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REVIEW

Role of CX3CL1 in Diseases

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Abstract Chemokines are a family of small 8–10 kDa inducible cytokines. Initially characterized as chemotactic factors, they are now considered to affect not just cellular recruitment. CX3CL1 is a unique chemokine that can exist in a soluble form, as a chemotactic cytokine, or in a membrane-attached form that acts as a binding molecule. Recently, the effects of CX3CL1 on diseases, such as inflammation and cancer, have been supported and confirmed by numerous publications. However, due to its dual effects, CX3CL1 exerts numerous effects on pathophysiological conditions that have both negative and positive consequences on pathogenesis and outcome. This review article summarizes the important scientific and clinical data that now point to a critical role for CX3CL1 in diseases.

Keywords CX3CL1 · Chemokine · Disease

Introduction

According to the mutual arrangement of cysteine residues and disulfide bridges within the chemokines, these cytokines are subdivided into four subgroups C, CC, CXC, and CX3C (Luster 1998). In other words, these subgroups are characterized by the number of interspersed amino acids between the first two cysteine residues in the primary structure. Thus, the CX3C subgroup contains three interspersed, non-conserved amino acids. Like the other three subgroups, the CX3C subgroup contains conserved cysteine residues at positions 8, 12, 34, and 50 in humans and other species (Harrison et al. 2001). However, unlike the other subgroups, which consist of more than one member, the CX3C subgroup consists of only one known member, CX3CL1. Furthermore, only CXCL16 and CX3CL1 are transmembrane proteins (Bazan et al. 1997; Ludwig and Weber 2007). CX3CL1 contains a mucin-like stalk, on top of which lies a chemokine domain. On the other end of the stalk is a single transmembrane region with a short intracellular C terminus (Bazan et al. 1997). This molecule exists in two forms: the membrane-attached form and the shed form. Because CX3CR1 contains a number of negatively charged side chains within its extracellular regions, the positively charged amino acids in CX3CL1 allow itself to mediate the capture and firm adhesion of CX3CR1-expressing cells under physiological and pathological conditions. Using site-directed mutagenesis, two residues in the chemokine domain, namely Lys-7 and Arg-47, were identified as the important determinants in mediating the CX3CL1–CX3CR1 interaction. These mutant CX3CL1s displayed not only reduced affinity for CX3CR1 in steady-state-like whole-cell binding assays but also inefficient capture or adhesion to CX3CR1-expressing cells under physiological flow (Harrison et al. 2001). Multiple cleavage sites in CX3CL1 mucin domain afford multiple distinct forms of this cytokine. However, the length of the stalk does not affect its effect on the binding affinity and stimulation of CX3CR1-expressing cells (Fong et al. 2000; Haskell et al. 2000). Therefore, the chemokine domain assumes the chemotactic activity, whereas the stalk in this setting appears to serve as a domain extender. Furthermore, the various shed forms of CX3CL1 may be related to the specific cell types within the different tissues (Fonovic et al. 2013).

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Synthesized as an intracellular 50–75-kDa precursor, CX3CL1 is rapidly processed, such as glycosylated, yielding the mature 100-kDa glycoprotein that is transported to the cell surface (Garton et al. 2001). The mature form can be cleaved from the cell surface to produce a soluble 85-kDa fragment that contains a 76 amino acid chemokine domain (Bazan et al. 1997). CX3CL1 is both constitutively and inducibly released from cells. Constitutive cleavage occurs under normal growth conditions, and a metalloprotease, ADAM-10, contributes to this process in unstimulated cells (Hundhausen et al. 2003). CX3CL1 shedding could be rapidly accelerated by stimuli. For example, inflammatory agents, such as lipopolysaccharide (LPS), interleukin (IL)-1β, or phorbol esters, enhance the cleavage of CX3CL1 through tumor necrosis factor (TNF)-α-converting enzyme (ADAM17) (Garton et al. 2001; Tsou et al. 2001). The modulation of cleavage rates provides a means of regulating the abundance of CX3CL1 and accessibility under different situations.

According to Liu et al. (2005), CX3CL1 is also cycled between the plasma membrane and the recycling endosomes, and this process is mediated by soluble *N*-ethylmaleimide factor attachment protein receptors (SNARE). As identified by confocal microscopy, CX3CL1 exists in the juxtanuclear space. After photobleaching the juxtanuclear CX3CL1, the original fluorescence gradually recovers. This observed phenomenon is considered to be constitutive internalization. Notably, when CX3CL1 is stripped from the cell surface, it is re-inserted into the plasma membrane in a time-dependent manner (Liu et al. 2005). Thus, CX3CL1 recycles between the superficial and internal cell compartments. Therefore, juxtanuclear CX3CL1 may likely serve as a storage depot that regulates the level of surface CX3CL1, whereas the surface CX3CL1 acts as an adhesive and chemoattractant molecule via cleavage. Consequently, the γ-secretase complex is responsible for the cleavage of the remaining C-terminal fragment, which may be further degraded or fulfill as yet unknown functions as signaling molecules (Schulte et al. 2007).

Located on chromosome 16q13, the promoter regions of the CX3CL1 gene contain the binding sites for NF-κB, AP-1, STAT-1, and p53. The induction of CX3CL1 under various circumstances is related to these relevant transcription factors. CX3CL1, which binds to the seven transmembrane G protein-coupled receptor CX3CR1, induces its own expression via pertussis toxin-sensitive G-proteins, phosphoinositide-3 kinase, phosphoinositide-dependent kinase 1, Akt, NIK, IKK, and NF-κB activation (Chandrasekar et al. 2003). Studies of inflammatory factors, such as IL-1β, TNF-α, and LPS, supported the central role of NF-κB in the regulation of CX3CL1 transcription (Chandrasekar et al. 2003; Garcia et al. 2000). Shiga toxin 2 upregulates the expression of CX3CL1, and this process involves both the NF-κB and AP-1 signaling pathways. Conversely, the Clostridium difficile toxin A-dependent induction of CX3CL1 is mediated by a signaling cascade involving p38 MAPK/IKK/NF-κB and does not depend on AP-1 (Ko et al. 2014; Zanchi et al. 2008). Furthermore, the expression of CX3CL1 is enhanced in human umbilical vein endothelial cells stimulated with interferon (IFN)-γ via STAT-1 (Imaizumi et al. 2000). In the tumor field, Shiraishi et al. (2000) identified a potential p53-binding site in the promoter of the CX3CL1 gene that could bind to p53 protein and the induction of CX3CL1 via the ectopic expression of p53 in p53-defective cells. CX3CL1 expression is under the control of post-transcriptional regulation as well. Furthermore, the AU-rich element, a crucial cis-element in the 3′ untranslated region, plays a pivotal role in stabilization (Matsumiya et al. 2010).

The above-mentioned fundamental characteristics of CX3CL1 are depicted in Fig. 1. As indicated by many studies, the inappropriate expression or function of CX3CL1 is involved in various clinical disease. Several reviews have been focused on the role of CX3CL1 in one disease entity, such as cancer (Marchesi et al. 2010), neuropathy (Cotter et al. 2002), vasculitis (Kasama et al. 2010), and so on. However, there is relatively lack of the overview of CX3CL1 in different kinds of diseases. Given the dual roles of CX3CL1 and some patients with multi-system diseases, this review aims to inspire and motivate researchers to take a comprehensive look at the role of CX3CL1 in diseases. The following chapter will discuss the relationship between CX3CL1 and diseases in detail (Fig. 2).

Atherosclerosis and Cardiovascular Disease

According to the pathogenesis of atherosclerosis, injury to the arterial endothelium initiates the interaction of cellular populations of the peripheral blood, particularly monocytes, with the cell components of the arterial wall (Ross and Glomset 1976; Weber 2008). Multiple cytokines, including chemokines, orchestrate the progression of this inflammatory response. Therefore, all chemokines have been studied in the field of cardiovascular disease in general and in atherosclerotic vascular disease in particular. Furthermore, growing evidence indicates that CX3CL1 plays an important role in atherosclerosis and cardiovascular disease.

