signaling pathways. *EMBO J.* **2001**, 20, 2497–2507. [CrossRef]  

5. Murphy, P.M.; Baggioni, M.; Charo, I.F.; Hébert, C.A.; Horuk, R.; Matsushima, K.; Miller, L.H.; Oppenheim, J.J.; Power, C.A. International union of pharmacology. XXII. Nomenclature for chemokine receptors. *Pharmacol. Rev.* **2000**, 52, 145–176. [PubMed]

6. Kennedy, J.; Kelner, G.S.; Klenestüber, S.; Schall, T.J.; Weiss, M.C.; Yssel, H.; Schneider, P.V.; Cocks, B.G.; Bacon, K.B.; Zlotnik, A. Molecular cloning and functional characterization of human lymphotactin. *J. Immunol.* **1995**, 155, 203–209. [PubMed]

7. Hughes, C.E.; Nibbs, R.J.B. A guide to chemokines and their receptors. *FEBS J.* **2003**, 274, 2944–2971. [CrossRef]

8. Stone, M.J.; Hayward, J.A.; Huang, C.; Huma, E.Z.; Sanchez, J. Mechanisms of Regulation of the Chemokine-Receptor Network. *Int. J. Mol. Sci.* **2017**, 18, 342. [CrossRef]

9. Wilson, S.; Wilkinson, G.; Milligan, G. The CXCR1 and CXCR2 receptors form constitutive homo- and heterodimers selectively and with equal apparent affinities. *J. Biol. Chem.* **2005**, 280, 28663–28674. [CrossRef]  

10. Sohy, D.; Yano, H.; de Nadal, P.; Urizar, E.; Guillaume, A.; Parmentier, M.; Springael, J.Y. Hetero-oligomerization of CCR2, CCR5, and CXCR4 and the proteineffects of “selective” antagonists. *J. Biol. Chem.* **2009**, 284, 31270–31279. [CrossRef]

11. Petkovic, V.; Moghini, C.; Paolotti, S.; Ugucioni, M.; Gerber, B. Eotaxin-3/CCL26 is a natural antagonist for CC chemokine receptors 1 and 5. A human chemokine with a regulatory role. *J. Biol. Chem.* **2004**, 279, 23357–23363. [CrossRef] [PubMed]

12. Nibbs, R.J.; Graham, G.J. Immune regulation by atypical chemokine receptors. *Nat. Rev. Immunol.* **2013**, 13, 815–829. [CrossRef] [PubMed]

13. Bachelier, F.; Ben-Baruch, A.; Burkhardt, A.M.; Combadiere, C.; Farber, J.M.; Graham, G.J.; Horuk, R.; Sarre-Ulrich, A.H.; Locati, M.; Luster, A.D.; et al. International Union of Basic and Clinical Pharmacology. LXXXIX. Update on the extended family of chemokine receptors and introducing a new nomenclature for atypical chemokine receptors. *Pharmacol. Rev.* **2013**, 66, 1–79. [CrossRef] [PubMed]

14. Cardona, A.E.; Sasse, M.E.; Liu, L.; Cardona, S.M.; Mizutani, M.; Savarin, C.; Hu, T.; Ransohoff, R.M. Scavenging roles of chemokinereceptors: Chemokine receptor deficiency is associated with increased levels of ligand in circulation and tissues. *Blood* **2008**, 112, 256–263. [CrossRef] [PubMed]

15. Fukuma, N.; Akimitsu, N.; Hamamoto, H.; Kusuhara, H.; Sugiyama, Y.; Sekimizu, K. A role of the Duffy antigen for the maintenance of plasma chemokine concentrations. *Biochem. Biophys. Res. Commun.* **2003**, 303, 137–139. [CrossRef]

16. Lee, J.S.; Frevert, C.W.; Wurfel, M.M.; Peiper, S.C.; Wong, V.A.; Ballman, K.K.; Ruzinski, J.T.; Rhim, J.S.; Martin, T.R.; Goodman, R.B. Duffy antigen facilitates movement of chemokine across the endothelium in vitro and promotes neutrophil transmigration in vitro and in vivo. *J. Immunol.* **2003**, 170, 5244–5251. [CrossRef] [PubMed]

17. Pruenster, M.; Mudde, L.; Bombosi, P.; Dimitrova, S.; Zsak, M.; Middleton, J.; Richmond, A.; Graham, G.J.; Segerer, S.; Nibbs, R.J.; et al. The Duffy antigen receptor for chemokines transports chemokines and supports their promigratory activity. *Nat. Immunol.* **2009**, 10, 101–108. [CrossRef] [PubMed]

18. Elemam, N.M.; Khalil, B.A.; Maghazachi, A.A. Chemokines and chemokine receptors. In *Encyclopedia of Infection and Immunity*; Rezaei, N., Ed.; Elsevier: Oxford, UK, 2022; pp. 193–205.

19. Kleist, A.B.; Getschman, A.E.; Ziarek, J.J.; Nevin, A.M.; Gauthier, P.A.; Chevigné, A.; Szpadowska, M.; Volkman, B.F. New paradigms in chemokine receptor signal transduction: Moving beyond the two-site model. *Biochem. Pharmacol.* **2016**, 114, 53–68. [CrossRef]

20. Salazar-Mather, T.P.; Hokeness, K.L. Cytokine and chemokine networks: Pathways to antiviral defense. *Curr. Top. Microbiol. Immunol.* **2006**, 303, 29–46. [CrossRef]

21. Decalf, J.R.M.; Fernandes, S.; Longman, R.; Ablolay, M.; Audat, F.O.; Lefrere, F.O.; Rice, C.M.; Pol, S.; Albert, M.L. Plasmacytoid dendritic cellsin initiate a complex chemokine and cytokine network and are a viable drug target in chronic HCV patients. *J. Exp. Med.* **2007**, 204, 2423–2437. [CrossRef]

22. Mahalingam, S.; Friedland, J.S.; Heise, M.T.; Rulli, N.E.; Meanger, J.; Lidbury, B.A. Chemokines and viruses: Friends or foes? *Trends Microbiol.* **2003**, 11, 383–391. [CrossRef]

23. Murphy, P.M. Viral exploitation and subversion of the immune system through chemokine mimicry. *Nat. Immunol.* **2001**, 2, 116–122. [CrossRef] [PubMed]

24. Loetscher, M.; Loetscher, P.; Brass, N.; Meese, E.; Moser, B. Lymphocyte-specific chemokine receptor CXCR3: Regulation, chemokine binding and gene localization. *Eur. J. Immunol.* **1998**, 28, 3696–3705. [CrossRef]

25. Qin, S.; Rottman, J.B.; Myers, P.; Kassam, N.; Weinblatt, M.; Loetscher, M.; Koch, A.E.; Moser, B.; Mackay, C.R. The chemokine receptors CXCR3 and CCR5 mark subsets of T cells associated with certain inflammatory reactions. *J. Clin. Investig.* **1998**, 101, 746–754. [CrossRef] [PubMed]

