

Review Article

Role of the CX3CL1-CX3CR1 axis in chronic inflammatory lung diseases

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Abstract: Persistent inflammation is often present in patients with lung diseases such as chronic obstructive pulmonary diseases (COPD) and pulmonary hypertension. Circulatory leukocyte migration through the lung vascular endothelium contributes to the structural destruction and remodeling seen in these chronic lung diseases. An inflammatory chemokine CX3CL1/fractalkine is associated with inflammatory lung diseases. Membrane-anchored CX3CL1 serves as an adhesion molecule to capture subsets of mononuclear leukocytes that express the sole receptor, CX3CR1. The extracellular chemokine domain of CX3CL1 can be cleaved/shed by a disintegrin and metalloproteinase domain (ADAM) from stimulus-exposed cells. Soluble CX3CL1 chemoattracts and activates CX3CR1⁺ leukocytes such as CD8⁺, CD4⁺, and $\gamma\delta$ T lymphocytes, natural killer cells, dendritic cells, and monocytes/macrophages. CX3CR1⁺ leukocyte attachment to and migration through the lung vascular endothelium lead to mononuclear cell accumulation in the lung vessel walls and parenchyma. Infiltrated CX3CR1⁺ immune cells can release mediators to induce injury, stimulate proliferation, and/or chemoattract inflammatory cells. This contributes to structural destruction and remodeling in the development of inflammatory lung diseases. Limited clinical success in treating chronic pulmonary diseases-associated lung functional decline indicates the urgency and significance of understanding upstream signaling that triggers inflammation. This article reviews the advances in the CX3CL1-CX3CR1 axis-mediated modulation of mononuclear leukocyte adhesion and migration in inflammatory lung diseases such as COPD and pulmonary hypertension. Better understanding of the constant flow of circulating leukocytes into the lung vessel wall and parenchyma will help set a stage for the development of novel therapeutic approaches to treat or even cure chronic lung diseases including COPD and pulmonary hypertension.

Keywords: Chemokine, fractalkine, inflammation, pulmonary, COPD, endothelium, vasculature

Inflammatory lung diseases and CX3CL1/CX3CR1 expression

Persistent inflammation is often present in patients with lung diseases such as chronic obstructive pulmonary diseases (COPD) and pulmonary hypertension (PH)[1-15]. Infiltration and accumulation of immune cells in the lung contribute to structural destruction and remodeling in the pathogenesis of these chronic lung diseases [16-17]. Endothelial cells (EC) respond to stimuli and overproduce a proinflammatory chemokine, fractalkine/CX3CL1 [18-23]. This leads to the endothelial attachment of the subset mononuclear leukocytes that express the sole CX3CL1 receptor, CX3CR1 [23-29]. Membrane-anchored CX3CL1 has been reported to

serve as a pro-adhesion molecule to capture mononuclear leukocytes rapidly and firmly under high blood flow [27, 30]. The extracellular chemokine domain of CX3CL1 can be cleaved/shed by a disintegrin and metalloproteinase domain 17 (ADAM17) from stimulus-exposed endothelial cells [31-32]. ADAM17 is a member of the ADAM family involved in proteolytic ectodomain shedding [33-35]. ADAM17 has been shown to cleave a variety of transmembrane proteins including TNF α precursor and CX3CL1 [31, 36-38]. ADAM10 and ADAM17 are involved in constitutive and inducible cleavage of CX3CL1, respectively [31-32]. The extracellular chemokine domain of CX3CL1 can be cleaved/shed by ADAM17 from stimulus-exposed endothelial cells [31-32]. Soluble CX3CL1 *chemoat-*

The CX3CL1-CX3CR1 axis in lung diseases

Table 1. Elevation of CX3CL1 and its receptor CX3CR1 in lung diseases

Lung Disease	CX3CL1/CX3CR1	Reference
COPD	Increased CX3CL1	McComb et al [39]; Rao et al[78]; Ning et al[52]
PH	Increased CX3CL1/CX3CR1	Balabanian et al[61]; Perros et al[59]; Song et al[13]; Marasini[64]
Pulmonary fibrosis	Increased CX3CL1	Hasegawa et al[63]

tracts and activates CX3CR1⁺ leukocytes such as CD8⁺, CD4⁺, and $\gamma\delta$ T lymphocytes, natural killer (NK) cells, dendritic cells (DC), and monocytes [25, 31, 39-45]. Leukocyte trafficking is modulated by multiple signal transduction pathways including CX3CL1-CX3CR1 signaling.