Endothelial cells synthesize CX3CL1. Because CX3CL1 plays an important role in the interaction between monocytes and endothelial cells, its expression is tightly regulated in endothelial cells. TNF-α, IL-1, LPS, and IFN-γ stimulate CX3CL1 expression, whereas the soluble form of

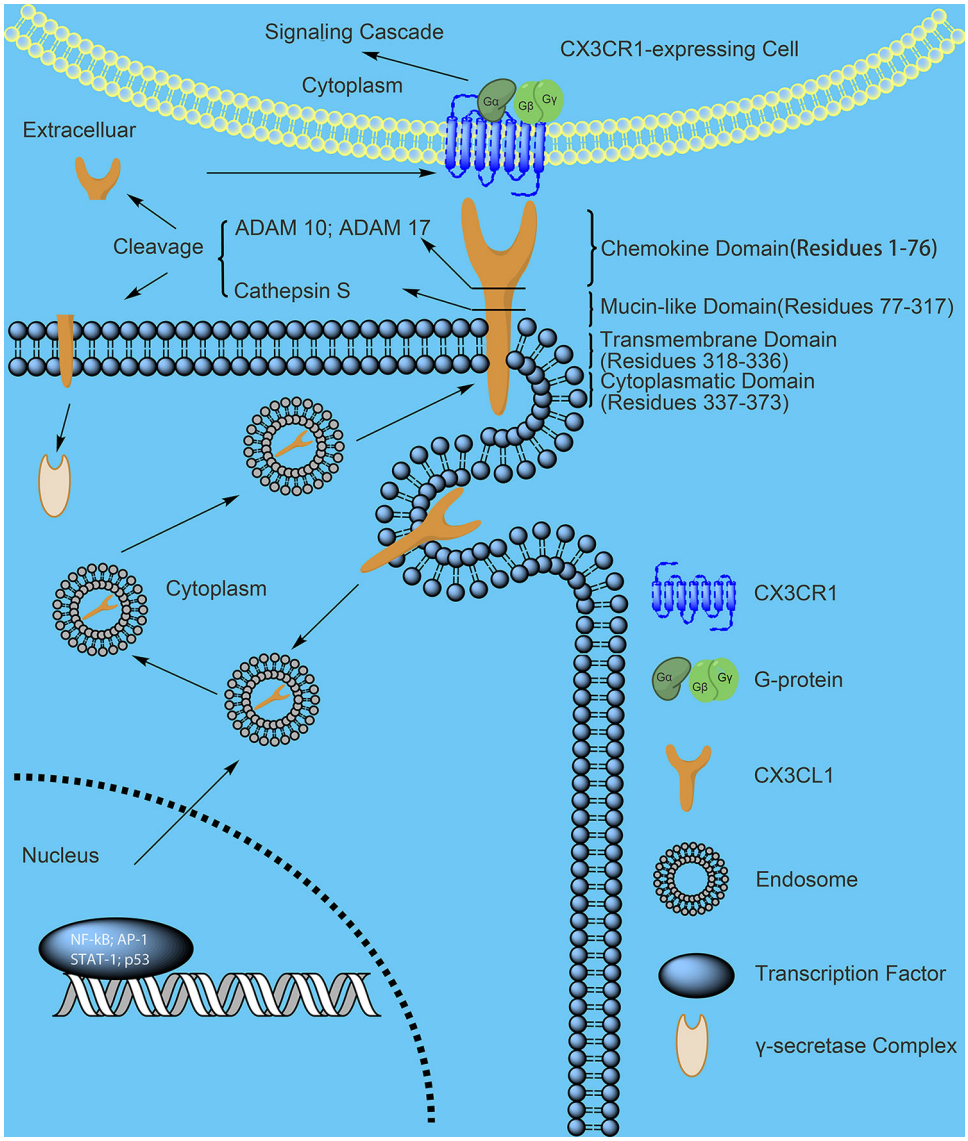

Fig. 1 Schematic diagram of CX3CL1

IL-6 receptor-α, 15-deoxy-Δ12,14-prostaglandin J2, and hypoxia downregulate its expression (Imaizumi et al. 2004). In the early stages of atherogenesis, oxidized low-density lipoprotein induces the expression of CX3CL1 by vascular smooth muscle cells and endothelial cells. Subsequently, CX3CL1 initiates the recruitment of monocytes in atherosclerotic lesions under arterial shear, a process that is assisted by P-selectin exposure on adherent platelets (Schulz et al. 2007). Cross talk between smooth muscle cells and activated monocytes augments the expression of pro-atherogenic molecules via the CX3CL1/CX3CR1 axis (Butoi et al. 2011). In more advanced stages of the disease, CX3CL1 promotes neo-angiogenesis and the migration of vascular smooth muscle cells (Apostolakis and Spandidos 2013). Additionally, CX3CL1 induces endothelial cell injury (Yoneda et al. 2000) and exerts anti-apoptosis and proliferative effects on monocytes and vascular smooth muscle cells (Landsman et al. 2009; White et al. 2010). Therefore, CX3CL1 is involved in all stages of atherogenesis, and it even changes the components of plaques to affect their stability. Because CX3CL1 is related to both the severity of atherosclerotic disease and the instability of plaques, the results of some therapeutic studies based on the CX3CL1/CX3CR1 axis are promising.

In vivo, the expression CX3CL1 is higher in mice fed a high-fat diet (Liu et al. 2010). Knocking out the gene encoding CX3CR1 in apoE$^{-/-}$ mice resulted in a significant reduction in macrophage recruitment to the vessel wall and decreased the formation of atherosclerotic lesions (Lesnik et al. 2003). In clinical research, the serum levels of CX3CL1 have been implicated in carotid artery stenosis (Stolla et al. 2012), unstable angina (Damas et al. 2005; Li

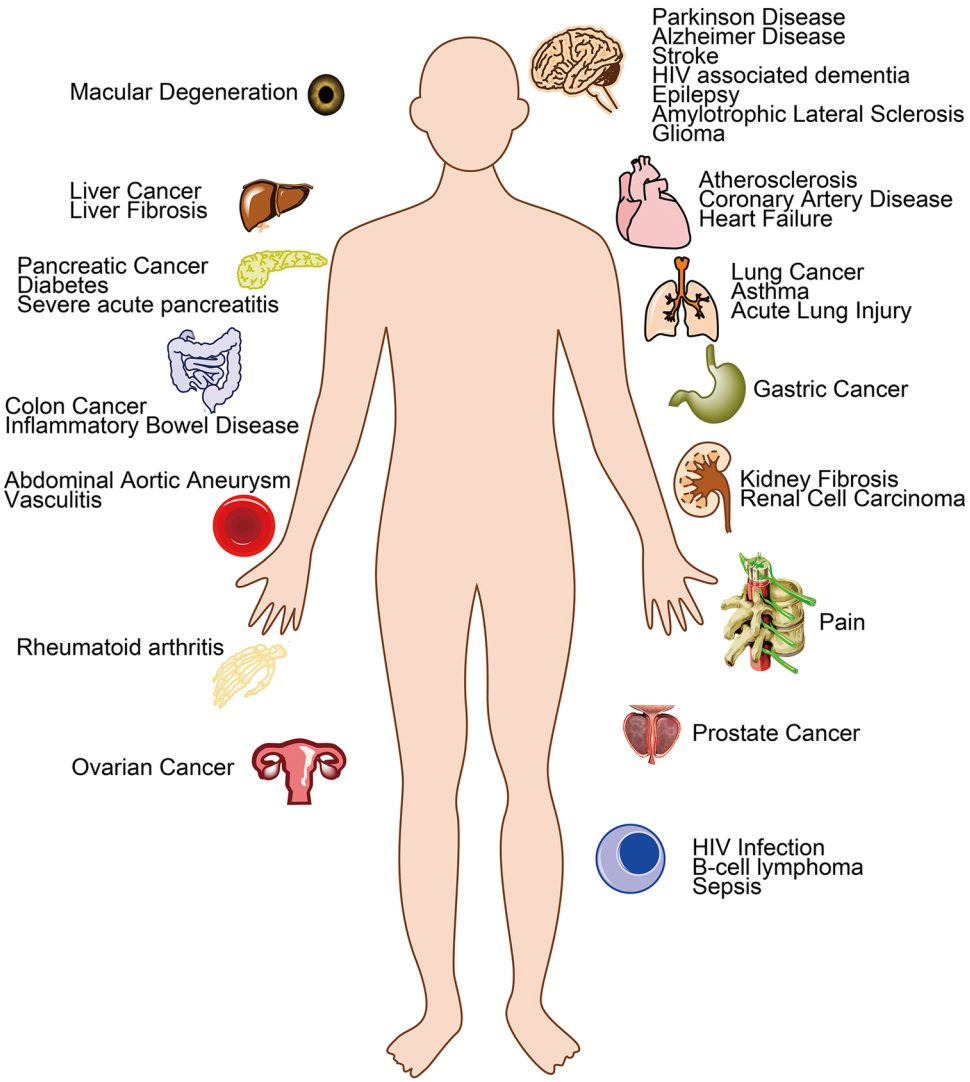

Fig. 2 CX3CL1 and diseases

et al. 2012), systolic heart failure (Richter et al. 2012), abdominal aortic aneurysm (Patel et al. 2008), and chronic obstructive pulmonary disease-associated cardiovascular disorders (Rius et al. 2013). As a biomarker, CX3CL1 at higher levels indicates a worse pathogenic condition and poorer prognosis in the above-mentioned diseases.