26. Sallusto, F.; Lenig, D.; Mackay, C.R.; Lanzavecchia, A. Flexible programs of chemokine receptor expression on human polarized T helper 1 and T helper 2 cells. *Cell Signal.* **2004**, 16, 991–1000. [CrossRef]
28. Kelsen, S.G.; Aksoy, M.O.; Yang, Y.; Shahabuddin, S.; Litvin, J.; Safadi, F.; Rogers, T.J. The chemokine receptor CXCR3 and its splice variant are expressed in human airway epithelial cells. *Am. J. Physiol.-Lung Cell. Mol. Physiol.* 2004, 287, L584–L591. [CrossRef]

29. Lasagni, L.; Francalanci, M.; Annunziato, F.; Lazzeri, E.; Giannini, S.; Cosmi, L.; Sagrini, C.; Mazzinghi, B.; Orlando, C.; Maggi, E.; et al. An alternatively spliced variant of CXCR3 mediates the induction of endothelial cell growth induced by IP-10, Mig, and I-TAC, and acts as functional receptor for platelet factor 4. *J. Exp. Med.* 2003, 197, 1537–1549. [CrossRef]

30. Bodnar, R.J.; Yates, C.C.; Wells, A. IP-10 blocks vascular endothelial growth factor-induced endothelial cell motility and tube formation via inhibition of calpain. *Circ. Res.* 2006, 98, 617–625. [CrossRef]

31. Bonecchi, R.; Locati, M.; Galliera, E.; Vulcano, M.; Sironi, M.; Fra, A.M.; Gobbi, M.; Vecchi, A.; Sozzani, S.; Haribabu, B.; et al. Differential Recognition and Scavenging of Native and Truncated Macrophage-Derived Chemokine (Macrophage-Derived Chemokine/CC Chemokine Ligand 22) by the D6 Decoy Receptor. *J. Immunol.* 2004, 172, 4972. [CrossRef]

32. Chevigné, A.; Janji, B.; Meyrath, M.; Reynolds, N.; D’Uonnolo, G.; Uchański, T.; Xiao, M.; Berchem, G.; Ollert, M.; Kwon, Y.-J.; et al. CXCL10 Is an Agonist of the CC Family Chemokine Scavenger Receptor ACKR2/D6. *Cancers* 2021, 13, 1054. [CrossRef] [PubMed]

33. Dyer, K.D.; Percopo, C.M.; Fischer, E.R.; Gabryszewski, S.J.; Rosenberg, H.F. Pneumoviruses infect eosinophils and elicit MyD88-dependent release of chemoattractant cytokines and interleukin-6. *Blood* 2009, 114, 2649–2656. [CrossRef] [PubMed]

34. Luster, A.D.; Ravetch, J.V. Biochemical characterization of a gamma interferon-inducible cytokine (IP-10). *J. Exp. Med.* 1987, 166, 1084–1097. [CrossRef]

35. Lo, B.K.; Yu, M.; Zloty, D.; Cowan, B.; Shapiro, J.; McElwee, K.J. CXCR3/ligands are significantly involved in the tumorigenesis of basal cell carcinomas. *Am. J. Pathol.* 2010, 176, 2435–2446. [CrossRef]

36. Angiolillo, A.L.; Sgadari, C.; Taub, D.D.; Liao, F.; Farber, J.M.; Maheshwari, S.; Kleinman, H.K.; Reaman, G.H.; Tosato, G. Human interferon-inducible protein 10 is a potent inhibitor of angiogenesis in vivo. *J. Exp. Med.* 1995, 182, 153–162. [CrossRef]

37. Persano, L.; Crescenzi, M.; Indraccolo, S. Anti-angiogenic gene therapy of cancer: Current status and future prospects. *Mol. Aspects Med.* 2007, 28, 87–114. [CrossRef]

38. Belperio, J.A.; Keane, M.P.; Arenberg, D.A.; Addison, C.L.; Ehler, J.E.; Burdick, M.D.; Strieter, R.M. CXC chemokines in angiogenesis. *J. Leukoc. Biol.* 2000, 68, 1–8. [CrossRef]

39. Strieter, R.M.; Polverini, P.J.; Kunkel, S.L.; Arenberg, D.A.; Burdick, M.D.; Kasper, J.; Dzuiba, J.; Van Damme, J.; Walz, A.; Marriott, D.; et al. The functional role of the ELR motif in CXC chemokine-mediated angiogenesis. *J. Biol. Chem.* 1995, 270, 27348–27357. [CrossRef] [PubMed]

40. Swaminathan, G.J.; Holloway, D.E.; Colvin, R.A.; Campanella, G.K.; Papageorgiou, A.C.; Luster, A.D.; Acharya, K.R. Crystal structures of oligomeric forms of the IP-10/CXCL10 chemokine. *Structure* 2003, 11, 521–532. [CrossRef]

41. Ohmori, Y.; Hamilton, T.A. Cooperative interaction between interferon (IFN) stimulus response element and kappa B sequence motifs controls IFN gamma- and lipopolysaccharide-stimulated transcription from the murine IP-10 promoter. *J. Biol. Chem.* 1993, 268, 6677–6688. [CrossRef]

42. Majumder, S.; Zhou, L.Z.; Chaturvedi, P.; Babcock, G.; Aras, S.; Ransohoff, R.M. Regulation of human IP-10 gene expression in astrocytoma cells by inflammatory cytokines. *J. Neurosci. Res.* 1998, 54, 169–180. [CrossRef]

43. Varley, C.L.; Armitage, S.; Hassanshahiraviz, G.; Dickson, A.J. Regulation of the C-X-C chemokine, mob-1, gene expression in primary rat hepatocytes. *Am. J. Physiol.-Lung Cell. Mol. Physiol.* 2000, 278, C74–C82. [CrossRef] [PubMed]

44. Romagnani, P.; Lazzeri, E.; Lasagni, L.; Movsazian, L.; Rotondi, M.; Annunziato, F.; Maurenzig, L.; Cosmi, L.; et al. IP-10 and Mig production by glomerular cells in human proliferative glomerulonephritis and regulation by nitric oxide. *J. Am. Soc. Nephrol.* 2002, 13, 53–64. [CrossRef]

45. Han, B.; Logsdon, C.D. Cholecystokinin induction of mob-1 chemokine expression in pancreatic acinar cells requires NF-kappaB activation. *Am. J. Physiol.* 1999, 277, C74–C82. [CrossRef] [PubMed]

46. Han, B.; Logsdon, C.D. CCK stimulates mob-1 expression and NF-kappaB activation via protein kinase C and intracellular Ca(2+). *Am. J. Physiol.-Cell Physiol.* 2000, 278, C344–C351. [CrossRef] [PubMed]