A number of extracellular stimuli can trigger inflammatory responses in the lungs. For example, smoke-induced activation of the lung vascular endothelium is the initial event in a cellular cascade that transmits smoke stimulation to lung inflammatory responses in the pathogenesis of COPD [46-47]. Persistent inflammation including vascular inflammation occurs in COPD [48], even when the vessels are distant from airways [47]. Endothelial dysfunction with impaired relaxation is characteristic of vascular lesions in COPD [49]. Activated EC release mediators to promote leukocyte trafficking in COPD [50-51]. T cells, predominantly CD8⁺ T cells, are present in the lung parenchyma of smokers with COPD. This can attract other inflammatory cells like neutrophils and macrophages. These infiltrated inflammatory cells play a critical role in vessel wall remodeling and parenchymal destruction seen in the lungs of COPD patients [3]. The early signaling events that transmit smoke-induced endothelial activation to immune cell/leukocyte infiltration in the lung are unclear. Gene profiling reveals an increase in CX3CL1 expression in the lung tissues of smokers who developed COPD when compared to smokers without COPD, suggesting upregulation of CX3CL1 expression plays a role in tobacco smoke-induced COPD [52]. Smoke stimulates CX3CL1 expression in the mouse pulmonary vasculature and lungs [52-53].

Chronic inflammation occurs in the lungs of PH patients, and elevation of CX3CL1 expression correlates with PH. Chronic alveolar hypoxia is present in persons living at high altitude as well as some patients with COPD [54-58]. The levels of plasma and cellular CX3CL1 are increased in the circulation and lungs with COPD and/or PH [39, 52, 59-62]. Exposure of human or animal lungs to low levels of oxygen often leads to overproduction of CX3CL1 and PH [39, 52, 59-62]. Systemic inflammation is linked to PH and fibrosis [63-64]. The levels of serum CX3CL1 and CX3CR1 in monocytes/macrophages are increased in patients with systemic sclerosis [63]. These increases in CX3CL1/CX3CR1 levels are also correlated with the severity of pulmonary fibrosis. In addition, the frequencies of mutations in the CX3CR1 alleles are increased in a subgroup of patients with systemic sclerosis-associated PH [64]. The correlation of increased CX3CL1/CX3CR1 and inflammatory lung diseases is summarized in **Table 1**. These observations support the notion that overexpression of CX3CL1/CX3CR1 triggered by stimuli such as smoking and hypoxia contributes to the pathophysiology of inflammatory lung diseases.

Stimulus-induced CX3CL1/CX3CR1 expression in lung cells

Upregulation of CX3CL1/CX3CR1 expression can be an upstream signaling event in the cell to transmit environmental stimulation to inflammatory responses. A variety of cells in the lung has been shown to respond to stimuli that overproduce CX3CL1/CX3CR1 (**Table 2**). For instance, exposure of human smooth muscle cells to high glucose results in upregulation of CX3CL1 [65]. Interferon-gamma stimulates

The CX3CL1-CX3CR1 axis in lung diseases

Table 2. Upregulation of CX3CL1 and CX3CR1 expression in the cells/tissues of the lungs

