Review



# Changes and Functions of CX3CL1 in Viral Infection and Associated Diseases

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*Review*

# Changes and Functions of CX3CL1 in Viral Infection and Associated Diseases

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**Abstract:** CX3CL1, also named fractalkine or neurotactin, the only known member of the CX3C chemokine family that can chemoattract several immune cells. CX3CL1 exists in both membrane-anchored and soluble forms, each mediating distinct biological activities. CX3CL1 signals are transmitted through its unique receptor, CX3CR1, primarily expressed in microglia of central nervous system (CNS). In the CNS, CX3CL1 acts as a regulator of microglia activation in response to brain disorders or inflammation. Recently, there has been a growing interest in the roles of CX3CL1 in regulating cell adhesion, chemotaxis, and host immune response in viral infection. Here, we provide a comprehensive review of the changes and function of CX3CL1 in various viral infections such as human immunodeficiency virus (HIV), SARS-CoV-2, influenza virus and cytomegalovirus (CMV) infection, to highlight the emerging roles of CX3CL1 in viral infection and the associated diseases.

**Keywords:** CX3CL1; CX3CR1; **c**hemokine; viral infection

## 1. Introduction

Viruses give rise to a range of serious diseases that still pose challenges to contemporary medicine in terms of prevention and treatment. This is mainly attributed to the excessive activation of immune cells such as macrophages (Mφs), lymphocytes, and dendritic cells (DCs) via multiple signalling pathways [1]. Chemokines constitute the largest family of cytokines, comprising approximately 50 endogenous chemokines in both humans and mice [2]. Chemokines are highly conserved small polypeptides consisting of 70-100 amino acids. They were initially identified by their chemotactic properties towards bone marrow-derived cells. Based on the location of the first two conserved cysteine residues, chemokines are classified into four distinct families: CC, CXC, CX3C, and C subfamilies [3]. C-X3-C motif ligand 1 (CX3CL1) belongs to the CX3C subfamily and possesses the characteristics of both homeostatic chemokines and inflammatory chemokines [4]. It is referred to as fractalkine in humans and neurotactin in mice, respectively, by two distinct research teams [5,6]. CX3CL1 and its receptor CX3CR1 were discovered more than twenty years ago [7], and a large amount of evidence has emerged linking the CX3CL1-CX3CR1 axis to various diseases, such as atherosclerosis [8], allergic diseases [9], neurodegeneration [10] and cancers [11]. In innate immunity during viral infections, the binding of viral RNA to the helicase domains of retinoic acid inducible gene-1 and oligomerisation domain-containing protein-like receptor-3 in myeloid cells activates the pro-inflammatory transcription factor nuclear factor (NF)-κB and the inflammasome [12–14], thereby inducing the release of CX3CL1 [12]. It's worth noting that CX3CL1 is a critical element in the development of virus infection and related diseases, facilitating the migration of immune cells to distant organs [15,16].

CX3CL1 presents in two forms: one is an 80-95 kDa glycoprotein with intracellular and transmembrane domains anchored to the membrane, and the other is cleaved by metalloproteinases

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A Disintegrin And Metalloprotease 10 (ADAM10), ADAM17 or cathepsin S [17], and released into the extracellular space to serve as a chemokine [18,19]. Both membrane-bound CX3CL1 (mCX3CL1) and soluble isoforms of CX3CL1 (sCX3CL1) can bind to CX3CR1 [20]. Compared with other chemokines and cytokines that can interact with various receptors, CX3CL1 binds only to one reported receptor, CX3CR1, to exert its biological effects. In the periphery, CX3CR1 is expressed by natural killer (NK) cells, DCs, monocytes, Mφs, and specific subsets of T cells, while in the central nervous system (CNS), CX3CR1 is mainly expressed by microglia [21]. Since both CX3CL1 and CX3CR1 are expressed in various cells, it is not surprising that the CX3CL1-CX3CR1 axis may play a broader role, including stimulating cell proliferation [22,23] or migration [24,25], participating in angiogenesis [26,27], and apoptosis resistance [28]. Additionally, CX3CL1 can contribute to the recruitment of effector T cells to peripheral tissues and lymphoid organs [29], and participates in adhesion between monocytes and endothelial cells [30].

In this article, we look again at the changes of CX3CL1 and its functional roles. Moreover, we review the accumulated evidence that the interactions of CX3CL1-CX3CR1 mediate significant events in viral infection and associated diseases, especially through the recruitment of immune effector cells from the innate immune system by their chemotactic and adhesive properties.