47. Lee, E.Y.; Lee, Z.H.; Song, Y.W. CXCL10 and autoimmune diseases. *Autoimmun. Rev.* 2009, 8, 379–383. [CrossRef]

48. Liu, M.; Guo, S.; Stiles, J.K. The emerging role of CXCL10 gene and disease progression in male hepatitis B virus carriers. *Gastroenterology* 2008, 134, 716–726. [CrossRef] [PubMed]
53. Haebeler, H.A.; Kuziel, W.A.; Dieterich, H.J.; Casola, A.; Gatalica, Z.; Garofalo, R.P. Inducible expression of inflammatory chemokines in respiratory syncytial virus-infected mice: Role of MIP-1alpha in lung pathology. J. Virol. 2001, 75, 878–890. [CrossRef]

54. Tripp, R.A.; Jones, L.; Anderson, L.J. Respiratory syncytial virus G and/or SH glycoproteins modify CC and CXC chemokine mRNA expression in the BALB/c mouse. J. Virol. 2000, 74, 6227–6229. [CrossRef]

55. Schneider, D.; Ganesan, S.; Comstock, A.T.; Meldrum, C.A.; Mahidhara, R.; Goldsmith, A.M.; Curtis, J.L.; Martinez, F.J.; Hershenson, M.B.; Sajjan, U. Increased cytokine response of rhinovirus-infected airway epithelial cells in chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. 2010, 182, 332–340. [CrossRef]

56. Mihm, S.; Schwayer, S.; Ramadori, G. Expression of the chemokine IP-10 correlates with the accumulation of hepatitis IFN-gamma and IL-18 mRNA in chronic hepatitis C but not in hepatitis B. J. Med. Virol. 2003, 70, 562–570. [CrossRef]

57. Mahanty, S.; Gupta, M.; Paragas, J.; Bray, M.; Ahmed, R.; Rollin, P.E. Protection from lethal infection is determined by innate immune responses in a mouse model of Ebola virus infection. Virology 2003, 312, 415–424. [CrossRef]

58. Nightingale, Z.D.; Patkar, C.; Rothman, A.L. Viral replication and paracrine effects result in distinct, functional responses of dendritic cells following infection with dengue 2 virus. J. Leukoc. Biol. 2008, 84, 1028–1038. [CrossRef] [PubMed]

59. Warke, R.V.; Becerra, A.; zawadzka, A.; Schmidt, D.J.; Martin, K.J.; Giaya, K.; Dinsmore, J.H.; Woda, M.; Hendricks, G.; Levine, T.; et al. Efficient dengue virus (DENV) infection of human muscle satellite cells upregulates type I interferon response genes and differentially modulates MHC I expression on bystander and DENV-infected cells. J. Gen. Virol. 2008, 89, 1605–1615. [CrossRef] [PubMed]

60. Covalada, L.; Fuller, F.J.; Payne, S.L. EIAV S2 enhances pro-inflammatory cytokine and chemokine response in infected macrophages. Virology 2010, 397, 217–223. [CrossRef]

61. Glass, W.G.; Subbarao, K.; Murphy, B.; Murphy, P.M. Mechanisms of host defense following severe acute respiratory syndrome-coronavirus (SARS-CoV) pulmonary infection of mice. J. Immunol. 2004, 173, 4030–4039. [CrossRef]

62. Tsunoda, I.; Lane, T.E.; Blackett, K.; Fujinami, R.S. Distinct roles for IP-10/CXCL10 in three animal models, Théiler’s virus infection, EAE, and MHV infection, for multiple sclerosis: Implication of differing roles for IP-10. Mult. Scler. 2004, 10, 26–34. [CrossRef] [PubMed]

63. Christensen, J.E.; de Lemos, C.; Moos, T.; Christensen, J.P.; Thomsen, A.R. CXCL10 is the key ligand for CXCR3 on CD8+ effector T cells involved in immune surveillance of the lymphocytic choriomeningitis virus-infected central nervous system. J. Immunol. 2006, 176, 4235–4243. [CrossRef] [PubMed]

64. Stiles, L.N.; Hosking, M.P.; Edwards, R.A.; Strieuter, R.M.; Lane, T.E. Differential roles for CXCR3 in CD4+ and CD8+ T cell trafficking following viral infection of the CNS. Eur. J. Immunol. 2006, 36, 613–622. [CrossRef] [PubMed]

65. De Lemos, C.; Christensen, J.E.; Nansen, A.; Moos, T.; Lu, B.; Gerard, C.; Christensen, J.P.; Thomsen, A.R. Opposing effects of CXCR3 and CCR5 deficiency on CD8+ T cell-mediated inflammation in the central nervous system of virus-infected mice. J. Immunol. 2005, 175, 1767–1775. [CrossRef]

66. Li, H.; Gang, Z.; Yuling, H.; Luokun, X.; Jie, X.; Hao, L.; Li, W.; Chunsong, H.; Junyan, L.; Mingshen, J.; et al. Different neurotropic pathogens elicit neurotoxic CCR9-or neurosupportive CXCR3-expressing microglia. J. Immunol. 2006, 177, 3644–3656. [CrossRef]

67. Gandhi, K.S.; McKay, F.C.; Diefenbach, E.; Crozett, B.; Schibeci, S.D.; Heard, R.N.; Stewart, G.J.; Booth, D.R.; Arthur, J.W. Novel approaches to detect serum biomarkers for clinical response to interferon-β treatment in multiple sclerosis. PLoS ONE 2010, 5, e10484. [CrossRef]

68. Treacy, O.; Ryan, A.E.; Heinzl, T.; O’Flynn, L.; Cregg, M.; Odoardi, F.; Lohan, P.; O’Brien, T.; Nosov, M.; et al. Adenoviral transduction of mesenchymal stem cells: In vitro responses and in vivo immune responses after cell transplantation. PLoS ONE 2012, 7, e42662. [CrossRef]

69. Rubin, S.M. Management of multiple sclerosis: A overview. Dis. Month 2013, 59, 253–260. [CrossRef]

70. Iwakura, Y.; Ishigame, H. The IL-23/IL-17 axis in inflammation. J. Clin. Investig. 2006, 116, 1218–1222. [CrossRef]

71. Kakimi, K.; Lane, T.E.; Wieland, S.; Asensio, V.C.; Campbell, I.L.; Chisari, F.V.; Guidotti, L.G. Blocking chemokine responsive of rhinovirus-infected airway epithelial cells in chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. 2010, 182, 332–340. [CrossRef]

72. Loetscher, M.; Gerber, B.; Loetscher, P.; Jones, L.; Bruegger, O.; Baggiolini, M.; Moser, B. Chemokine receptor specific for IP10 and mig: Structure, function, and expression in activated T-lymphocytes. J. Immunol. 1999, 162, 415–424. [CrossRef] [PubMed]