Cell/tissue	CX3CL1/CX3CR1	Reference
EC	Increased CX3CL1	Hatakeyama et al[67]; Imaizumi[19]; Matsumiya et al[107]; Popovic et al[99]; Umehara et al[94]
Epithelial cells	Increased CX3CL1	Lucas et al[108]
Smooth muscle cells	Increased CX3CL1/CX3CR1	Ollivier et al[109]; Bursill et al.[110]; Chandrasekar et al.[111]; Chen et al.[112]; Dragomir et al[65]; Lucas et al[45]; Ludwig et al[113]; Perros et al[59]; Sukkar et al[114]; Yoshikawa et al[30]
Fibroblasts	Increased CX3CL1/CX3CR1	Fahy et al[115]; Klosowska et al[116]; Sawai et al[117]
Monocytes/macrophages	Increased CX3CR1	Ancuta et al[18]; Apostolakis et al[118]; Green et al[27]; Landsman et al[119]
Lymphocytes	Increased CX3CR1/CX3CL1	Foussat et al[120]; Kobayashi et al[121]; McComb et al[39]; Muehlhoefer et al[122]; Nishimura et al[123]; Truman et al[43]
DC	Increased CX3CR1	Auffray et al[79]; del Rio et al[124]; Dichmann et al[97]; Foussat et al[120]; Jung et al[125]; Kikuchi et al[126]; Niess et al[127]; Papadopoulos et al[128]

CX3CL1 expression in bronchial epithelial cells [66]. The levels of CX3CL1 in bronchoalveolar lavage fluids are increased in patients with inflammatory diseases. Exposure of EC to interferon-gamma, resistin, cigarette smoke, or shear stress leads to upregulation of CX3CL1 [19, 22, 39, 67-68]. Cigarette smoke induces CX3CR1 expression in mononuclear phagocytes and T lymphocytes [39].

Mononuclear leukocyte recruitment in vascular lesions through CX3CL1-CX3CR1 signaling promotes obstructive remodeling [69]. Neointimal smooth muscle cells develop a proinflammatory phenotype via chemokine pathways including CX3CL1-CX3CR1 [70]. Since CX3CR1^{-/-} mice do not show this recruitment [71], it indicates that the CX3CL1-CX3CR1 axis is critical to inflammatory remodeling. CX3CL1 expression is in-