CX3CL1 interacts with its single receptor, CX3CR1. As a result, the genetic variations of CX3CR1 affect susceptibility to coronary artery disease. Genetic studies have identified two non-synonymous polymorphisms, a valine-to-isoleucine substitution at position 249 (CX3CR1-V249I) and a threonine-to-methionine substitution at position 280 (CX3CR1-T280M) (McDermott et al. 2000). Several studies have confirmed the atheroprotective effect of these polymorphisms of the CX3CR1 due to the decreased reactivity of the CX3CL1/CX3CR1 axis (Apostolakis et al. 2009; McDermott et al. 2001).

Vasculitis

The progression of vasculitis also correlates with the interactions between endothelial cells and invading monocytes. CX3CL1 has been implicated in endothelium inflammation. Therefore, CX3CL1 may capture cytotoxic effector cells that express CX3CR1 and then promote their extravasation into tissue. In theory, the upregulated expression of CX3CL1 combined with the accumulation of activated inflammatory cells forms the foundation of vasculitis (Kasama et al. 2010).

Indeed, serum samples from 18 patients with microscopic polyangiitis contained higher levels of CX3CL1 than serum samples from healthy individuals. The elevated CX3CL1 levels correlated positively with disease activity as well as with the C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR). Simultaneously, the

increased expression of cell-surface CX3CR1 was observed on peripheral blood CD4 and CD8 T cells from patients. Notably, the CX3CL1 levels and CX3CR1 expression were decreased during clinical remission after treatment (Matsunawa et al. 2009). Elevated serum CX3CL1 levels accompanied by increased expression of its receptor, CX3CR1, in peripheral blood monocytes have also been observed in Wegener's granulomatosis (WG). As a result, CX3CL1-induced chemotaxis, adhesion, and responses were enhanced, and these functions are involved in the pathogenesis of the granulomatous vasculitis that characterizes WG (Bjerkeli et al. 2007). In addition, Matsunawa et al. (2006) showed that the serum levels of CX3CL1 were higher in rheumatoid arthritis patients with rheumatoid vasculitis than in arthritis patients without rheumatoid vasculitis. Notably, the serum CX3CL1 levels were correlated well with the vasculitis disease activity and inflammation markers. After successful treatment, the serum CX3CL1 levels diminished with clinical improvement (Matsunawa et al. 2006). Morimura et al. (2013) provided both scientific and clinical evidence to support the contribution of CX3CL1 to the development of leukocytoclastic vasculitis. Edema and hemorrhage were significantly reduced in CX3CR1$^{-/-}$ mice, whereas the CX3CL1 levels in the serum and on endothelial cells were significantly higher in patients with polyarteritis nodosa than in healthy controls (Morimura et al. 2013). Therefore, interactions between CX3CL1 and CX3CR1 lead to vasculitis via regulating monocyte recruitment and cytokine expression.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease of the synovia that eventually leads to small joint destruction. Initially, inflammatory synovitis consists of leukocytes transmigrating through the vascular endothelium to invade the synovia. These leukocytes and other cells produce inflammatory exudate in the joint cavity, including chemokines, and this exudate disrupts osteoclast precursors and their subsequent differentiation and maturation, leading to the joint injury (Harris 1990).

In rat adjuvant-induced arthritis, a model of RA, macrophages, fibroblasts, endothelial cells, and dendritic cells in synovial tissue were CX3CL1 immuno-positive, while lymphocytes expressing CX3CR1 were found among macrophages, fibroblasts, and dendritic cells in synovial tissue (Ruth et al. 2001). This finding suggests that CX3CL1 participates in the development of RA. Nanki et al. (2002) found that CX3CR1 expression by peripheral CD4 and CD8 T cells was upregulated in RA patients, and these cells produced IFN-γ and TNF-α and expressed cytotoxic molecules, such as granzyme A and perforin. Furthermore, CX3CR1/CD3 T cells infiltrated the RA synovium. This study also found that CX3CL1 was expressed by endothelial cells and synoviocytes in the RA synovium but not in the osteoarthritic synovium (Nanki et al. 2002).

In addition to the dual role of CX3CL1 as a chemotactic molecule and cellular adhesion molecule for monocytes and lymphocytes, Volin et al. (2001) confirmed a new function for CX3CL1 as an angiogenic mediator and suggested that this chemokine may mediate angiogenesis in RA. Angiogenesis leads to the vascular proliferation found in the RA pannus. Thus, CX3CL1 plays a crucial role in the pathogenesis of RA through these effects. Several studies have targeted CX3CL1 in RA. For example, the level of CX3CL1 was significantly reduced in RA patients who responded to infliximab, and this change was accompanied by diminished CRP and ESR levels (Odai et al. 2009).

Human Immunodeficiency Virus Infection

Earlier reports indicated that the entry of human immunodeficiency virus (HIV) into host cells required the formation of an entry complex (Berger et al. 1999). During infection, HIV glycoprotein 120 binds to CD4 on the host cells, leading to the exposure of the V3 loop in gp120 and subsequent interaction with a chemokine receptor. CXCR4 is needed to infect T cell lines as a coreceptor, whereas CCR5 is a coreceptor for the infection of macrophages and activated T cells. CX3CR1 is also a HIV coreceptor, though its activity is relatively limited compared with those of CCR5 and CXCR4.

In the lymph nodes of HIV patients, the increased expression of CX3CL1 may affect the adhesion and migration of Th lymphocytes and their interaction with dendritic cells, which consequently influences the equilibrium between the depletion and renewal of the Th lymphocyte compartment (Foussat et al. 2001). Through such effect, CX3CL1 influences the pathophysiology of HIV infection. In addition to chemoattraction and adhesion, CX3CL1 has been found to inhibit HIV infection: CX3CL1 potently, effectively, and specifically blocks the functional interaction of CX3CR1 with HIV (Combadiere et al. 1998). Given the importance of this coreceptor to HIV transmission and pathogenesis, CX3CR1 polymorphisms unsurprisingly influence the susceptibility of HIV infection. In the Caucasian population, a particular variant haplotype, CX3CR1-I249 M280, is associated with accelerated HIV disease progression, which is ascribed to decreased CX3CL1 binding affinity (Faure et al. 2000).

CX3CL1 is neuroprotective in HIV patients. Human immunodeficiency virus encephalitis is associated with

progressive dementia in adults and encephalopathy in children. Soluble neurotoxic factors, such as HIV neurotoxin platelet activating factor and the regulatory HIV gene product Tat, contribute to neuronal dysfunction and death. CX3CL1 can protect cultured neurons when co-administered with such neurotoxic factors produced by HIV-infected mononuclear phagocytes (Tong et al. 2000). The protective functions of CX3CL1 are reported to modulate the protein levels and phosphorylation status of Bcl-2 family proteins via the activation of the Akt and NF-κB signaling pathways (Boehme et al. 2000; Meucci et al. 2000). However, in HIV-associated dementia, a late-stage complication of advanced HIV disease, CX3CL1 overexpression may recruit and activate HIV-infected mononuclear phagocytes to produce toxic factors, which ultimately affects neuronal survival and induces neural inflammation (Cotter et al. 2002). Thus, CX3CL1 constitutively acts as neuroimmune modulator recruiting peripheral mononuclear phagocytes. However, this feature has opposite effect on the different stages of neurologic disease in HIV. Therefore, it is essential to maintain the balance between CX3CL1 and mononuclear phagocytes.

Neuropathy

CX3CR1 localizes to microglia, and CX3CL1 localizes to neurons. These factors regulate the communication between microglia and neurons under both normal and pathological conditions (Harrison et al. 1998). The molecular mechanisms underlying microglial responses to CX3CL1 involve transient calcium mobilization, chemotaxis, the production of matrix metalloproteinases 2 and 9, and a cascade reaction of protein phosphorylation and enzyme activation (Cross and Woodroofe 1999; Maciejewski-Lenoir et al. 1999). In addition, CX3CL1 is reported to protect microglia from Fas-mediated cell death and reduce microglia reactivity to toxic stimuli (Biber et al. 2007; Boehme et al. 2000). Because the suppression of inflammatory cytokines is related to the suppression of NF-κB activation and/or translocation, the downregulation of NF-κB is presumably involved in this process. Furthermore, because microglia rapidly react to protect normal neurons and eliminate damaged neurons in the brain, microglia may act as sentinels for neurons (Nimmerjahn et al. 2005). Taken together, these data suggest that the activity of CX3CL1 may result from the direct activation of signaling pathways in microglia. Specifically, CX3CL1 may prevent activated microglia from producing pro-inflammatory cytokines and reactive oxygen species, release neuroprotective adenosine to stimulate astrocyte to upregulate the expression of the glutamate transporter, and modulate the entry of hematogenous leukocytes into brain (Cardona et al. 2006; Zujovic et al. 2000).