73. Arai, K.; Liu, Z.X.; Lane, T.; Dennert, G. IP-10 and Mig facilitate accumulation of T cells in the virus-infected liver. Cell. Immunol. 2002, 219, 48–56. [CrossRef]

74. Maghazachi, A.A.; Skålhegg, B.S.; Rolstad, B.; Al-Aoukaty, A. Interferon-inducible protein-10 and lymphotactin induce the chemotaxis and mobilization of intracellular calcium in natural killer cells through pertussis toxin-sensitive and-insensitive heterotrimeric G-proteins. FASEB J. 1997, 11, 765–774. [CrossRef] [PubMed]

75. Mahalingam, S.; Farber, J.M.; Karupiah, G. The interferon-inducible chemokines MuMig and Crg-2 exhibit antiviral activity In vivo. J. Virol. 1999, 73, 1479–1491. [CrossRef] [PubMed]

76. Cole, A.M.; Ganz, T.; Liese, A.M.; Burdick, M.D.; Liu, L.; Strieuter, R.M. Cutting edge: IFN-inducible ELR-CXC chemokines display defensin-like antimicrobial activity. J. Immunol. 2001, 167, 623–627. [CrossRef] [PubMed]
77. Chen, J.P.; Lu, H.L.; Lai, S.L.; Campanella, G.S.; Sung, J.M.; Lu, M.Y.; Wu-Hsieh, B.A.; Lin, Y.L.; Lane, T.E.; Luster, A.D.; et al. Dengue virus induces expression of CXC chemokine ligand 10/IFN-gamma-inducible protein 10, which competitively inhibits viral binding to cell surface heparan sulfate. *J. Immunol.* 2006, 177, 3185–3192. [CrossRef] [PubMed]

78. Yuan, J.; Liu, Z.; Lim, T.; Zhang, H.; He, J.; Walker, E.; Shier, C.; Wang, Y.; Su, Y.; Salì, A.; et al. CXCL10 inhibits viral replication through recruitment of natural killer cells in coxsackievirus B3-induced myocarditis. *Circ. Res.* 2009, 104, 628–638. [CrossRef] [PubMed]

79. Lombardi, A.; Cantini, G.; Mello, T.; Francalanci, M.; Gelmini, S.; Cosmi, L.; Santarlasci, V.; Degl’Innocenti, S.; Luciani, P.; Deledda, C.; et al. Molecular mechanisms underlying the pro-inflammatory synergistic effect of tumor necrosis factor alpha and interferon gamma in human microvascular endothelium. *Europ. J. Cell Biol.* 2009, 88, 731–742. [CrossRef]

80. Dhillon, N.K.; Peng, F.; Ransohoff, R.M.; Buch, S. PDGF synergistically enhances IFN-γ-induced expression of CXCL10 in blood-derived macrophages: Implications for HIV dementia. *J. Immunol.* 2007, 179, 2722. [CrossRef]

81. Hardaker, E.L.; Bacon, A.M.; Carlson, K.; Roshak, A.K.; Foley, J.J.; Schmidt, D.B.; Buckley, P.T.; Comegys, M.; Panetttieri, R.A., Jr.; Sara, H.M.; et al. Regulation of TNF-alpha- and IFN-gamma-induced CXCL10 expression: Participation of the airway smooth muscle in the pulmonary inflammatory response in chronic obstructive pulmonary disease. *FASEB J.* 2004, 18, 191–193. [CrossRef]

82. Kanda, N.; Watanabe, S. Substance P enhances the production of interferon-induced protein of 10 kDa by human keratinocytes in synergy with interferon gamma. *J. Invest. Dermatol.* 2002, 119, 1290–1297. [CrossRef] [PubMed]

83. Loos, T.; Dekeyzer, L.; Struyf, S.; Schutyser, E.; Gijsbers, K.; Gouwy, M.; Fraeyman, A.; Put, W.; Ronsse, J.; Grillet, B.; et al. TLR ligands and cytokines induce CXC3 ligands in endothelial cells: Enhanced CXCL9 in autoimmune arthritis. *Lab. Invest.* 2006, 86, 902–916. [CrossRef] [PubMed]

84. Brentano, F.; Schorr, O.; Gay, R.E.; Gay, S.; Kyburz, D. RNA released from necrotic synovial fluid cells activates rheumatoid arthritis synovial fibroblasts via Toll-like receptor 3. *Arthritis Rheum.* 2005, 52, 2656–2665. [CrossRef] [PubMed]

85. Cheng, G.; Nazar, A.S.; Shin, H.S.; Vanguri, P.; Shin, M.L. IP-10 gene transcription by virus in astrocytes requires cooperation of ISRE with adjacent kappaB site but not IRF-1 or viral transcription. *J. Interferon Cytokine Res.* 1998, 18, 987–997. [CrossRef] [PubMed]

86. Lebre, M.C.; van der Aar, A.M.; van Baarsen, L.; van Capel, T.M.; Schuitemaker, J.H.; Kapsenberg, M.L.; de Jong, E.C. Human keratinocytes express functional Toll-like receptor 3, 4, 5, and 9. *J. Investig. Dermatol.* 2007, 127, 331–341. [CrossRef] [PubMed]

87. Morris, G.E.; Parker, L.C.; Ward, J.R.; Jones, E.C.; Whyte, M.K.; Brightling, C.E.; Bradding, P.; Dower, S.K.; Sabroe, I. Cooperative molecular and cellular networks regulate Toll-like receptor-dependent inflammatory responses. *FASEB J.* 2006, 20, 2153–2155. [CrossRef]

88. Taima, K.; Imaizumi, T.; Yamashita, K.; Ishikawa, A.; Fujita, T.; Yoshida, H.; Takanashi, S.; Okumura, K.; Satoh, K. Expression of IP-10/CXCL10 is upregulated by double-stranded RNA in BEAS-2B bronchial epithelial cells. *Respiration* 2006, 73, 360–364. [CrossRef]

89. Magjumer, S.; Zhou, L.Z.; Chaturvedi, P.; Babcock, G.; Aras, S.; Ransohoff, R.M. p48/STAT-1alpha-containing complexes play a predominant role in induction of IFN-gamma-inducible protein, 10 kDa (IP-10) by IFN-gamma alone or in synergy with TNF-alpha. *J. Immunol.* 1998, 161, 4736–4744.