## 2. CX3CL1 and Its Regulation of Chemotaxis and Adhesion

### *2.1. Structural Characteristics of CX3CL1 and Its Cellular Distribution*

In 1997, CX3CL1, as the sole representative member of the CX3C (delta) subfamily of chemokines, was initially identified and characterized by Bazan et al. [5]. A few weeks later, another research team confirmed the presence of the CX3C subfamily member designated as neurotactin in mice [6]. The human CX3CL1 encoding gene consists of three exons and is located on the long arm of the human chromosome 16q21, in the region of 57372490-57385044, functioning as both a chemoattractant and an adhesion molecule [31,32]. The respective genes are situated on chromosome 8 (8qC5) in the mouse and chromosome 19 (19p12) in the rat [33,34]. The polypeptide structure of CX3CL1 differs from that of other chemokines. It is produced as a motif encompassing three amino acid residues between two cysteine residues, forming disulfide bonds that stabilize the tertiary structure of the molecule [5,6]. The full-length CXC3L1 constitutes a 373-amino-acid type I transmembrane glycoprotein, comprising an extracellular N-terminal domain (aa 1-76), a mucin-like stalk (aa 77-317), a transmembrane alpha-helix (aa 318-336), and a short cytoplasmic tail (aa 337-373) [35,36]. CX3CL1 is expressed at a low level in the liver and kidneys, while at a higher level in the brain, colon, heart, and lungs [5]. It is highly expressed in (Mφs), epithelial cells, DCs, renal mesangial cells, neurons, and smooth muscle cells, and can be induced in fibroblasts, endothelial cells, and astrocytes by several cytokines such as IFN-γ, TNF-α, IL-1β, and TGF-β [37–39].

### *2.2. Functions of Membrane-Anchored CX3CL1*

Recently, the role of the CX3CL1-CX3CR1 axis in inducing the chemotaxis and adhesion of leucocyte populations has been extensively studied by several research groups. The full-length mCX3CL1 functions as an adhesion molecule, promoting the retention of leucocytes to epithelial or endothelial cells through its G protein-coupled, 7-transmembrane domain receptor CX3CR1 [40,41]. The activation of CX3CR1 leads to calcium influx and the modification of the cAMP level, followed by the transduction of downstream signals such as MAPKs and Akt/PKB [42–44]. The glycosylation of the mucin-like stalk and the intracellular domain are essential for the adhesive function of CX3CL1. It is hypothesized that the mucin-like stalk within CX3CL1 is critical for the mechanism of CX3CL1-CX3CR1-mediated cell-cell adhesion [45,46]. Glycosylation ensures the accessibility of CX3CL1 to CX3CR1 buried in the membrane of the counter-adhesive cell, while the intracellular domain anchors CX3CL1 in the cell membrane [47]. It has been reported that CX3CL1 promotes the adhesion of neutrophils, macrophages, $CD8^+$ T cells, $CD4^+$ T cells, and DCs in patients with solitary juvenile polyps and epithelial ovarian cancer [48,49]. In endothelial cells, mCX3CL1 acts as an adhesion molecule that influences neutrophil binding and adhesion, and facilitates the penetration of immune

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cells through the vascular endothelium regardless of the integrin-related mechanism [4,50]. In the experiment of osteoblast binding, the addition of anti-CX3CL1 mAb results in significant inhibition of osteoclast maturation, while the addition of recombinant CX3CL1 does not increase maturation. This indicates the mCX3CL1-mediated adhesion plays an important role in the maturation of osteoclasts [50]. NK cells expressing CX3CR1 efficiently adhered to the full-length CX3CL1, but not to the truncated forms of the chemokine domain or mucin domain, indicating that mCX3CL1 functions as an adhesion molecule in the interaction between NK cells and endothelial cells in endothelial cell injury [51]. Given that mCX3CL1 functions as an adhesion protein to cells expressing CX3CR1, it causes immune system cells to remain on the vascular wall, close to the site of the inflammatory response, allowing these cells to migrate across the endothelium [52–55]. After entering the organization, mCX3CL1 can induces the proliferation of leukocytes like monocytes and $CD16^+$ NK cells. However, there is no CX3CR1 expression in eosinophils and neutrophils, so CX3CL1 does not directly act on these cells [56].