Using transgenic mouse models, Cardona et al. (2006) showed that CX3CR1 deficiency dysregulated microglial responses, resulting in neurotoxicity under pathological conditions, such as epilepsy, Parkinson disease, and amyotrophic lateral sclerosis. Therefore, the expression of CX3CR1 appears to benefit neuroprotection and survival (Cardona et al. 2006). However, the effects of the CX3CL1/CX3CR1 axis in neuropathy are extremely context dependent, and relevant studies in this field have yielded contradictory conclusions. In Alzheimer disease (AD), CX3CR1 deficiency worsens AD-related neuronal and behavioral deficits, which is associated with aberrant microglial activation and elevated inflammatory cytokines but not with plaque deposition (Cho et al. 2011). This finding agrees with the reduced CX3CL1 levels in the cortex and hippocampus regions of AD autopsy brain sections. In contrast, several studies reported a potentially toxic effect for CX3CL1 in AD pathogenesis. A loss of neuron–microglial CX3CL1 signaling leads to reduced β-amyloid deposition in mouse models of AD, which is potentially mediated by the altered activation and phagocytic capability of CX3CR1-deficient microglia (Lee et al. 2010). The dysregulated microglial activity results in enhanced release of pro-inflammatory cytokines, which can subsequently bind to their corresponding receptors on neurons and induce activation of p38 MAPK, thus leading to enhanced phosphorylation and aggregation of microtubule-associated protein tau (Bhaskar et al. 2010). Suppressing CX3CL1 signaling with CX3CR1 siRNA in rats reduced the neuro-inflammatory response, and Aβ-induced neuro-inflammation and neurotoxicity (Wu et al. 2013). Together, it is plausible that CX3CR1 deficiency may be protective while at early stages of Aβ pathology, and the effects of CX3CR1 deficiency are neurotoxic as the disease progresses toward the late stage (Bhaskar et al. 2010). It is interesting to note that the neuroprotective capacity of CX3CL1 resides upon its soluble isoform in AD and Parkinson's disease (Morganti et al. 2012; Nash et al. 2013, 2015). Therefore, maybe only soluble subtype of CX3CL1 can access into the cytoplasm after binding to CX3CR1 and consequently triggers downstream signal pathways.

In ischemic conditions, damaged neurons expressing phosphatidylserine on their surface are vulnerable to be taken up and destroyed by microglia, which in turn improves experimental stroke outcome (Neumann et al. 2009). Low plasma CX3CL1 levels 180 days after stroke were associated with a poor outcome for patients and higher systemic markers of inflammation, including white blood cell counts and CRP (Donohue et al. 2012). In

apparent contrast, some studies confirmed that the lack of CX3CL1/CX3CR1 signaling reduced ischemic volume and inhibited neuronal cell death (Denes et al. 2008; Soriano et al. 2002). Recently, it is suggested that the activation state of microglia, pro-(M1) or anti-inflammatory phenotype (M2), determines whether CX3CL1 is neuroprotective or neurotoxic in a certain context (Lauro et al. 2015). Overall, these data highlight that the effect of CX3CL1 on neuroprotection and neurotoxicity in the context of neuropathy is complex.

Cancer

Reports on the clinical role of CX3CL1 in tumors are also contradictory. Given the dual function of CX3CL1 as a chemoattractant for leukocytes and an adhesion molecule for tumor cells, CX3CL1 unsurprisingly exerts both pro-tumor and anti-tumor effects.

Animal models have shown that natural killer (NK) cells, T cells, and dendritic cells participate in CX3CL1-induced anti-tumor immunity (Guo et al. 2003a, b). CX3CL1 also reduced primary tumor growth and spontaneous liver metastases in a mouse model, which was amplified by targeted IL-2 therapy (Zeng et al. 2005). On clinic, the CX3CL1/CX3CR1 axis has been implicated in the prognosis of patients after radical resection for hepatocellular carcinoma. A high expression of both CX3CL1 and CX3CR1 was associated with significantly fewer local and distant recurrences and a better prognosis in terms of disease-free and overall survival (Matsubara et al. 2007). In gastric adenocarcinoma, tumor cells excreted CX3CL1 to recruit CD8 T cells and NK cells, thereby inducing both innate and adaptive immunity, which yielded a better prognosis (Hyakudomi et al. 2008).

CX3CL1 and CX3CR1 are reportedly expressed in other tumors, such as breast cancer (Andre et al. 2006; Tsang et al. 2013), prostate cancer (Shulby et al. 2004), pancreatic cancer (Celesti et al. 2013), ovarian cancer (Kim et al. 2012), renal cell cancer (Yao et al. 2014), colon cancer (Zheng et al. 2013), and B cell lymphoma (Andreasson et al. 2008). These authors showed that the pro-tumoral effects of CX3CL1 counteract its potential anti-tumor effect. For example, CX3CR1 was associated with metastasis to the brain in breast cancer (Andre et al. 2006), and CX3CL1 expression both positively correlated with increased tumor-infiltrating lymphocytes and negatively correlated with overall survival (Tsang et al. 2013). In addition to the promotion of metastasis via conventional routes of tumor dissemination, including the blood, lymphatic vessels, and coelomic cavities, CX3CL1 can promote cancer cells to migrate along nerves, a process named perineural invasion (PNI) (Pour et al. 2003). Study from Marchesi et al. (2008) showed that pancreatic ductal adenocarcinoma cell lines and surgical specimens expressed CX3CR1, whereas neurons and nerve fibers expressed CX3CL1. In vivo experiments showed that only CX3CR1-transfected tumor cells infiltrated the local peripheral nerves. Furthermore, higher CX3CR1 expression was significantly associated with more prominent, pathologically detected PNI, which in turn was strongly associated with local and earlier tumor recurrence (Marchesi et al. 2008). However, neither CX3CL1 nor CX3CR1 is a reliable surrogate marker of PNI in oral squamous cell carcinoma (Doumas et al. 2015). Furthermore, Sciume et al. (2010) indicated that endogenous expression of CX3CL1 negatively regulated glioma invasion. This regulation was likely mediated by the promotion of tumor cell aggregation, because the blockade of endogenous CX3CL1 function markedly delayed tumor cell aggregation and increased their invasiveness (Sciume et al. 2010). These results highlight the complicated functions of CX3CL1 in carcinogenesis and metastasis.

Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is the most common cause of legal blindness in the elderly in developed countries (Klein et al. 2004). The early clinically hallmark of AMD are drusen consisting of extracellular lipid and protein deposits between the basal lamina of the retinal pigment epithelium (RPE) and Bruch's membrane (Bird et al. 1995). AMD then slowly progresses to two late clinical forms: geographic atrophy, a slow progressing atrophic form that is characterized by a loss of choriocapillaris, adjacent RPE and photoreceptor cells, and exudative AMD, a rapidly progressing exudative form that is characterized by choroidal neovascularization (CNV) with subsequent hemorrhages and acute photoreceptor and RPE cell loss. Thus, AMD is responsible for the majority of legal blindness (Klein et al. 2007).

In addition to conventional risk factors for the onset of AMD, such as age, smoking, and family history, recent studies have identified CX3CR1 polymorphisms as a genetic risk factor for AMD (Combadiere et al. 2007; Tuo et al. 2004). These studies showed that two single nucleotide polymorphisms in CX3CR1, V249I, and T280M, decreased the number of receptor binding sites and the ligand affinity, thus leading AMD development. However, other studies failed to identify significant associations between CX3CR1 variants and AMD (Gupta et al. 2014; Schaumberg et al. 2014). Because microglial cells and monocytes expressing CX3CR1 are activated and accumulated in the subretinal space in AMD, a CX3CR1-deficient mouse model was employed to decipher the effect

of CX3CR1 dysfunction on AMD. In sharp contrast to the observed inhibition of CX3CR1$^{-/-}$ on monocyte aggression in other inflamed tissues, an increased accumulation of subretinal microglial cells and monocytes was observed in AMD (Combadiere et al. 2007). The resulting prolonged presence of subretinal microglial cells and monocytes evolved into lipid-bloated subretinal microglial cells with a drusen-like appearance under a funduscope (Raoul et al. 2008a). Another consequence of this prolonged presence is photoreceptor degeneration and changes in the RPE structure and distribution (Ma et al. 2009; Raoul et al. 2008b). In addition, this phenomenon also induces CNV (Combadiere et al. 2007). Therefore, the role of CX3CL1 for AMD is still under the spot light. Well-designed prospective trials with less confounding variables are necessary to draw final conclusions in this field.

Type 2 Diabetes

The leukocyte infiltration of adipose tissue is a critical step for obesity-related metabolic diseases, including type 2 diabetes. In this process, the CX3CL1/CX3CR1 axis plays a key role in monocyte adhesion to adipocytes, the local production of cytokines, and the consequent systemic inflammation and insulin resistance. This role is supported by evidence from Shah et al. (2011), who showed that CX3CL1 was expressed and secreted by human adipocytes. In this study, the CX3CL1 levels in the subcutaneous adipose tissue of obese subjects were higher than that in the adipose tissue of lean controls, and the plasma CX3CL1 levels were increased in patients with type 2 diabetes (Shah et al. 2011).