90. Oslund, K.L.; Zhou, X.; Lee, B.; Zhu, L.; Duong, T.; Shih, R.; Baumgart, N.; Hung, L.-Y.; Wu, R.; Chen, Y. Synergistic Up-regulation of CXCL10 by Virus and IFN-γ in Human Airway Epithelial Cells. *PloS ONE* 2014, 9, e100978. [CrossRef]

91. Carpentier, P.A.; Williams, B.R.; Miller, S.D. Distinct roles of protein kinase R and toll-like receptor 3 in the activation of astrocytes by viral stimuli. *Glia* 2007, 55, 239–252. [CrossRef]

92. Imaizumi, T.; Kumagai, M.; Taima, K.; Fujita, T.; Yoshida, H.; Satoh, K. Involvement of retinoic acid-inducible gene-I in the interferon gamma inducible protein 10 (IP-10) expression induced by polytropic murine retroviruses Map to separate regions of the viral envelope gene. *J. Virol.* 2001, 75, 2048–2056. [CrossRef]

93. Berghäll, H.; Särn, J.; Sarkanen, J.; Julkunen, I.; Fisher, P.B.; Vainionpää, R.; Matikainen, S. The interferon-inducible RNA helicase, mda-5, is involved in measles virus-induced expression of antiviral cytokines. *Microbes Infect.* 2006, 8, 2138–2144. [CrossRef]

94. Chen, J.; Subbarao, K. The immunobiology of SARS*. *Annu. Rev. Immunol.* 2007, 25, 443–472. [CrossRef] [PubMed]

95. Hsieh, Y.H.; Chen, C.W.; Schmitz, S.F.; King, C.C.; Chen, W.J.; Wu, Y.C.; Ho, M.S. Candidate genes associated with susceptibility for SARS-coronavirus. *Bull. Math. Biol.* 2010, 72, 122–132. [CrossRef]

96. Sgadari, C.; Angiolillo, A.L.; Cherney, B.W.; Pike, S.E.; Farber, J.M.; Koniaris, L.G.; Vanguri, P.; Burd, P.R.; Sheik, N.; Gupta, G.; et al. Interferon-inducible protein-10 identified as a mediator of tumor necrosis in vivo. *Proc. Natl. Acad. Sci. USA* 1996, 93, 13791–13796. [CrossRef]

97. Lane, B.R.; King, S.R.; Bock, P.J.; Strieter, R.M.; Coffey, M.J.; Markovitz, D.M. The C-C-X chemokine IP-10 stimulates HIV-1 replication. *Virology* 2003, 307, 122–134. [CrossRef]

98. Peterson, K.E.; Robertson, S.J.; Portis, J.L.; Chesebro, B. Differences in cytokine and chemokine responses during neurological disease induced by polytropic murine retroviruses Map to separate regions of the viral envelope gene. *J. Virol.* 2001, 75, 2848–2856. [CrossRef]
100. Lagging, M.; Romero, A.I.; Westin, J.; Norkrans, G.; Dhillon, A.P.; Pawlotsky, J.-M.; Zeuzem, S.; von Wagner, M.; Negro, F.; Schalm, S.W.; et al. IP-10 predicts viral response and therapeutic outcome in difficult-to-treat patients with HCV genotype 1 infection. *Hepatology* 2006, 44, 1671–1677. [CrossRef]

101. Stylianou, E.; Aukrust, P.; Bendtzen, K.; Müller, F.; Froiland, S.S. Interferons and interferon (IFN)-inducible protein 10 during highly active anti-retroviral therapy (HAART)-possible immunosuppressive role of IFN-alpha in HIV infection. *Clin. Exp. Immunol.* 2000, 119, 479–485. [CrossRef]

102. Lam, C.W.; Chan, M.H.; Wong, C.K.; Lam, C.W.; Wu, A.K.; Ip, W.K.; Lee, N.L.; Chan, I.H.; Lit, L.C.; Hui, D.S.; Chan, M.H.; Chung, S.S.; et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. *Clin. Exp. Immunol.* 2004, 136, 95–103. [CrossRef]

103. Wong, C.K.; Lam, C.W.; Wu, A.K.; Ip, W.K.; Lee, N.L.; Chan, I.H.; Lit, L.C.; Hui, D.S.; Chan, M.H.; Chung, S.S.; et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. *Clin. Exp. Immunol.* 2004, 136, 95–103. [CrossRef]

104. Ozga, A.J.; Chow, M.T.; Lopes, M.E.; Servis, R.L.; Di Pilato, M.; Dehio, P.; Lian, J.; Mempel, T.R.; Luster, A.D. CXCL10 chemokine regulates heterogeneity of the CD8+ T cell response and viral set point during chronic infection. *Immunity* 2022, 55, 82–97.e88. [CrossRef] [PubMed]

105. Kang, W.; Shin, E.C. Clinical implications of chemokines in acute and chronic hepatitis C virus infection. *Yonsei Med. J.* 2011, 52, 871–878. [CrossRef] [PubMed]

106. Zeremski, M.; Petrovic, L.M.; Talal, A.H. The role of chemokines as inflammatory mediators in chronic hepatitis C virus infection. *J. Viral Hepat.* 2007, 14, 675–687. [CrossRef] [PubMed]

107. Sung, P.S.; Hong, S.-H.; Lee, J.; Park, S.-H.; Yoon, S.K.; Chung, W.J.; Shin, E.-C. CXCL10 is produced in hepatitis A virus-infected hepatocytes in an IFN-dependent manner. *J. Immunol.* 2007, 178, 6387. [CrossRef] [PubMed]

108. Kauffman, J.; Wagoner, J.; Lovelace, E.S.; Thirstrup, D.; Mohar, I.; Smith, W.; Giugliano, S.; Li, K.; Crispe, I.N.; Rosen, H.R.; et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. *Clin. Exp. Immunol.* 2004, 136, 95–103. [CrossRef]

109. Brownell, J.; Bruckner, J.; Wagoner, J.; Ip, W.K.; Lee, N.L.; Hui, D.S.; Chan, M.H.; Chung, S.S.; et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. *Clin. Exp. Immunol.* 2004, 136, 95–103. [CrossRef]

110. Brownell, J.; Wagoner, J.; Thomas, E.; Loo, Y.M.; Gale, M., Jr.; Liang, T.J.; Polyak, S.J. Direct, interferon-independent, parallel pathways to CXCL10 induction in HCV-infected hepatocytes. *J. Clin. Investig.* 2007, 119, 1582–1590. [CrossRef] [PubMed]

111. Curbishley, S.M.; Eksteen, B.; Gladue, R.P.; Lalor, P.; Adams, D.H. CXCR3 activation promotes lymphocyte transendothelial migration across human hepatic endothelium under fluid flow. *Am. J. Pathol.* 2005, 167, 887–899. [CrossRef] [PubMed]

112. Harvey, C.E.; Post, J.J.; Palladini, P.; Freeman, A.J.; Ffrench, R.A.; Kumar, R.K.; Marinos, G.; Lloyd, A.R. Expression of the chemokine IP-10 (CXCL10) by hepatocytes in chronic hepatitis C virus infection correlates with histological severity and lobular inflammation. *J. Hepatol.* 2017, 63, 564–570. [CrossRef] [PubMed]