The CX3CL1-CX3CR1 axis in lung diseases

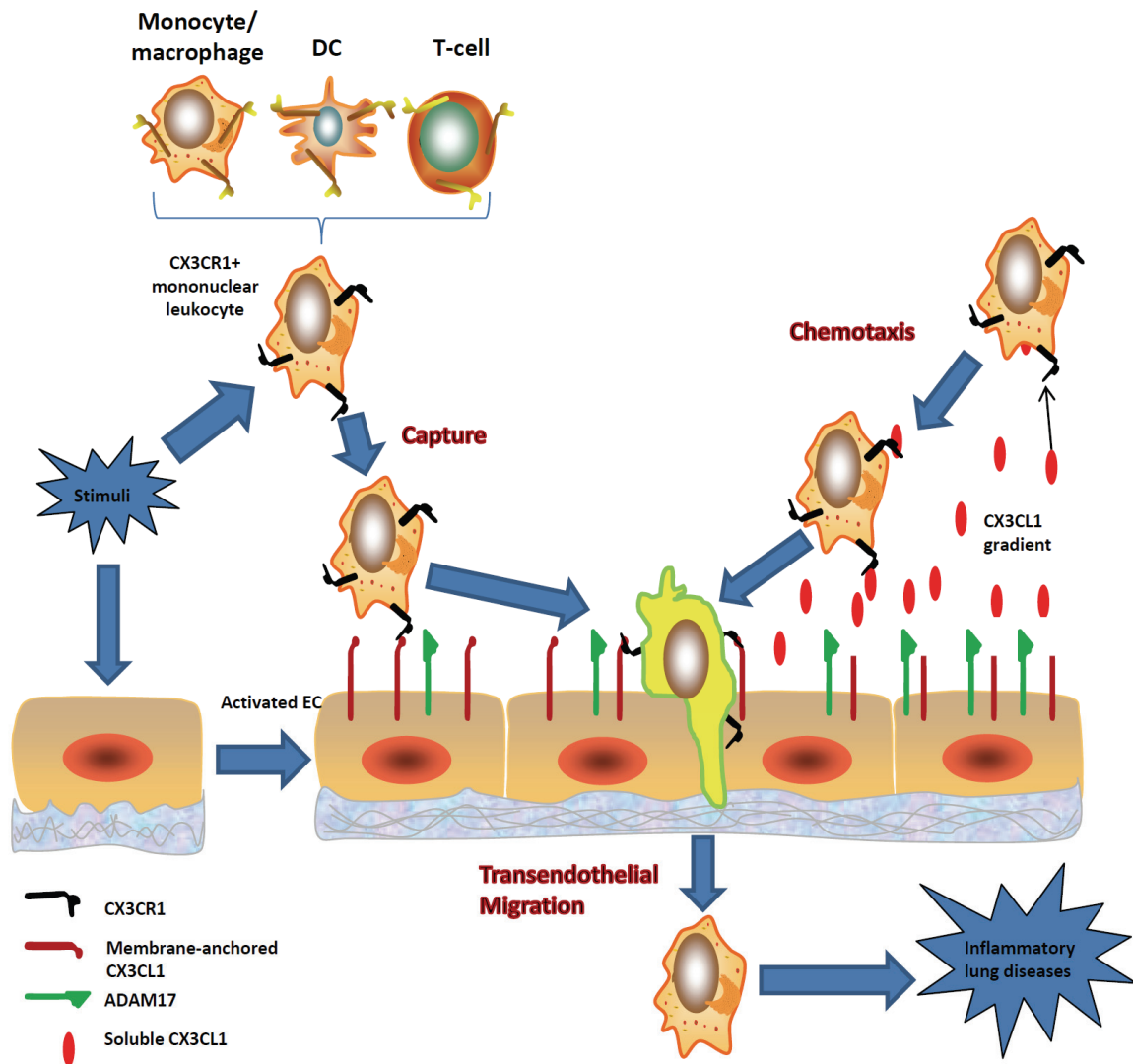


Figure 1. CX3CL1-CX3CR1 modulation of environmental stimulus-induced leukocyte trafficking in chronic lung diseases. *Capture:* Stimuli trigger endothelial CX3CL1 expression, which enhances CX3CR1⁺ leukocyte attachment to the activated lung vascular endothelium. This leads to CX3CR1⁺ leukocyte infiltration. *Chemotaxis:* Stimulus-induced CX3CL1 shedding by ADAM promotes CX3CR1⁺ leukocyte chemotaxis and inflammation. *Transendothelial migration:* Stimulus-induced CX3CL1 interaction with CX3CR1 promotes the transendothelial migration of CX3CR1⁺ leukocytes, inflammatory cell accumulation in vessel walls/parenchyma, and lung structural remodeling and destruction.

created in COPD, which leads to the recruitment of CX3CR1⁺ cells into the lung parenchyma of mice chronically exposed to tobacco smoke [39]. Current studies suggest that endothelial CX3CL1 expression contributes to CX3CR1⁺ leukocyte adhesion, transendothelial migration, and chemotaxis in inflammatory lung diseases (**Figure 1**). The following observations support the notion. First, CX3CL1 serves as an

adhesion molecule [27, 30]. Tobacco smoke-induced overproduction of CX3CL1 on the activated endothelium can capture CX3CR1⁺ leukocytes [72-77]. Second, tobacco smoke-induced CX3CL1-CX3CR1 interaction can enhance leukocyte transendothelial migration [39, 75]. Third, CX3CL1 shedded from the smoke-activated endothelium can act as a potent chemotactic agent for CX3CR1⁺ leukocytes [28, 31, 43].