In the model of adipose tissue inflammation, insulin sensitivity negatively correlated with CX3CL1 expression (Mehta et al. 2012). A synthetic PPARγ agonist, such as rosiglitazone, is commonly used to treat type 2 diabetes. This drug suppresses CX3CL1 expression and signaling. These properties are associated with the following mechanisms: rosiglitazone represses the transcription of the CX3CL1 gene and prevents the plasma membrane translocation of CX3CR1 in macrophages. Rosiglitazone also impedes the nuclear export of CX3CL1 in endothelial cells (Wan and Evans 2010). However, in contrast to these findings, CX3CR1 deficiency is associated with abnormal β cells, as observed in diabetic islets, and CX3CL1 treatment repairs these defects by improving insulin secretion and glucose uptake. The specific underlying mechanisms of this effect include the potentiation of insulin secretion, anti-apoptosis, and the maintenance of gene expression in β cells (Lee et al. 2013). Although the role of CX3CL1 in type 2 diabetes is controversial, the dynamic observation of CX3CL1 as a biomarker may be useful in clinical practice.

Pain

Activated spinal microglia are thought to play a pivotal role in neuropathic pain sensation. Such activated spinal microglia release a variety of modulators, including neurotransmitters, pro-inflammatory cytokines, and chemokines, which act on neurons to induce abnormal neuronal activity at the level of spinal cord "pain centers" in the dorsal horn, thereby leading to a hypersensitivity or hyperalgesic response subsequent to the initial painful stimulus (O'Callaghan and Miller 2010). Because CX3CR1 is expressed on microglia and CX3CL1 is expressed on neurons, neuron–microglia cross talk during central pain processing seems to be largely dependent on the CX3CL1/CX3CR1 axis. Previous studies have confirmed that the expression of CX3CR1 in the ipsilateral spinal cord is upregulated under conditions of neuropathic pain (Lindia et al. 2005) and inflammatory pain (Sun et al. 2007). Thus, a mouse model of CX3CR1 depletion and highly selective blocking antibodies have been employed to investigate the role of CX3CL1 on the modulation of central pain processing.

Staniland et al. (2010) used CX3CR1 knockout (KO) mice to examine pain behavior in the absence of CX3CL1 signaling. They suggested that the lack of CX3CL1/CX3CR1 signaling attenuated hyperalgesia and allodynia in a modality-dependent fashion. In a model of inflammatory pain, KO mice displayed mechanical allodynia fully without thermal hyperalgesia, whereas both mechanical allodynia and thermal hyperalgesia were less severe in KO mice than in wild-type (WT) mice in a model of neuropathic pain. Injured neurons have been suggested to be able to directly facilitate neuropathic pain and increase the excitability of uninjured DRG neurons (Meng et al. 2013; Wu et al. 2002). After spinal nerve ligation, an intrathecal injection of a neutralizing antibody against CX3CR1 not only suppressed mechanical allodynia but also increased activation level of p38 MAPK in spinal microglia (Zhuang et al. 2007). Therefore, p38 MAPK signaling following CX3CR1 activation is critical for the development of neuropathic pain. Huang et al. (2014) reported that CX3CL1-recruited macrophages contributed to paclitaxel-induced DRG neuronal apoptosis and painful peripheral neuropathy via the activation of p38 MAPK in macrophages. This evidence further confirms the pain-modulating feature of CX3CL1 and highlights the importance of the involvement of macrophages that express CX3CR1.

In addition to neuropathic and inflammatory pain, the CX3CL1/p38 MAPK signaling cascade potentially plays an important role in facilitating the processing of bone cancer pain, which involves multiple mechanisms, such as

tumorigenic, neuropathic, and inflammatory mechanisms (Mantyh 2006). Induced by Walker 256 cell inoculation, the expression level of CX3CR1 in the spinal cord gradually increased following bone cancer pain. Intrathecal anti-CX3CR1 therapy not only delayed the initiation of mechanical allodynia but also attenuated the established pain sensitization, which was ascribed to the blockade of CX3CR1 that in turn suppressed the activation of microglia and the expression of p38 MAPK in the spinal cord dorsal horn (Hu et al. 2012). As a consequence, CX3CL1/p38 signaling plays an important role in facilitating a variety of pain models.

Inflammation

The CX3CL1/CX3CR1 axis involves both acute and chronic inflammations. Acute inflammations include sepsis, severe acute pancreatitis, and acute lung injury, which are characterized by major perturbations of the immune homeostasis. For example, neutrophils and macrophages infiltrate into the peritoneal cavity in septic peritonitis. This infiltration is able to clear bacteria from the peritoneum. However, exaggerated systemic inflammation may be simultaneously activated. Considering the key role of chemokines in the modulation of leukocyte migration, CX3CL1 has been implicated as a potential therapeutic target in animal models of sepsis. Based on a microarray study, Pachot et al. (2006) identified a panel of 28 genes whose peripheral blood mRNA expression could efficiently discriminate survivors of septic shock from non-survivors. Among numerous genes suggesting that the immune functions of survivors were improved, the change in CX3CR1 was the most pronounced, an approximately eightfold increase compared with non-survivors. Because CX3CR1 is known to amplify inflammation, impaired monocyte recruitment may contribute to the inability of non-survivors to correctly clear the primary infection. In another report, Pachot et al. (2008) observed that CX3CR1 expression was severely downregulated in monocytes at both the mRNA and protein levels, and this downregulation was associated with a lack of functionality upon CX3CL1 challenge. In a mouse model of cecal ligation and puncture-induced sepsis, elevated CX3CL1 mRNA level and the downregulation of CX3CR1 mRNA expression were observed in the investigated murine tissues. This downregulation appeared to be mediated by NF-κB, which is likely via a reduction in the release of pro-inflammatory cytokines (Raspe et al. 2013). Furthermore, exogenous CX3CL1 reduced the myeloperoxidase activity in lungs and attenuated lung morphological changes in histological sections from cecal ligation and puncture-induced sepsis (He et al. 2009).

The involvement of CX3CL1 in chronic inflammatory conditions, such as asthma, inflammatory bowel disease, and fibrogenesis, has also been discussed. In people with asthma, CX3CL1 expression is increased in airway smooth muscle, lung endothelium, and epithelium cells upon allergen challenge (El-Shazly et al. 2006; Rimaniol et al. 2003). Although a fraction of CD4 T cells express CX3CR1, CX3CR1 is dispensable for T cell migration to the lung. However, T cell maintenance and survival in inflamed airways is CX3CR1 dependent. Thus, CX3CR1 antagonist treatment reduced lung disease in WT mice during allergen sensitization and challenge (Mionnet et al. 2010). In the murine intestine, CX3CR1 is a highly specific marker of macrophages and a critical component in the maintenance of macrophage homeostasis in the mucosal lamina propria. The deletion of CX3CR1 or CX3CL1 in vivo results in a specific and significant reduction in macrophages, which increases the translocation of commensal bacteria to the mesenteric lymph nodes, enhances the Th17 responses, and exacerbates disease during intestinal inflammation. Additionally, either the transfer of CX3CR1-sufficient macrophages or neutralization of IL-17A limited the disease severity of CX3CR1-deficient mice (Medina-Contreras et al. 2011). However, reports of the fibrogenic role (pro- or anti-fibrogenic) of CX3CL1 in fibrogenesis are conflicting. Tomonori's data indicate that CX3CL1/CX3CR1 interaction inhibited the inflammatory properties of Kupffer cells/macrophages to result in decreased liver inflammation and fibrosis (Aoyama et al. 2010). These data contradict the reported upregulation of macrophage infiltration and the expression of TGF-β and type I collagen in a kidney fibrosis mouse model due to the CX3CL1/CX3CR1 axis (Shimizu et al. 2011). However, even in liver fibrosis, the expression of CX3CL1 was higher in HIV/hepatitis C virus co-infected patients with advanced fibrosis than those with mild or no fibrosis (Garcia-Alvarez et al. 2011), which contradicts the above-mentioned study and others (Karlmark et al. 2010). Further studies are needed to identify the mechanism responsible for the discrepancies between these studies.