113. Helbig, K.J.; Ruszkiewicz, A.; Semendric, L.; Harley, H.A.J.; McColl, S.R.; Beard, M.R. Expression of the CXCR3 ligand I-TAC by hepatocytes in chronic hepatitis C and its correlation with hepatic inflammation. *Hepatology* 2004, 39, 1220–1229. [CrossRef] [PubMed]

114. Harvey, C.E.; Post, J.J.; Palladini, P.; Freeman, A.J.; Ffrench, R.A.; Kumar, R.K.; Marinos, G.; Lloyd, A.R. Expression of the chemokine IP-10 (CXCL10) by hepatocytes in chronic hepatitis C virus infection correlates with histological severity and lobular inflammation. *J. Leukoc. Biol.* 2004, 76, 564–569. [CrossRef] [PubMed]

115. Harvey, C.E.; Post, J.J.; Palladini, P.; Freeman, A.J.; Ffrench, R.A.; Kumar, R.K.; Marinos, G.; Lloyd, A.R. Expression of the chemokine IP-10 (CXCL10) by hepatocytes in chronic hepatitis C virus infection correlates with histological severity and lobular inflammation. *J. Leukoc. Biol.* 2004, 76, 564–569. [CrossRef] [PubMed]

116. Harvey, C.E.; Post, J.J.; Palladini, P.; Freeman, A.J.; Ffrench, R.A.; Kumar, R.K.; Marinos, G.; Lloyd, A.R. Expression of the chemokine IP-10 (CXCL10) by hepatocytes in chronic hepatitis C virus infection correlates with histological severity and lobular inflammation. *J. Leukoc. Biol.* 2004, 76, 564–569. [CrossRef] [PubMed]

117. Yin, X.; Li, X.; Ambarder, C.; Hu, Z.; Lhomme, S.; Feng, Z. Hepatitis E virus persists in the presence of type III interferon response. *PLoS Pathog.* 2017, 13, e1006417. [CrossRef] [PubMed]

118. Sayed, I.M.; Verbhoey, L.; Cocquerel, L.; Abravanel, F.; Foquet, L.; Montpellier, C.; Debing, Y.; Farhoudi, A.; Wychowski, C.; Dubuisson, J.; et al. Study of hepatitis E virus infection of genotype 1 and 3 in mice with humanised liver. *Gut* 2017, 66, 920–929. [CrossRef] [PubMed]

119. Marion, O.; Lhomme, S.; Nayrac, M.; Dubois, M.; Pucelle, M.; Requena, M.; Migueres, M.; Abravanel, F.; Peron, J.M.; Carrere, N.; et al. Hepatitis E virus replication in human intestinal cells. *Gut* 2020, 69, 901. [CrossRef] [PubMed]

120. Devhare, P.; Madiyal, M.; Mukhopadhyay, C.; Shetty, S.; Shastry, S. Interplay between Hepatitis E Virus and Host Cell Pattern Recognition Receptors. *Int. J. Mol. Sci.* 2021, 22, 9259. [CrossRef] [PubMed]

121. Peeters, M.; Schenk, J.; De Somer, T.; Roskams, T.; Locus, T.; Klamper, S.; Subissi, L.; Stärkel, P.; Talal, A.H. Intrahepatic CXCR3-associated chemokines correlate with viral set point during chronic infection. *Hepatology* 2019; 70, 1617–1625. [CrossRef] [PubMed]
123. Larrubia, J.R.; Benito-Martinez, S.; Calvino, M.; Sanz-de-Villalobos, E.; Parra-Cid, T. Role of chemokines and their receptors in viral persistence and liver damage during chronic hepatitis C virus infection. *World J. Gastroenterol.* 2008, 14, 7149–7159. [CrossRef] [PubMed]

124. Skinner, D.; Marro, B.S.; Lane, T.E. Chemokine CXCL10 and coronavirus-induced neurologic disease. *Viral Immunol.* 2019, 32, 25–37. [CrossRef] [PubMed]

125. Hayney, M.S.; Henriquez, K.M.; Barnett, J.H.; Ewers, T.; Champion, H.M.; Flannery, S.; Barrett, B. Serum IFN-γ-induced protein 10 (IP-10) as a biomarker for severity of acute respiratory infection in healthy adults. *J. Clin. Virol.* 2017, 90, 32–37. [CrossRef] [PubMed]

126. Almansa, R.; Sanchez-Garcia, M.; Herrera, A.; Calzada, S.; Roig, V.; Barbado, J.; Rico, L.; Bobillo, F.; Eiros, J.M.; Iglesias, V.; et al. Host response cytokine signatures in viral and nonviral acute exacerbations of chronic obstructive pulmonary disease. *J. Interferon Cytokine Res.* 2011, 31, 409–413. [CrossRef]

127. Quint, J.K.; Donaldson, G.C.; Goldring, J.J.; Baghai-Ravary, R.; Hurst, J.R.; Wedzicha, J.A. Serum IP-10 as a biomarker of human rhinovirus infection at exacerbation of COPD. *Chest* 2010, 137, 812–822. [CrossRef]

128. Chen, J.; Lau, Y.F.; Lamirande, E.W.; Paddock, C.D.; Bartlett, J.H.; Zaki, S.R.; Subbarao, K. Cellular immune responses to severe acute respiratory syndrome coronavirus (SARS-CoV) infection in senescent BALB/c mice: CD4+ T cells are important in control of SARS-CoV infection. *J. Virol.* 2010, 84, 1289–1301. [CrossRef]

129. Cameron, M.J.; Ran, L.; Xu, L.; Danesh, A.; Bermejo-Martin, J.F.; Cameron, C.M.; Muller, M.P.; Gold, W.L.; Richardson, S.E.; Poutanen, S.M.; et al. Interferon-mediated immunopathological events are associated with atypical innate and adaptive immune responses in patients with severe acute respiratory syndrome. *J. Virol.* 2007, 81, 8692–8706. [CrossRef]

130. Tynell, J.; Westenius, V.; Rönkkö, E.; Munster, V.J.; Melén, K.; Österlund, P.; Jülkenen, I. Middle East respiratory syndrome coronavirus shows poor replication but significant induction of antiviral responses in human monocyte-derived macrophages and dendritic cells. *J. Gen. Virol.* 2016, 97, 344–355. [CrossRef]

131. Zhou, J.; Chu, H.; Li, C.; Wong, B.H.; Cheng, Z.S.; Poon, V.K.; Sun, T.; Lau, C.C.; Wong, K.K.; Chan, J.Y.; et al. Serum cytokine and chemokine profile in relation to the severity of coronavirus disease 2019 in China. *J. Infect. Dis.* 2020, 222, 746–754. [CrossRef] [PubMed]