### *2.3. Functions of Soluble CX3CL1*

The mature form of this protein can be cleaved by ADAM10, while its shedding under inflammatory conditions is primarily mediated by ADAM17 [18,19]. Additionally, CX3CL1 cleavage at the cell surface is also mediated by the lysosomal cysteine protease cathepsin S [17] yielding soluble forms that can interact with CX3CR1 and possess chemoattractive activity. In both the physiological and pathological states, sCX3CL1 functions as a chemoattractant for $CX3CR1^+$ cells [57–60]. In peripheral tissues, sCX3CL1 functions as a chemotactic peptide to form a concentration gradient in the extracellular matrix, attracting leukocytes to the sites of inflammation. Meanwhile, mCX3CL1 provides an adhesive function to capture circulating cells expressing CX3CR1 in endothelial cells, resulting in the migration of leukocytes to the tissues [61,62]. For instance, sCX3CL1 can regulate the adhesion and capture of circulating monocytes at the sites of atherogenesis [63]. Studies on the Cigarette smoke and lipopolysaccharide models of acute inflammation in transgenic *Cx3cr1*$^{gfp/gfp}$ mice, as well as human endothelial cells and monocytes, demonstrated that sCX3CL1-mediated $CX3CR1^+$ monocyte adhesion and migration. These studies suggest that sCX3CL1 may fine-tune the CX3CL1-CX3CR1 axis specifically involved in endothelial-monocyte cross-talk and leukocyte recruitment to the alveolar space. Inhibitors of sCX3CL1 signaling could be exploited to reduce lung infection [64].

### *2.4. Regulation Mechanisms of CX3CL1 Expression*

As research continues to deepen, the regulatory cellular mechanisms of CX3CL1/CX3CR1-mediated cell adhesion and migration have been continuously discovered. Once leukocytes undergo transendothelial migration from the lumen of blood vessels to extravascular tissues, a dynamic cascade of molecular events associated with the interactions between leukocytes and endothelial cells will be triggered in both normal physiological and certain pathological conditions [65]. Stimulation of human umbilical arterial and venous endothelial cells with Ang-II increased CX3CL1 expression. Knockdown of *Nox5* with small interfering RNA or pharmacological inhibition of extracellular signal-regulated kinases1/2, p38 mitogen-activated protein kinase, and nuclear factor-κB (NF-κB) also abolished the effect of tumor necrosis factor-$\alpha$ on Ang-II-induced CX3CL1 upregulation and mononuclear cell arrest [66]. Meanwhile, CX3CL1 enhances the function of intercellular adhesion molecule-1 through the CX3CR1/PI3K/Akt/NF-κB signaling pathway, and promotes the metastasis of osteosarcoma [67]. Following adhesion associated with the interaction between CX3CL1 and CX3CR1, leukocytes are capable of enhancing adhesion in a directly selectin- and integrin-independent manner [68], or through synergistic effects with the activation and synthesis of other adhesion molecules [69–71]. In patients with chronic kidney disease, $CD16^+$ monocytes enhance STAT1 and NF-κB p65 phosphorylation of endothelial cells, and upregulate their expression of CX3CL1, IL-1β, CCL, CXCL, ICAM1, and VCAM1. This outlines a mechanism whereby the CX3CR1 dose-dependently modulates monocyte-contact-dependent gene expression in human endothelium, increasing cardiovascular risk [72]. Furthermore, ursodeoxycholic acid-induced suppression of IFN-

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γ and CX3CL1 production attenuates the chemotactic and adhesive abilities of liver-infiltrating T cells in primary biliary cholangitis [73]. Overall, these data indicate that the CX3CL1/ CX3CR1 axis is currently considered a key phenomenon in the pathogenesis of inflammatory diseases.

## 3. CX3CL1 and Its Receptor in Viral Infection and Associated Diseases

### *3.1. CX3CL1 and Its Receptor in HIV Infection*

Human immunodeficiency virus type 1 (HIV-1), which is the causative agent of acquired immunodeficiency syndrome (AIDS), has been discovered for more than four decades [74]. AIDS remains a major infectious disease threat to global public health. In 1998, CX3CR1 was identified as a fusion co-receptor of CX3CL1 and HIV-1 [75]. In patients with the homozygous CX3CR1-I249M280, a variant haplotype of isoleucine-249 and methionine-280, CX3CL1 binding is reduced, and the progression to AIDS is accelerated [15]. Thus, CX3CR1 is a key recessive genetic risk factor for HIV/AIDS [76]. Table 1 listed the changes of CX3CL1/CX3CR1 in various viral infections.