Conclusion

The scientific and clinical literature present convincing evidence to support a critical role for CX3CL1 in a broad range of disorders. However, studies of CX3CL1 have yielded conflicting results due to its dual roles in the mechanism of leukocyte chemotaxis and adhesion. These conflicting data at least partly reflect the lack of a simple relationship between CX3CL1 and diseases. Although the effects of the modulation of CX3CL1 are extremely context dependent, CX3CL1 signaling has emerged as a

promising therapeutic target in recent years. We are convinced that efforts to elucidate the precise role of CX3CL1 and finely regulate its spatial and temporal expression will provide exciting breakthroughs pertaining to CX3CL1-involved pathophysiological conditions.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Andre F, Cabioglu N, Assi H et al (2006) Expression of chemokine receptors predicts the site of metastatic relapse in patients with axillary node positive primary breast cancer. Ann Oncol 17:945–951

Andreasson U, Ek S, Merz H et al (2008) B cell lymphomas express CX3CR1 a non-B cell lineage adhesion molecule. Cancer Lett 259:138–145

Aoyama T, Inokuchi S, Brenner DA et al (2010) CX3CL1-CX3CR1 interaction prevents carbon tetrachloride-induced liver inflammation and fibrosis in mice. Hepatology 52:1390–1400

Apostolakis S, Spandidos D (2013) Chemokines and atherosclerosis: focus on the CX3CL1/CX3CR1 pathway. Acta Pharmacol Sin 34:1251–1256

Apostolakis S, Amanatidou V, Papadakis EG et al (2009) Genetic diversity of CX3CR1 gene and coronary artery disease: new insights through a meta-analysis. Atherosclerosis 207:8–15

Bazan JF, Bacon KB, Hardiman G et al (1997) A new class of membrane-bound chemokine with a CX3C motif. Nature 385:640–644

Berger EA, Murphy PM, Farber JM (1999) Chemokine receptors as HIV-1 coreceptors: roles in viral entry, tropism, and disease. Annu Rev Immunol 17:657–700

Bhaskar K, Konerth M, Kokiko-Cochran ON et al (2010) Regulation of tau pathology by the microglial fractalkine receptor. Neuron 68:19–31

Biber K, Neumann H, Inoue K et al (2007) Neuronal 'on' and 'off' signals control microglia. Trends Neurosci 30:596–602

Bird AC, Bressler NM, Bressler SB et al (1995) An international classification and grading system for age-related maculopathy and age-related macular degeneration. The International ARM Epidemiological Study Group. Surv Ophthalmol 39:367–374

Bjerkeli V, Damas JK, Fevang B et al (2007) Increased expression of fractalkine (CX3CL1) and its receptor, CX3CR1, in Wegener's granulomatosis—possible role in vascular inflammation. Rheumatology 46:1422–1427

Boehme SA, Lio FM, Maciejewski-Lenoir D et al (2000) The chemokine fractalkine inhibits Fas-mediated cell death of brain microglia. J Immunol 165:397–403

Butoi ED, Gan AM, Manduteanu I et al (2011) Cross talk between smooth muscle cells and monocytes/activated monocytes via CX3CL1/CX3CR1 axis augments expression of pro-atherogenic molecules. Biochim Biophys Acta 1813:2026–2035

Cardona AE, Pioro EP, Sasse ME et al (2006) Control of microglial neurotoxicity by the fractalkine receptor. Nat Neurosci 9:917–924

Celesti G, Di Caro G, Bianchi P et al (2013) Early expression of the fractalkine receptor CX3CR1 in pancreatic carcinogenesis. Br J Cancer 109:2424–2433

Chandrasekar B, Mummidi S, Perla RP et al (2003) Fractalkine (CX3CL1) stimulated by nuclear factor kappaB (NF-kappaB)-dependent inflammatory signals induces aortic smooth muscle cell proliferation through an autocrine pathway. Biochem J 373(Pt 2):547–558

Cho SH, Sun B, Zhou Y et al (2011) CX3CR1 protein signaling modulates microglial activation and protects against plaque-independent cognitive deficits in a mouse model of Alzheimer disease. J Biol Chem 286:32713–32722

Combadiere C, Salzwedel K, Smith ED et al (1998) Identification of CX3CR1. A chemotactic receptor for the human CX3C chemokine fractalkine and a fusion coreceptor for HIV-1. J Biol Chem 273:23799–23804

Combadiere C, Feumi C, Raoul W et al (2007) CX3CR1-dependent subretinal microglia cell accumulation is associated with cardinal features of age-related macular degeneration. J Clin Invest 117:2920–2928

Cotter R, Williams C, Ryan L et al (2002) Fractalkine (CX3CL1) and brain inflammation: implications for HIV-1-associated dementia. J Neurovirol 8:585–598

Cross AK, Woodroofe MN (1999) Chemokine modulation of matrix metalloproteinase and TIMP production in adult rat brain microglia and a human microglial cell line in vitro. Glia 28:183–189

Damas JK, Boullier A, Waehre T et al (2005) Expression of fractalkine (CX3CL1) and its receptor, CX3CR1, is elevated in coronary artery disease and is reduced during statin therapy. Arterioscler Thromb Vasc Biol 25:2567–2572

Denes A, Ferenczi S, Halasz J et al (2008) Role of CX3CR1 (fractalkine receptor) in brain damage and inflammation induced by focal cerebral ischemia in mouse. J Cereb Blood Flow Metab 28:1707–1721

Donohue MM, Cain K, Zierath D et al (2012) Higher plasma fractalkine is associated with better 6-month outcome from ischemic stroke. Stroke 43:2300–2306

Doumas S, Paterson JC, Norris PM et al (2015) Fractalkine (CX3CL1) and fractalkine receptor (CX3CR1) in squamous cell carcinoma of the tongue: markers of nerve invasion? Oral Maxillofac Surg 19:61–64

El-Shazly A, Berger P, Girodet PO et al (2006) Fraktalkine produced by airway smooth muscle cells contributes to mast cell recruitment in asthma. J Immunol 176:1860–1868

Faure S, Meyer L, Costagliola D et al (2000) Rapid progression to AIDS in HIV+ individuals with a structural variant of the chemokine receptor CX3CR1. Science 287:2274–2277

Fong AM, Erickson HP, Zachariah JP et al (2000) Ultrastructure and function of the fractalkine mucin domain in CX(3)C chemokine domain presentation. J Biol Chem 275:3781–3786

Fonovic UP, Jevnikar Z, Kos J (2013) Cathepsin S generates soluble CX3CL1 (fractalkine) in vascular smooth muscle cells. Biol Chem 394:1349–1352

Foussat A, Bouchet-Delbos L, Berrebi D et al (2001) Deregulation of the expression of the fractalkine/fractalkine receptor complex in HIV-1-infected patients. Blood 98:1678–1686

Garcia GE, Xia Y, Chen S et al (2000) NF-kappaB-dependent fractalkine induction in rat aortic endothelial cells stimulated by IL-1beta, TNF-alpha, and LPS. J Leukoc Biol 67:577–584

Garcia-Alvarez M, Berenguer J, Guzmán-Fulgencio M et al (2011) High plasma fractalkine (CX3CL1) levels are associated with