132. Elemam, N.M.; Hammoudeh, S.; Salameh, L.; Mahboub, B.; Alsafer, H.; Talaat, I.M.; Habib, P.; Siddiqi, M.; Hassan, K.O.; Al-Assaf, O.Y.; et al. Identifying immunological and clinical predictors of COVID-19 severity and sequelae by mathematical modeling. *Front. Immunol.* 2022, 13, 865845. [CrossRef] [PubMed]

133. Jiang, Y.; Xu, J.; Zhou, C.; Wu, Z.; Zhong, S.; Liu, J.; Luo, W.; Chen, T.; Qin, Q.; Deng, P. Characterization of cytokine/chemokine profiles of severe acute respiratory syndrome. *Am. J. Respir. Crit. Care Med.* 2005, 171, 850–857. [CrossRef] [PubMed]

134. Chu, H.; Chan, J.F.; Wang, Y.; Yuen, T.T.; Chai, Y.; Hou, Y.; Shuai, H.; Yang, D.; Hu, B.; Huang, X.; et al. Comparative replication and immune activation profiles of SARS-CoV-2 and SARS-CoV in human lungs: An ex vivo study with implications for the pathogenesis of COVID-19. *Clin. Infect. Dis.* 2020, 71, 1400–1409. [CrossRef] [PubMed]

135. Chi, Y.; Ge, Y.; Wu, B.; Zhang, W.; Wu, T.; Wen, T.; Liu, J.; Guo, X.; Huang, C.; Jiao, Y.; et al. Serum cytokine and chemokine profile in viral persistence and liver damage during chronic hepatitis C virus infection. *World J. Gastroenterol.* 2008, 14, 3036–3043. [CrossRef] [PubMed]

136. Gudowska-Sawczuk, M.; Mroczko, B. What is currently known about the role of CXCL10 in SARS-CoV-2 infection? *Viruses* 2020, 12, 2888. [CrossRef] [PubMed]

137. Lor, K.R.; Benito-Martinez, S.; Calzada, S.; Roig, V.; Barbado, J.; Rico, L.; Bobillo, F.; Eiros, J.M.; Iglesias, V.; et al. Host response cytokine signatures in viral and nonviral acute exacerbations of chronic obstructive pulmonary disease. *J. Interferon Cytokine Res.* 2011, 31, 409–413. [CrossRef]

138. Yang, Y.; Shen, C.; Li, J.; Yuan, J.; Wei, J.; Huang, F.; Wang, F.; Li, G.; Li, Y.; Xing, L.; et al. Plasma IP-10 and MCP-3 levels are highly associated with disease severity and predict the progression of COVID-19. *J. Allergy Clin. Immunol.* 2020, 146, 119–127.e114. [CrossRef]

139. Altara, R.; Manca, M.; Brandão, R.D.; Zeidan, A.; Booz, G.W.; Zouein, F.A. Emerging importance of chemokine receptor CXCR3 and its ligands in cardiovascular diseases. *Clin. Sci.* 2016, 130, 463–478. [CrossRef]

140. Huang, C.; Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Y.; Zhang, L.; Fan, G.; Xu, J.; Gu, X.; et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020, 395, 497–506. [CrossRef]

141. Lorè, K.; De Lorenzo, R.; Rancoita, P.M.V.; Cugnata, F.; Agresti, A.; Benedetti, F.; Bianchi, M.E.; Bonini, C.; Capobianco, A.; Conte, C.; et al. CXCL10 levels at hospital admission predict COVID-19 outcome: Hierarchical assessment of 53 putative inflammatory biomarkers in an observational study. *Mol. Med.* 2021, 27, 129. [CrossRef]

142. Wang, J.; Xu, Y.; Zhang, X.; Wang, S.; Peng, Z.; Guo, J.; Jiang, H.; Liu, J.; Xie, Y.; Wang, J.; et al. Leptin correlates with monocytes activation and severe condition in COVID-19 patients. *J. Leukoc. Biol.* 2021, 110, 9–20. [CrossRef] [PubMed]

143. Kwon, J.S.; Kim, J.Y.; Kim, M.C.; Park, S.Y.; Kim, B.N.; Bae, S.; Cha, H.H.; Jung, J.; Kim, M.J.; Lee, M.J.; et al. Factors of severity in patients with COVID-19: Cytokine/chemokine concentrations, viral load, and antibody responses. *Am. J. Trop. Med. Hyg.* 2020, 103, 2412–2418. [CrossRef] [PubMed]

144. Xu, Z.S.; Shu, T.; Kang, L.; Wu, D.; Zhou, X.; Liao, B.W.; Sun, X.L.; Zhou, X.; Wang, Y.Y. Temporal profiling of plasma cytokines, chemokines and growth factors from mild, severe and fatal COVID-19 patients. *Signal Transduct. Target. Ther.* 2020, 5, 100. [CrossRef] [PubMed]
Viruses 2022, 14, 2445
169. Yoshio, S.; Mano, Y.; Doi, H.; Shoji, H.; Shimakage, T.; Sakamoto, Y.; Kawai, H.; Matsuda, M.; Mori, T.; Osawa, Y.; et al. Cytokine and chemokine signatures associated with hepatitis B surface antigen loss in hepatitis B patients. JCI Insight 2018, 3, 122268. [CrossRef]

170. Kakimi, K.; Lane, T.E.; Chisari, F.V.; Guidotti, L.G. Cutting edge: Inhibition of hepatitis B virus replication by activated NK T cells does not require inflammatory cell recruitment to the liver. J. Immunol. 2001, 167, 6701–6705. [CrossRef]

171. Zhou, Y.; Wang, S.; Ma, J.-W.; Lei, Z.; Zhu, H.-F.; Duan, M.; Guo, Y.; Jiang, L.; Zhao, M.; et al. Hepatitis B virus protein X-induced expression of the CXC chemokine IP-10 is mediated through activation of NF-kB and increases migration of leukocytes. J. Biol. Chem. 2010, 285, 12159–12166. [CrossRef]

172. Sitia, G.; Isogawa, M.; Kakimi, K.; Wieland, S.F.; Chisari, F.V.; Guidotti, L.G. Depletion of neutrophils blocks the recruitment of antigen-nonspecific cells into the liver without affecting the antiviral activity of hepatitis B virus-specific cytotoxic T lymphocytes. Proc. Natl. Acad. Sci. USA 2002, 99, 13717–13722. [CrossRef] [PubMed]

173. Singh, K.P.; Zerbato, J.M.; Zhao, W.; Braat, S.; Deleage, C.; Tennakoon, G.S.; Mason, H.; Dantanarayana, A.; Rhodes, A.; Rhodes, J.W.; et al. Intrahepatic CXCL10 is strongly associated with liver fibrosis in HIV-Hepatitis B co-infection. PLoS Pathog. 2020, 16, e1008744. [CrossRef] [PubMed]