Mariangela Cavarelli et al. disclosed a novel function of $CX3CR1^{+}$ DCs in the early stages of HIV/simian immunodeficiency virus (SIV) transmission. It seemed that $CX3CR1^{+}$ DCs accumulated in the drainage lymph nodes, while Mφs remained in place during the transition from the $CX3CR1^{high}$ phenotype of tissue-resident to the $CX3CR1^{low}$ phenotype of pro-inflammatory [77]. It is suggested that SIV infection can cause a rapid shift from $CX3CR1^{high}$ to $CX3CR1^{low}$ in Mφs in the colonic mucosa of macaques, possibly to identify recently recruited cells in the intestine. During HIV-1/Treponema pallidum co-infection, compared with the healthy control group, the density of CX3CR1 was increased in all three monocyte subsets, the increase in CX3CR1 expression on monocytes indicates the presence of systemic inflammation during HIV-1/ Treponema pallidum co-infection[78].

Ongoing inflammation and associated complications cause an increase in HIV-1-associated neurological diseases (HAND), including HIV-dementia[79,80]. In the CNS, sCX3CL1 dysregulation in the brain was observed during HIV infection [81], CX3CL1 was up-regulated in the brain tissue and cerebrospinal fluid of HAND patients and released in response to proinflammatory stimuli, mainly in neurons, and in co-cultures of astrocytes and HIV-infected Mφs [80,82]. Based on these findings, the mechanism by which the HIV-1 mediates the disruption of the CX3CL1/CX3CR1 axis was investigated. It was found that the expression of CX3CR1 in microglia was inhibited by the HIV-1 Tat protein via the NF-κB-yy1 pathway in microglia, attenuating the functional response of microglia induced by CX3CL1 [83]. In addition, CX3CL1/CX3CR1 may mediate HIV-1 envelope protein gp120 neurotoxicity and suppress gp120-induced apoptosis in hippocampal neurons [84]. Table 1 listed the changes of CX3CL1/CX3CR1 in various viral infections.

**Table 1.** Expression of CX3CL1/CX3CR1 in viral infection and associated diseases.

| Virus | Cell/tissue/ organization | CX3CL1 expression status | CX3CR1 expression status | Ref |
|---|---|---|---|---|
| HIV | Neurons,Monocyte, DCs, Mφs | up | up | [80–82,85–87] |
| SARS-CoV-2 | serum sample | up | | [88,89] |
| Influenza strain (H1N1) | hippocampus | Down | | [90] |
| Influenza strain H5N1 and H9N2 | DF-1 cell line of chicken embryo fibroblasts<br>lung tissues of chicken | up | | [91,92] |
| RSV | human airway epithelial cells<br>and airway ciliated cells | up | up | [93,94] |
| CMV | CMV-specific CD8 or effector | | up | [95] |

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| | | | |
|---|---|---|---|
| HTNV | CD8 T cells nonclassical and intermediate monocyte subsets | up | [96] |
| CVB3 | left ventricle | up | [97] |

DCDCs, dendritic cells; Mφs, macrophages; RSV, Respiratory syncytial virus; CMV, cytomegalovirus; HTNV, hantaan virus; CVB3, Coxsackievirus B3.

The expression and function of CX3CR1 on T lymphocytes in HIV-infected patients have also been investigated. Compared with normal individuals, the frequency of CD8 cells expressing CX3CR1 was increased, and was correlated with disease progression in HIV-infected patients[98]. CX3CR1 was expressed on activated and differentiated CCR7- CD45RA$^{-}$ memory lymphocytes, and served as the main homing receptor. After binding to its ligand CX3CL1, it participated in the specific migratory pattern of late-stage differentiated CD8 cells and regulated the effector function of CD8 lymphocytes during HIV infection[98,99]. Additionally, platelet interactions can modulate the inflammatory function of CX3CR1$^{+}$CD8$^{+}$ T Cells in HIV infection[99]. The role of CX3CL1 in viral infections and related diseases is summarized in Table 2.