severe liver disease in HIV/HCV co-infected patients with HCV genotype 1. Cytokine 54:244–248
Garton KJ, Gough PJ, Blobel CP et al (2001) Tumor necrosis factor-alpha-converting enzyme (ADAM17) mediates the cleavage and shedding of fractalkine (CX3CL1). J Biol Chem 276:37993–38001
Guo J, Chen T, Wang B et al (2003a) Chemoattraction, adhesion and activation of natural killer cells are involved in the antitumor immune response induced by fractalkine/CX3CL1. Immunol Lett 89:1–7
Guo J, Zhang M, Wang B et al (2003b) Fractalkine transgene induces T-cell-dependent antitumor immunity through chemoattraction and activation of dendritic cells. Int J Cancer 103:212–220
Gupta D, Gupta V, Singh V et al (2014) Study of polymorphisms in CX3CR1, PLEKHA1 and VEGF genes as risk factors for age-related macular degeneration in Indian patients. Arch Med Res 45:489–494
Harris ED Jr (1990) Rheumatoid arthritis. Pathophysiology and implications for therapy. N Engl J Med 322:1277–1289
Harrison JK, Jiang Y, Chen S et al (1998) Role for neuronally derived fractalkine in mediating interactions between neurons and CX3CR1-expressing microglia. Proc Natl Acad Sci USA 95:10896–10901
Harrison JK, Fong AM, Swain PA et al (2001) Mutational analysis of the fractalkine chemokine domain. Basic amino acid residues differentially contribute to CX3CR1 binding, signaling, and cell adhesion. J Biol Chem 276:21632–21641
Haskell CA, Cleary MD, Charo IF (2000) Unique role of the chemokine domain of fractalkine in cell capture. Kinetics of receptor dissociation correlate with cell adhesion. J Biol Chem 275:34183–34189
He M, Moochhala SM, Adhikari S et al (2009) Administration of exogenous fractalkine, a CX3C chemokine, is capable of modulating inflammatory response in cecal ligation and puncture-induced sepsis. Shock 31:33–39
Hu JH, Yang JP, Liu L et al (2012) Involvement of CX3CR1 in bone cancer pain through the activation of microglia p38 MAPK pathway in the spinal cord. Brain Res 1465:1–9
Huang ZZ, Li D, Liu CC et al (2014) CX3CL1-mediated macrophage activation contributed to paclitaxel-induced DRG neuronal apoptosis and painful peripheral neuropathy. Brain Behav Immun 40:155–165
Hundhausen C, Misztela D, Berkhout TA et al (2003) The disintegrin-like metalloproteinase ADAM10 is involved in constitutive cleavage of CX3CL1 (fractalkine) and regulates CX3CL1-mediated cell-cell adhesion. Blood 102:1186–1195
Hyakudomi M, Matsubara T, Hyakudomi R et al (2008) Increased expression of fractalkine is correlated with a better prognosis and an increased number of both CD8 + T cells and natural killer cells in gastric adenocarcinoma. Ann Surg Oncol 15:1775–1782
Imaizumi T, Matsumiya T, Fujimoto K et al (2000) Interferon-gamma stimulates the expression of CX3CL1/fractalkine in cultured human endothelial cells. Tohoku J Exp Med 192:127–139
Imaizumi T, Yoshida H, Satoh K (2004) Regulation of CX3CL1/fractalkine expression in endothelial cells. J Atheroscler Thromb 11:15–21
Karlmark KR, Zimmermann HW, Roderburg C et al (2010) The fractalkine receptor CX(3)CR1 protects against liver fibrosis by controlling differentiation and survival of infiltrating hepatic monocytes. Hepatology 52:1769–1782
Kasama T, Wakabayashi K, Sato M et al (2010) Relevance of the CX3CL1/fractalkine-CX3CR1 pathway in vasculitis and vasculopathy. Transl Res 155:20–26
Kim M, Rooper L, Xie J et al (2012) Fractalkine receptor CX(3)CR1 is expressed in epithelial ovarian carcinoma cells and required for motility and adhesion to peritoneal mesothelial cells. Mol Cancer Res 10:11–24
Klein R, Peto T, Bird A et al (2004) The epidemiology of age-related macular degeneration. Am J Ophthalmol 137:486–495
Klein R, Klein BE, Knudtson MD et al (2007) Fifteen-year cumulative incidence of age-related macular degeneration: the Beaver Dam Eye Study. Ophthalmology 114:253–262
Ko SH, Jeon JI, Kim H et al (2014) Mitogen-activated protein kinase/IkappaB kinase/NF-kappaB-dependent and AP-1-independent CX3CL1 expression in intestinal epithelial cells stimulated with Clostridium difficile toxin A. J Mol Med 92:411–427
Landsman L, Bar-On L, Zernecke A et al (2009) CX3CR1 is required for monocyte homeostasis and atherogenesis by promoting cell survival. Blood 113:963–972
Lauro C, Catalano M, Trettel F et al (2015) Fractalkine in the nervous system: neuroprotective or neurotoxic molecule? Ann NY Acad Sci 1351:141–148
Lee S, Varvel NH, Konerth ME et al (2010) CX3CR1 deficiency alters microglial activation and reduces beta-amyloid deposition in two Alzheimer's disease mouse models. Am J Pathol 177:2549–2562
Lee YS, Morinaga H, Kim JJ et al (2013) The fractalkine/CX3CR1 system regulates beta cell function and insulin secretion. Cell 153:413–425
Lesnik P, Haskell CA, Charo IF (2003) Decreased atherosclerosis in CX3CR1−/− mice reveals a role for fractalkine in atherogenesis. J Clin Invest 111:333–340
Li J, Guo Y, Luan X et al (2012) Independent roles of monocyte chemoattractant protein-1, regulated on activation, normal T-cell expressed and secreted and fractalkine in the vulnerability of coronary atherosclerotic plaques. Circ J 76:2167–2173
Lindia JA, McGowan E, Jochnowitz N et al (2005) Induction of CX3CL1 expression in astrocytes and CX3CR1 in microglia in the spinal cord of a rat model of neuropathic pain. J Pain 6:434–438
Liu GY, Kulasingam V, Alexander RT et al (2005) Recycling of the membrane-anchored chemokine, CX3CL1. J Biol Chem 280:19858–19866
Liu H, Jiang D, Zhang S et al (2010) Aspirin inhibits fractalkine expression in atherosclerotic plaques and reduces atherosclerosis in ApoE gene knockout mice. Cardiovasc Drugs Ther 24:17–24
Ludwig A, Weber C (2007) Transmembrane chemokines: versatile 'special agents' in vascular inflammation. Thromb Haemost 97:694–703
Luster AD (1998) Chemokines–chemotactic cytokines that mediate inflammation. N Engl J Med 338:436–445
Ma W, Zhao L, Fontainhas AM et al (2009) Microglia in the mouse retina alter the structure and function of retinal pigmented epithelial cells: a potential cellular interaction relevant to AMD. PLoS ONE 4:e7945
Maciejewski-Lenoir D, Chen S, Feng L et al (1999) Characterization of fractalkine in rat brain cells: migratory and activation signals for CX3CR-1-expressing microglia. J Immunol 163:1628–1635
Mantyh PW (2006) Cancer pain and its impact on diagnosis, survival and quality of life. Nat Rev Neurosci 7:797–809
Marchesi F, Piemonti L, Fedele G et al (2008) The chemokine receptor CX3CR1 is involved in the neural tropism and malignant behavior of pancreatic ductal adenocarcinoma. Cancer Res 68:9060–9069
Marchesi F, Locatelli M, Solinas G et al (2010) Role of CX3CR1/CX3CL1 axis in primary and secondary involvement of the nervous system by cancer. J Neuroimmunol 224:39–44
Matsubara T, Ono T, Yamanoi A et al (2007) Fractalkine-CX3CR1 axis regulates tumor cell cycle and deteriorates prognosis after radical resection for hepatocellular carcinoma. J Surg Oncol 95:241–249

Matsumiya T, Ota K, Imaizumi T et al (2010) Characterization of synergistic induction of CX3CL1/fractalkine by TNF-alpha and IFN-gamma in vascular endothelial cells: an essential role for TNF-alpha in post-transcriptional regulation of CX3CL1. J Immunol 184:4205–4214

Matsunawa M, Isozaki T, Odai T et al (2006) Increased serum levels of soluble fractalkine (CX3CL1) correlate with disease activity in rheumatoid vasculitis. Arthritis Rheum 54:3408–3416

Matsunawa M, Odai T, Wakabayashi K et al (2009) Elevated serum levels of soluble CX3CL1 in patients with microscopic polyangiitis. Clin Exp Rheumatol 27:72–78

McDermott DH, Colla JS, Kleeberger CA et al (2000) Genetic polymorphism in CX3CR1 and risk of HIV disease. Science 290:2031

McDermott DH, Halcox JP, Schenke WH et al (2001) Association between polymorphism in the chemokine receptor CX3CR1 and coronary vascular endothelial dysfunction and atherosclerosis. Circ Res 89:401–407

Medina-Contreras O, Geem D, Laur O et al (2011) CX3CR1 regulates intestinal macrophage homeostasis, bacterial translocation, and colitogenic Th17 responses in mice. J Clin Invest 121:4787–4795

Mehta NN, Heffron SP, Patel PN et al (2012) A human model of inflammatory cardio-metabolic dysfunction; a double blind placebo-controlled crossover trial. J Transl Med 10:124

Meng C, Liang X, Li Q et al (2013) Changes of GTP cyclohydrolase I and neuronal apoptosis in rat spinal dorsal cord induced by sciatic nerve injury. Neurol Sci 34:2145–2150

Meucci O, Fatatis A, Simen AA et al (2000) Expression of CX3CR1 chemokine receptors on neurons and their role in neuronal survival. Proc Natl Acad Sci USA 97:8075–8080

Mionnet C, Buatois V, Kanda A et al (2010) CX3CR1 is required for airway inflammation by promoting T helper cell survival and maintenance in inflamed lung. Nat Med 16:1305–1312

Morganti JM, Nash KR, Grimmig BA et al (2012) The soluble isoform of CX3CL1 is necessary for neuroprotection in a mouse model of Parkinson's disease. J Neurosci 32:14592–14601

Morimura S, Sugaya M, Sato S (2013) Interaction between CX3CL1 and CX3CR1 regulates vasculitis induced by immune complex deposition. Am J Pathol 182:1640–1647

Nanki T, Imai T, Nagasaka K et al (2002) Migration of CX3CR1-positive T cells producing type 1 cytokines and cytotoxic molecules into the synovium of patients with rheumatoid arthritis. Arthritis Rheum 46:2878–2883

Nash KR, Lee DC, Hunt JB Jr et al (2013) Fractalkine overexpression suppresses tau pathology in a mouse model of tauopathy. Neurobiol Aging 34:1540–1548