174. Wuest, T.R.; Carr, D.J. Dysregulation of CXCR3 signaling due to CXCL10 deficiency impairs the antiviral response to herpes simplex virus 1 infection. J. Immunol. 2008, 181, 7985. [CrossRef]

175. Srivastava, R.; Khan, A.A.; Chilukuri, S.; Syed, S.A.; Tran, T.T.; Furness, J.; Bahraoui, E.; BenMohamed, L. CXCL10/CXCR3-dependent mobilization of herpes simplex virus-specific CD8+ T(EM) and CD8+ T(RM) cells within infected tissues allows efficient protection against recurrent herpesvirus infection and disease. J. Virol. 2017, 91, e00278–17. [CrossRef] [PubMed]

176. Carr, D.J.; Tomanek, L. Herpes simplex virus and the chemokines that mediate the inflammation. Curr. Top. Microbiol. Immunol. 2006, 303, 47–65. [CrossRef]

177. Wickham, S.; Lu, B.; Ash, J.; Carr, D.J. Chemokine receptor deficiency is associated with increased chemokine expression in the peripheral and central nervous systems and increased resistance to herpetic encephalitis. J. Neuroimmunol. 2005, 162, 51–59. [CrossRef]

178. Barbi, J.; Oghumu, S.; Lezama-Davila, C.M.; Satoskar, A.R. IFN-gamma and STAT1 are required for efficient induction of CXC chemokine receptor 3 (CXCR3) on CD4+ but not CD8+ T cells. Blood 2007, 110, 2215–2216. [CrossRef]

179. Cook, W.J.; Kramer, M.F.; Walker, R.M.; Burwell, T.J.; Holman, H.A.; Coen, D.M.; Knipe, D.M. Persistent expression of chemokine ligand 10 (CXCL10/IP-10) and CXC chemokine receptor 4 (CXCR4) in human microbial meningitis from herpes simplex encephalitis. Proc. Natl. Acad. Sci. USA 2002, 99, 13717–13722. [CrossRef] [PubMed]

180. O’Garra, A.; McEvoy, L.M.; Zlotnik, A. T-cell subsets: Chemokine receptors guide the way. Curr. Biol. 1998, 8, R646–R649. [CrossRef]

181. Sin, J.; Kim, J.J.; Pachuk, C.; Satishchandran, C.; Weaver, D.B. DNA vaccines encoding interleukin-8 and RANTES enhance antigen-specific Th1-type CD4+ T-cell-mediated protective immunity against herpes simplex virus type 2 in vivo. J. Virol. 2000, 74, 11173–11180. [CrossRef]

182. Thapa, M.; Carr Daniel, J.J. Herpes simplex virus type 2-induced mortality following genital infection is blocked by anti-tumor necrosis factor alpha antibody in CXCL10-deficient mice. J. Virol. 2008, 82, 10295–10301. [CrossRef] [PubMed]

183. Nakanishi, Y.; Lu, B.; Gerard, C.; Iwasaki, A. CD8+ T lymphocyte mobilization to virus-infected tissue requires CD4+ T-cell help. Nature 2009, 462, 510–513. [CrossRef]

184. Thapa, M.; Welner, R.S.; Pelayo, R.; Carr, D.J. CXCL9 and CXCL10 expression are critical for control of genital herpes simplex virus type 2 infection through mobilization of HSV-specific CTL and NK cells to the nervous system. J. Immunol. 2008, 180, 1098. [CrossRef]

185. Lind, L.; Studahl, M.; Persson Berg, L.; Eriksson, K. CXCL11 production in cerebrospinal fluid distinguishes herpes simplex virus 1 infection. J. Neuroinflamm. 2017, 14, 134. [CrossRef] [PubMed]

186. Zhang, M.; Deng, X.; Guan, X.; Geng, L.; Fu, M.; Zhang, B.; Chen, R.; Hu, H.; Hu, K.; Zhang, D.; et al. Herpes simplex virus type 2 infection-induced expression of CXCR3 ligands promotes CD4+ T cell migration and is regulated by the viral immediate-early protein ICP4. Front. Immunol. 2018, 9, 32–57. [CrossRef] [PubMed]

187. Pol, J.G.; Workenhe, S.T.; Konda, P.; Gujar, S.; Kroemer, G. Cytokines in oncolytic virotherapy. Cytokine Growth Factor Rev. 2020, 56, 4–27. [CrossRef] [PubMed]

188. Abraham, R.; Mudalair, P.; Padmanabhan, A.; Sreekumar, E. Induction of Cytopathogenicity in Human Glioblastoma Cells by Chikungunya Virus. PLoS ONE 2013, 8, e75884. [CrossRef]

189. Carew, J.S.; Espitia, C.M.; Zhao, W.; Mita, M.M.; Mita, A.C.; Nawrocki, S.T. Oncolytic reovirus inhibits angiogenesis through induction of CXCL10/IP-10 and abrogation of HIF activity in soft tissue sarcomas. Oncotarget 2017, 8, 49. [CrossRef]

190. Fu, X.; Rivera, A.; Tao, L.; Zhang, X. An HSV-2 based oncolytic virus can function as an attractant to guide migration of adoptively transferred T cells to tumor sites. Oncotarget 2014, 6, 2. [CrossRef]

191. Eckert, E.C.; Nace, R.A.; Tonne, J.M.; Evgin, L.; Vile, R.G.; Russell, S.J. Generation of a Tumor-Specific Chemokine Gradient Using Oncolytic Vesicular Stomatitis Virus Encoding CXCL9. Mol. Therapy-Oncol. 2020, 16, 63–74. [CrossRef]

192. Li, X.; Lu, M.; Yuan, M.; Ye, J.; Zhang, W.; Xu, L.; Wu, X.; Hui, B.; Yang, Y.; Wei, B.; et al. CXCL10-armed oncolytic adenovirus promotes tumor-infiltrating T-cell chemotaxis to enhance anti-PD-1 therapy. Oncoimmunology 2022, 11, 2118210. [CrossRef] [PubMed]
193. Ji, Q.; Wu, Y.; Albers, A.; Fang, M.; Qian, X. Strategies for Advanced Oncolytic Virotherapy: Current Technology Innovations and Clinical Approaches. *Pharmaceutics* 2022, 14, 1811. [CrossRef] [PubMed]

194. Champion, B.R.; Besneux, M.; Patsalidou, M.; Silva, A.; Zonca, M.; Marino, N.; Genova, G.D.; Illingworth, S.; Fedele, S.; Slater, L.; et al. Abstract 5013: NG-641: An oncolytic T-SiGn virus targeting cancer-associated fibroblasts in the stromal microenvironment of human carcinomas. *Cancer Res.* 2019, 79, 5013. [CrossRef]