**Table 2.** The role of CX3CL1 in viral infection and associated diseases.

| Virus | Roles |
|---|---|
| HIV | A. sCX3CL1 inhibits the apoptosis of hippocampal neurons induced by neurotoxic viral proteins. |
| | B. CX3CL1 is involved in neuronal damage through its interaction with microglia, which secrete proinflammatory cytokines. |
| | C. CX3CL1 promotes the accumulation of DCs in the lymph nodes. |
| SARS-CoV-2 | A. CX3CL1 facilitates recruitment and adhesion of CX3CR1$^{+}$ immune cells to target tissues. |
| | B. levels of CX3CL1 is associated with the duration of illness in severe COVID-19. |
| Influenza strain H1N1 | A. *Cx3cr1*$^{-/-}$ mice showed cell-autonomous microglial neurotoxicity. |
| | B. loss of CX3CL1 may lead to changes in both glial regulation and cognitive function. |
| Influenza strain H5N1 and H9N2 | A. CX3CL1 impedes neuron-microglia interactions, increased inflammation, and microglial activation. |
| | B. CX3CL1 is a chemotactic factor in responses to H5N1 infection in chickens |
| RSV | A. CX3CR1 leads to NF-κB activation and CX3CL1 production, and affects the cellular inflammatory response to RSV infection |
| CMV | Make CMV-specific CD8 T cells and effector CD8 T cells with the ability to migrate to inflamed vascular endothelium |
| HTNV | A. CX3CL1 level is associated with the severity of hemorrhagic fever with renal syndrome in humans |
| CVB3 | A. CX3CR1 plays a cardio-protective role in CVB3-infected mice. |

Based on these studies and the hypothesis that the transmission of HIV-1 infection in humans is caused by CX3CL1 trafficking of infected lymphocytes, the following possible immunological methods for preventing and treating HIV-1/AIDS patients are proposed: developing a canarypox-protein HIV vaccine regimen (ALVAC-HIV plus AIDSVAX B/E), designing and testing CX3CL1 antagonists, HIV-specific neutralizing monoclonal antibodies, and other new immunotherapeutic strategies for HIV-1 infection [99–102].

### *3.2. CX3CL1 and Its Receptor in COVID-19*

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SARS-CoV-2 is the causative agent of coronavirus disease-2019 (COVID-19), which causes severe symptoms of pneumonia [103]. During the stage of COVID-19-associated hyperinflammation, cells are highly activated and produce large amounts of cytokines, chemokines, and other soluble mediators of immune inflammatory responses, commonly referred to as cytokine storms [104,105]. Recently, Selma Rivas-Fuentes et al., have proposed a hypothesis that during SARS-CoV-2 infection, CX3CL1 could be positively regulated in the endothelium and contribute to the perpetuation of a pro-thrombotic loop [106]. Previous studies have demonstrated that CX3CL1 is cleaved in an inflammatory environment [107,108]. During the COVID-19 infection, the levels of CX3CL1 in the serum inflammatory mediators were higher in critical illness patients than those in severe COVID-19 patients. Moreover, the levels of CX3CL1 were associated with the duration of illness in severe COVID-19 [109]. Patients with chronic obstructive pulmonary disease have systemic inflammatory dysregulation driven by several cytokines, including CX3CL1, which are involved in chemokine signaling pathways associated with the response to severe COVID-19 virus infection [89,110,111].

The pathogenesis of immune inflammatory reaction is related to the migration of leukocytes to target tissues, which is driven by chemokines such as CX3CL1 [2].The initial over-expression of CX3CL1 is conducive to the recruitment of $CX3CR1^{+}$ immune cells to the lung, including monocytes and Mφs [35,112], which could produce an inflammatory environment and even lead to organ dysfunction [113]. Moreover, this has been demonstrated in other coronaviruses, where transmission and homing of leukocytes with different patterns of circulating chemokine levels, with lower increases in CX3CL1 and other chemokines, show good prognostic value [114]. Increased levels of cerebrospinal fluid chemokines, including CX3CL1, might facilitate the trafficking of monocytes to cerebrospinal fluid, and potentially contribute to the development of neurological symptoms in patients with COVID-19 [88]. As reported by Zhu *et al.*, the migration of DCs and monocytes/Mφs may be mediated by CX3CR1 in COVID-19 patients treated with stem cells [115].