Modulation of leukocyte attachment via CX3CL1 interaction with CX3CR1

The first key step in lung inflammatory cell infiltration of the low resistance but high flow system is the attachment of circulatory leukocytes to the endothelium. Stimuli trigger endothelial activation and leukocyte adhesion. For instance, tobacco smoke has been shown to enhance the attachment of leukocytes to the vascular endothelium [72-78]. Exposure of mice to second-hand smoke promotes leukocyte adhesion on the lung microvascular endothelium [78]. CX3CR1 deficiency impairs monocyte accumulation in arterial intima, suggesting a key role of the CX3CL1-CX3CR1 axis in COPD immunopathology [27, 79-80]. Inflammatory chemokines regulate leukocyte trafficking and COPD-related remodeling [81-84]. Expression of CX3CL1 and its receptor in the lung endothelium and leukocytes are upregulated in COPD [39, 52]. Overexpression of endothelial CX3CL1 following tobacco smoke exposure may act as a lung vascular gateway. CX3CR1⁺ leukocytes are captured rapidly and then migrate into the lung, contributing to inflammation in the lungs of patients with COPD.

Hypoxia-induced inflammatory response results in EC activation with enhanced lymphocyte and DC adhesion [17, 85-89]. Endothelial cells treated with TNF- α and hypoxia/reoxygenation induced a strong NK cell adhesion [90]. Idiopathic pulmonary arterial hypertension-related inflammatory infiltrates have been seen in the range of plexiform lesions with local expression of chemokines CCL2, CCL5, and CX3CL1 [55, 59, 91-93]. Expression of CX3CL1 and its receptor in the lung endothelium and T-lymphocytes are upregulated in PH [61, 94]. These observations support the notion that overexpression of endothelial CX3CL1 following hypoxia exposure is associated with CX3CR1⁺ leukocyte adhesion and transendothelial migration into the artery tissues, leading to vascular remodeling and progression of PH.

CX3CL1-promoted CX3CR1⁺ cell migration

Transendothelial migration of attached leukocytes is essential for immune cell trafficking and accumulation in the lungs. Tobacco smoke stimulates the migration of lung leukocytes including T-cells and monocytes *in vitro* and *in vivo* [39, 75]. McComb and his colleagues have reported that exposure of mice to acute or

chronic tobacco smoke results in upregulation of CX3CL1 and CX3CR1, the influx of inflammatory cells including monocytes/macrophages and lymphocytes into the lungs, and the development of COPD [39]. Experimental results support the notion that tobacco smoke-induced activation of the endothelium and migration of monocytes play a role in the accumulation of lung monocytes/macrophages [75]. Smoke-enhanced interaction between the CX3CL1⁺ endothelium and CX3CR1⁺ leukocytes is expected to promote the onward transendothelial migration of the mononuclear leukocytes, resulting in inflammatory cell accumulation and the development of COPD.

Hypoxia constitutes a stimulus for EC activation and circulating monocyte/mononuclear fibrocyte migration in the lung [17, 95]. Alveolar hypoxia is present in a variety of lung disorders such as COPD (blocked airways and destructed structures for the oxygen-CO₂ exchange), lung cancers, chronic inflammation (systemic inflammation such as scleroderma, interstitial lung diseases, and bacterial infections). The local hypoxic microenvironment may serve as a stimulus to promote the transendothelial migration of leukocytes including monocytes/macrophages [95]. The recruited immune cells adapt to the hypoxic environment through the alteration of the gene expression [95]. Proinflammatory mediators released from infiltrates contribute to structural modulations including cell differentiation, proliferation, and remodeling in the development and progression of PH [54]. Balabanian et al have found that the levels of CX3CL1/CX3CR1 in PH patients are higher than that in control subjects [61]. It is unclear about the link between upregulation of CX3CL1/CX3CR1 expression and the development of PH. However, CX3CL1 is known to mediate CX3CR1⁺ cell migration. For instance, CX3CL1 preferentially modulates the transendothelial migration of monocytes expressing CX3CR1 [96]. CX3CL1 induces chemotaxis of immature and mature DC [97]. The CX3CL1-CX3CR1 axis contributes to transmigration of neuroblastoma cells through bone-marrow endothelium [98]. In addition, thrombin-induced CX3CL1 expression is associated with an increase in monocyte transendothelial migration [99]. These observations support the notion that PH-related upregulation of CX3CL1 in the lung plays a critical role in leukocyte trafficking and monocyte/macrophage accumulation in vascular remodeling.