Nash KR, Moran P, Finneran DJ et al (2015) Fractalkine over expression suppresses alpha-synuclein-mediated neurodegeneration. Mol Ther 23:17–23

Neumann H, Kotter MR, Franklin RJ (2009) Debris clearance by microglia: an essential link between degeneration and regeneration. Brain 132(Pt 2):288–295

Nimmerjahn A, Kirchhoff F, Helmchen F (2005) Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. Science 308:1314–1318

O'Callaghan JP, Miller DB (2010) Spinal glia and chronic pain. Metabolism 59(Suppl 1):S21–S26

Odai T, Matsunawa M, Takahashi R et al (2009) Correlation of CX3CL1 and CX3CR1 levels with response to infliximab therapy in patients with rheumatoid arthritis. J Rheumatol 36:1158–1165

Pachot A, Lepape A, Vey S et al (2006) Systemic transcriptional analysis in survivor and non-survivor septic shock patients: a preliminary study. Immunol Lett 106:63–71

Pachot A, Cazalis MA, Venet F et al (2008) Decreased expression of the fractalkine receptor CX3CR1 on circulating monocytes as new feature of sepsis-induced immunosuppression. J Immunol 180:6421–6429

Patel A, Jagadesham VP, Porter KE et al (2008) Characterisation of fractalkine/CX3CL1 and fractalkine receptor (CX3CR1) expression in abdominal aortic aneurysm disease. Eur J Vasc Endovasc Surg 36:20–27

Pour PM, Bell RH, Batra SK (2003) Neural invasion in the staging of pancreatic cancer. Pancreas 26:322–325

Raoul W, Feumi C, Keller N et al (2008a) Lipid-bloated subretinal microglial cells are at the origin of drusen appearance in CX3CR1-deficient mice. Ophthalmic Res 40:115–119

Raoul W, Keller N, Rodero M et al (2008b) Role of the chemokine receptor CX3CR1 in the mobilization of phagocytic retinal microglial cells. J Neuroimmunol 198:56–61

Raspe C, Hocherl K, Rath S et al (2013) NF-kappaB-mediated inverse regulation of fractalkine and CX3CR1 during CLP-induced sepsis. Cytokine 61:97–103

Richter B, Koller L, Hohensinner PJ et al (2012) Fractalkine is an independent predictor of mortality in patients with advanced heart failure. Thromb Haemost 108:1220–1227

Rimaniol AC, Till SJ, Garcia G et al (2003) The CX3C chemokine fractalkine in allergic asthma and rhinitis. J Allergy Clin Immunol 112:1139–1146

Rius C, Company C, Piqueras L et al (2013) Critical role of fractalkine (CX3CL1) in cigarette smoke-induced mononuclear cell adhesion to the arterial endothelium. Thorax 68:177–186

Ross R, Glomset JA (1976) The pathogenesis of atherosclerosis (first of two parts). N Engl J Med 295:369–377

Ruth JH, Volin MV, Haines GK 3rd et al (2001) Fractalkine, a novel chemokine in rheumatoid arthritis and in rat adjuvant-induced arthritis. Arthritis Rheum 44:1568–1581

Schaumberg DA, Rose L, DeAngelis MM et al (2014) Prospective study of common variants in CX3CR1 and risk of macular degeneration: pooled analysis from 5 long-term studies. JAMA Ophthalmol 132:84–95

Schulte A, Schulz B, Andrzejewski MG et al (2007) Sequential processing of the transmembrane chemokines CX3CL1 and CXCL16 by alpha- and gamma-secretases. Biochem Biophys Res Commun 358:233–240

Schulz C, Schäfer A, Stolla M et al (2007) Chemokine fractalkine mediates leukocyte recruitment to inflammatory endothelial cells in flowing whole blood: a critical role for P-selectin expressed on activated platelets. Circulation 116:764–773

Sciume G, Soriani A, Piccoli M et al (2010) CX3CR1/CX3CL1 axis negatively controls glioma cell invasion and is modulated by transforming growth factor-beta1. Neuro Oncol 12:701–710

Shah R, Hinkle CC, Ferguson JF et al (2011) Fractalkine is a novel human adipochemokine associated with type 2 diabetes. Diabetes 60:1512–1518

Shimizu K, Furuichi K, Sakai N et al (2011) Fractalkine and its receptor, CX3CR1, promote hypertensive interstitial fibrosis in the kidney. Hypertens Res 34:747–752

Shiraishi K, Fukuda S, Mori T et al (2000) Identification of fractalkine, a CX3C-type chemokine, as a direct target of p53. Cancer Res 60:3722–3726

Shulby SA, Dolloff NG, Stearns ME et al (2004) CX3CR1-fractalkine expression regulates cellular mechanisms involved in adhesion, migration, and survival of human prostate cancer cells. Cancer Res 64:4693–4698

Soriano SG, Amaravadi LS, Wang YF et al (2002) Mice deficient in fractalkine are less susceptible to cerebral ischemia-reperfusion injury. J Neuroimmunol 125:59–65

Staniland AA, Clark AK, Wodarski R et al (2010) Reduced inflammatory and neuropathic pain and decreased spinal

microglial response in fractalkine receptor (CX3CR1) knockout mice. J Neurochem 114:1143–1157

Stolla M, Pelisek J, von Brühl ML et al (2012) Fractalkine is expressed in early and advanced atherosclerotic lesions and supports monocyte recruitment via CX3CR1. PLoS ONE 7:e43572

Sun S, Cao H, Han M et al (2007) New evidence for the involvement of spinal fractalkine receptor in pain facilitation and spinal glial activation in rat model of monoarthritis. Pain 129:64–75

Tong N, Perry SW, Zhang Q et al (2000) Neuronal fractalkine expression in HIV-1 encephalitis: roles for macrophage recruitment and neuroprotection in the central nervous system. J Immunol 164:1333–1339

Tsang JY, Ni YB, Chan SK et al (2013) CX3CL1 expression is associated with poor outcome in breast cancer patients. Breast Cancer Res Treat 140:495–504

Tsou CL, Haskell CA, Charo IF (2001) Tumor necrosis factor-alpha-converting enzyme mediates the inducible cleavage of fractalkine. J Biol Chem 276:44622–44626

Tuo J, Smith BC, Bojanowski CM et al (2004) The involvement of sequence variation and expression of CX3CR1 in the pathogenesis of age-related macular degeneration. FASEB J 18:1297–1299

Volin MV, Woods JM, Amin MA et al (2001) Fractalkine: a novel angiogenic chemokine in rheumatoid arthritis. Am J Pathol 159:1521–1530

Wan Y, Evans RM (2010) Rosiglitazone activation of PPAR-gamma suppresses fractalkine signaling. J Mol Endocrinol 44:135–142

Weber C (2008) Chemokines in atherosclerosis, thrombosis, and vascular biology. Arterioscler Thrombs Vasc Biol 28:1896

White GE, Tan TC, John AE et al (2010) Fractalkine has anti-apoptotic and proliferative effects on human vascular smooth muscle cells via epidermal growth factor receptor signalling. Cardiovasc Res 85:825–835

Wu G, Ringkamp M, Murinson BB et al (2002) Degeneration of myelinated efferent fibers induces spontaneous activity in uninjured C-fiber afferents. J Neurosci 22:7746–7753

Wu J, Bie B, Yang H et al (2013) Suppression of central chemokine fractalkine receptor signaling alleviates amyloid-induced memory deficiency. Neurobiol Aging 34:2843–2852

Yao X, Qi L, Chen X et al (2014) Expression of CX3CR1 associates with cellular migration, metastasis, and prognosis in human clear cell renal cell carcinoma. Urol Oncol 32:162–170

Yoneda O, Imai T, Goda S et al (2000) Fractalkine-mediated endothelial cell injury by NK cells. J Immunol 164:4055–4062

Zanchi C, Zoja C, Morigi M et al (2008) Fractalkine and CX3CR1 mediate leukocyte capture by endothelium in response to Shiga toxin. J Immunol 181:1460–1469

Zeng Y, Jiang J, Huebener N et al (2005) Fractalkine gene therapy for neuroblastoma is more effective in combination with targeted IL-2. Cancer Lett 228:187–193

Zheng J, Yang M, Shao J et al (2013) Chemokine receptor CX3CR1 contributes to macrophage survival in tumor metastasis. Mol Cancer 12:141

Zhuang ZY, Kawasaki Y, Tan PH et al (2007) Role of the CX3CR1/p38 MAPK pathway in spinal microglia for the development of neuropathic pain following nerve injury-induced cleavage of fractalkine. Brain Behav Immun 21:642–651

Zujovic V, Benavides J, Vige X et al (2000) Fractalkine modulates TNF-alpha secretion and neurotoxicity induced by microglial activation. Glia 29:305–315