In addition, the CX3CR1 inhibitor has been developed, and it is expected to be applied in human clinical trials in the future [21]. Experimental data analysis supports the protective effect of AZD8797 (allosteric antagonist of CX3CR1) on SARS-CoV-2-induced injury. The CX3CL1/CX3CR1 signaling pathway may provide a promising target for reducing the neural impact of SARS-CoV-2 [116]. CX3CR1 is one of the potential genes associated with COVID-19 and comorbidity, which provides a basis for further guiding drug and vaccine development to improve treatment efficacy and the development of personalized treatments [117].

### *3.3. CX3CL1 and Its Receptor in Influenza*

Influenza is a common disease that has been reported to emerge into the human population many times over past centuries, sometimes with devastating consequences [118]. Their recently emerging and re-emerging strains are the culprits of seasonal and occasional epidemics and pose a serious threat to global public health systems [119]. Influenza virus infections are characterized by the infiltration of leukocytes into infected tissues, especially monocytes. Since pro-inflammatory cytokines lack chemotaxis activity, researchers have focused their interest on members of the chemokine superfamily [120]. The chemokines (CCL4, CCL19, CCL10, and CX3CL1) were upregulated in highly pathogenic avian influenza H5N1 (A/duck/India/02CA10/ 2011)-infected lung tissues of chickens, which may be the key factors determining the severity and outcome of influenza infection in chickens [92,121]. Especially, in the convalescent phase, cytokines including CX3CL1 and CD200, are still highly expressed in the brain [10,91]. At this stage, the weight and mobility of the infected mice were completely restored, while the emotional disorders, spatial learning, and memory abilities did not return to normal. This effect may be the delayed damage caused by non-neurotic influenza infection involving these aforementioned cytokines [91].

However, some research results suggest that the loss of CX3CL1 during influenza infection may lead to impairment of both glial regulation and cognitive function. The previously environmental enrichment-induced increase in CX3CL1 may lay the foundation for limiting the induction of neuroinflammation and better maintaining neuronal structure and synaptic plasticity during influenza virus infection [90]. Siran Lin et al. were the first research group to use a statistical model

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trained with high-throughput expression data in influenza [122]. After analyzing 180 samples from the GEO dataset comprehensively, a risk score model involving six genes (*CX3CR1, KLRD1, MMP8, PRTN3, RETN,* and *SCD*) was established. They found that the expression of CX3CR1 was inversely related to H1N1 disease severity [122,123]. Virus-specific memory $CX3CR1^{+}CD8^{+}$T cells are increased in infection, but only a small number are present in the chronic infected state [124,125]. Pulmonary $CX3CR1^{high}$ T cells produce interferon gamma to limit early viral infection in an antigen-independent manner, enhancing the long-term antibacterial activity of alveolar Mφs [126]. Moreover, glucocorticoid-induced TNFR-related protein (GITR) contributes to the accumulation of differentiated effector cells, including $CD8^{+}$ T cell subsets defined by CX3CR1 and Ly6C expression, as well as memory precursors, but there are some differences between subsets [127].

Influenza A virus-induced mouse pneumonia is a common model for studying the effects of aging on pneumonia-induced muscle function [128]. In young mice after influenza A infection, the population of tissue-resident Mφs expressing CX3CR1 in skeletal muscle expands without the recruitment of monocytes from the bone marrow. This was followed by the proliferation of muscle satellite cells. Further experiments showed that the phagocytic function of tissue-resident Mφs in the skeletal muscle of older mice was lost. These findings suggest that the signaling induced by phagocytosis in $CX3CR1^{+}$ tissue-resident skeletal muscle Mφs is necessary for the proliferation of satellite cells during muscle recovery after influenza A virus-induced pneumonia [120,129]. Vaccination and antiviral therapy are the foundational approaches to limiting the public health impact of influenza [130]. Based on the role of CX3CL1/CX3CR1 in influenza, rational immunotherapy is becoming a promising strategy for improving the outcomes of influenza virus infection.

### *3.4. CX3CL1 and Its Receptor in Respiratory Syncytial Virus Infection*

Respiratory syncytial virus (RSV) is a top cause of severe pneumonia in infants and the most common cause of acute lower respiratory infection in young children [131,132]. Among adults, RSV infection produces a wide range of clinical symptoms similar to those of influenza virus infection [133,134]. The two RSV surface proteins, fusion glycoprotein (F protein) and glycoprotein (G protein), are key factors in RSV attachment and entry into cells. They bind to cell surface heparin sulfate proteoglycans via their heparin-binding domains, thereby inducing protective host immune responses [135]. Previous work found that the G protein also has a CX3C chemokine motif (amino acids 182–186) that facilitates RSV attachment to susceptible cells expressing CX3CR1, to infect primary airway cultures [136–138]. CX3CL1 mimicry has been shown to promote RSV infection and alter CX3CL1-mediated chemotaxis of human, cotton rat, and mouse leukocytes [136,139–141].