CX3CL1-stimulated chemotaxis and infiltration of leukocytes in lung inflammation

Accumulation of monocytes is an essential event in inflammatory responses of the lung [95]. Monocytes migrate along chemotactic gradients within the lung vasculature. Tobacco smoke stimulates leukocyte chemotaxis [100]. Smoke-increased CX3CL1 expression can promote lung mononuclear leukocyte chemotaxis via the CX3CL1-CX3CR1 axis. Leukocyte recruitment requires intercellular communication between infiltrating leukocytes and the endothelium through mediators such as CX3CL1. ADAM-induced cleavage of CX3CL1 is associated with the recruitment of CX3CR1⁺ leukocytes to CX3CL1-expressing cells [31-32]. Tobacco smoke exposure is linked to increases in ADAM17 activity [101-102], which can enhance CX3CL1 shedding. Tobacco smoke-induced recruitment and accumulation of CX3CR1⁺ leukocytes can therefore contribute to alveolar wall destruction. Soluble CX3CL1 stimulates CX3CR1⁺ leukocyte chemotaxis [27, 42, 44, 103]. Extravasations of inflammatory cells are found in the alveolus [54, 104]. CX3CL1-mediated chemotaxis of CX3CR1⁺ leukocytes can contribute to accumulation of inflammatory cells in the lung and development of COPD. Tobacco smoke-increased CX3CL1 expression may promote lung mononuclear leukocyte chemotaxis via the CX3CL1-CX3CR1 axis in the development of emphysema.

Hypoxia promotes leukocyte chemotaxis [95, 105-106]. Soluble CX3CL1 stimulates CX3CR1⁺ leukocyte chemotaxis [27, 42, 44, 103]. Hypoxic recruitment and accumulation of CX3CR1⁺ leukocytes contribute to the wall thickening and the "muscularization" of the precapillary segment. Extravasations of inflammatory and mesenchymal precursor cells were found in the alveolus [54, 104]. These infiltrated cells can differentiate into smooth muscle-like cells and/or release mediators to promote cell proliferation, differentiation, and transdifferentiation in hypoxic distal muscularization [54]. PH-associated elevation of CX3CL1/CX3CR1 appears to be correlated with monocyte infiltration in vascular remodeling processes.

CX3CL1-CX3CR1 signaling: a potential target for treatment of inflammatory lung diseases

Limited clinical success in treating chronic lung

diseases-associated lung structural remodeling and functional decline indicates the urgency and significance of understanding upstream signaling that triggers inflammation. The constant flow of circulating leukocytes into the lung vessel wall and parenchyma contributes to cell proliferation, damage, and/or death in the pathogenesis of COPD and PH. CX3CL1 may act as a powerful gatekeeper that responds to stimuli, such as smoke/hypoxia, to allow CX3CR1⁺ leukocyte migration through the endothelial barrier. Elucidating the role of CX3CL1-CX3CR1 axis in environmental stimulus-induced leukocyte capturing, chemotaxis, and trafficking can help set a stage for the development of novel therapeutic approaches to treat or even cure COPD. For instance, antibodies or small molecules may be used to block the CX3CL1-CX3CR1 interaction. This may reduce or prevent leukocyte infiltration/accumulation, structural remodeling/destruction, and functional decline in the development and progression of chronic lung diseases including COPD and PH.

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The CX3CL1-CX3CR1 axis in lung diseases

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The CX3CL1-CX3CR1 axis in lung diseases

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