Tatiana Chirkova et al. studied the role of CX3CR1 through mutation in the RSV CX3C motif during RSV infection [93]. Imaging flow cytometry and RSV attachment assay showed that CX3CR1, expressed on airway ciliated cells, interacts with RSV G protein, facilitating virus attachment and infection of human airway epithelial cells, and modulates cell responses to infection[93,94]. In addition, studies suggest that the interaction of CX3CR1 engagement by the RSV G protein CX3C motif results in intercellular signaling and nucleolin expression, although its role in virus attachment and fusion in RSV infection is still being determined [142]. Dania Zhivaki et al. found after binding of surface Ig on neonatal Breg (nBreg) cells, RSV induces the upregulation of CX3CR1 and activates nBreg cells, which results in IL-10 production through the binding of G protein and CX3CR1. In the presence of the CX3CL1, RSV infection was strongly decreased, concomitant with the inhibition of the IL-10 secretion in nBreg cells [139] and the decrease of pulmonary inflammation in RSV infected mice[143].

However, compared to wild-type (WT) mice, RSV infection in CX3CR1-deficient ($CX3CR1^{-/-}$) neonatal mice resulted in significantly greater neutrophil inflammation in the lungs, accompanied by increased mucus production [144]. A similar study showed that infants carrying a specific I249 M280 CX3CR1 mutation experience more severe bronchiolitis after RSV infection than those without this mutation [93]. These diverse observations highlight the need for further study of host-viral interactions that cause severe disease in infants infected with RSV.

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*3.5. CX3CL1 and Its Receptor in Cytomegalovirus Infection*

It was reported that "human cytomegalovirus (HCMV) encodes G protein–coupled receptors (GPCRs) US28 and US27, which facilitate viral pathogenesis through engagement of host G proteins", destroying the host's immunity [145]. CX3CR1 promotes efficient cell capture when bound to mCX3CL1, while CMV US28 increases cell migration when bound to the same ligand [146]. In experimental animal models, the researchers investigated whether CMV-specific cells in lymph nodes were as abundant as in peripheral blood. An interesting phenomenon was observed that CX3CR1 transcripts were highly present at the peak response, and remained detectable in the latency stage, while the expression of CX3CR1 wasn't induced on EBV-specific $CD8^+$ T cells or influenza virus–reactive T cells obtained from a healthy donor [147]. Therefore, in both acute and latent infection, CX3CR1 appears to be a discriminative marker for CMV-specific effector cells. Upon activation of these effector CD8 T cells, they migrate from the lymphatic compartment to the site of inflammation, where they adhere to endothelial cells and extravasate into inflamed tissues [148,149]. Nicole E. Winchester et al. found that CMV infection facilitates the costimulation of $CX3CR1^+CD57^+CD28^-$CD8 T cells in HIV infection and atherosclerosis via the CD2-LFA-3 axis [150].

In response to murine CMV infection, circulating NK cells were found to be recruited to the salivary glands in a CX3CR1-dependent manner, and then they formed a long-lived memory-like natural killer cell, tissue-resident population that suppresses autoimmunity by TRAIL-dependent elimination of $CD4^+$ T cells [151]. Among individuals with HIV, $CX3CR1^+$, $GPR56^+$, $CD57^+$T, and $CD4^+$ T cells are often CMV-specific and are associated with diabetes, coronary arterial calcium, and non-alcoholic fatty liver disease[152]. There is evidence that CMV-specific $CD4^+$ T cells have been shown to cause endothelial damage in the presence of viral antigens, and the higher the frequency of CMV-specific $CD4^+$ T cells, the more injury occurred in the donors[153–155]. The reason for the injury is the production of CX3CL1 induced by endothelial cells with the release of IFN-$\gamma$ and TNF-$\alpha$ from T cells[156]. Moreover, CX3CL1-CX3CR1 interactions play an important role in recruiting NK cells and Mφs and mediate endothelial injury. The specific antibodies against CX3CR1 significantly reduce the chemoattraction of $CX3CR1^+$ cells and prevent endothelial damage in CMV infection [155]. Accordingly, they hypothesized that CMV-specific CD8 T cells expressing CX3CR1 with the ability to migrate to inflamed vascular endothelium. The endothelial-expressed lymph node homing receptor CX3CR1 was an important cell population in individuals with HIV/CMV co-infection, which could promote tumor and viral clearance and may provide a source of cells that respond to immunotherapies in the future [95,124,157–159].

*3.6. CX3CL1 and Its Receptor in Other Viral Diseases*

Dengue virus (DENV)-specific $CD4^+$ T cells significantly up-regulate CX3CR1, elicit highly polarized states, and mediate direct cytotoxic activity [160,161]. The expression of CX3CR1 on CD4 and CD8 T cells is similar after induction by DENV, ZIKV, and hepatitis B virus (HBV) infections, as well as DENV/ZIKV co-infections, which facilitates the regulation of viral processes by precisely controlling inflammatory cells that target the affected tissue [162–164]. During DENV and Japanese encephalitis virus infections, large numbers of $CD11b^+$ $Ly6C^{hi}$ $CCR2^{hi}$ $CX3CR1^{low}$ inflammatory monocytes infiltrate the liver [165]. It has been demonstrated that CX3CR1 knockout exacerbates Coxsackievirus B3-induced myocarditis [97]. Moreover, the CX3CR1-CX3CL1 axis plays a key role in mediating the transmission of infectious genomic RNA in the pathogenesis of Japanese encephalitis virus [166]. As well as in those with hemorrhagic fever with renal syndrome (HFRS), and the expression of CX3CR1 on non-classical and intermediate monocyte subsets may offer new insights into the role of CX3CL1/CX3CR1 in the pathogenesis of HFRS [96].

Additionally, the concentration of CX3CL1 in the serum of HBV patients is significantly correlated with disease prognosis [167]. When DENV infects, the activation of mast cells causes the production of CX3CL1, which facilitates the recruitment of natural killer (NK) and NKT cells and viral clearance[168]. Elevated plasma CX3CL1 levels are associated with the severity of liver disease in HIV/hepatitis C virus (HCV) co-infected patients with HCV genotype-1 [169]. Two forms of CX3CL1 display differential activity in adeno-associated virus-treated CX3CL1 knockout mice,

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specifically, knocking out CX3CL1 leads to severe cognitive deficits, which can be mitigated by sCX3CL1 treatment, while mCX3CL1 can only partially alleviate them[20]. Under physiological conditions, mCX3CL1 has been shown to play a major role in the recruitment and adhesion of infiltrating leukocytes [20]. sCX3CL1 not only acts as a chemotactic agent involved in cell migration, but also serves as a neuroprotective signaling molecule, mediating the anti-inflammatory activity of CX3CL1 in the brain [20]. Proinflammatory mediators, such as sCX3CL1, which are maintained at or below baseline throughout SEOV infection, may mediate SEOV persistence in the lungs [170]. A novel mechanism of CX3CL1 production has been discovered: rhinovirus 16 infection enhances the cleavage of the allergen protease from the apical epithelial surface to produce active CX3CL1, which may contribute to the synergistic effect of allergen exposure and rhinovirus infection in triggering asthma exacerbation and airway remodeling [171]. The role of the CX3CL1/CX3CR1 signaling pathway in the immune pathogenesis of various diseases will guide the future development of therapeutic agents, particularly viral CX3CR1 antagonists, aimed at preventing or slowing the progression of related diseases [170,172,173].

## 4. Conclusions

CX3CL1 is a distinctive chemotactic factor produced and secreted by various cells, including immune cells, endothelial cells, and epithelial cells, with the dual functions of adhesion molecules and chemotactic agents. sCX3CL1 induces the migration of CX3CR1-expressing NK cells, cytotoxic T lymphocytes, and Mφs, while mCX3CL1 captures and enhances the subsequent migration of these cells upon stimulation by other chemokines. The expression level of CX3CL1 is associated with the state of the disease, and its improper expression affects various processes such as leukocyte recruitment, angiogenesis, cell survival and cell adhesion. Based on the role of the CX3CL1/CX3CR1 system in various clinical diseases, the CX3CL1/CX3CR1 axis has emerged as a promising potential therapeutic target at the appropriate stage due to its ability to drive inflammation.

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