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REVIEW ARTICLE

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Fractalkine in rheumatoid arthritis and allied conditions

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Abstract Leukocyte adhesion and trafficking at the endothelium requires both adhesion molecules and chemotactic factors. Fractalkine (CX3C) is a unique chemokine, and is expressed on tumor necrosis factor-α- and interleukin-1-activated endothelial cells (ECs). Fractalkine receptor, CX3CR1, is expressed on NK cells, monocytes, and some portion of CD4- and CD8-positive T cells. Interactions between fractalkine and CX3CR1 can mediate not only chemotaxis, but also cell adhesion in the absence of substrates for other adhesion molecules. Furthermore, fractalkine activates NK cells, leading to increased cytotoxicity and interferon-γ production. Recently, accumulating evidence has shown that fractalkine is involved in the pathogenesis of rheumatoid arthritis and allied conditions. This review examines new concepts underlying fractalkine-mediated leukocyte migration and tissue damage, focusing primarily on the pathophysiological roles of fractalkine in rheumatic diseases.

Key words Chemokines · Fractalkine (CX3C) · Inflammation · Rheumatic disease · Vascular biology

Introduction

The migration of leukocytes into extravascular tissues involves a cascade of molecular events including the elaboration of chemotactic factors, the response to these factors, the interaction of leukocytes with endothelial cells (ECs), and leukocyte transmigration through the blood vessel wall.[1,2] The endothelium plays an important role in the recruitment and emigration of circulating leukocytes into sites of inflammation and immune responses, and ECs can be the primary target of immunologic injury, which results in vasculopathy and organ dysfunction.[1–3]

Chemokines were first described as chemoattractant cytokines synthesized at sites of inflammation and are major regulatory proteins for leukocyte recruitment and trafficking.[4,5] More than 50 chemokines have been identified to date and are subdivided into four subfamilies, C-, CC-, CXC-, and CX3C-chemokine, based on the number and spacing of the first two cysteines in a conserved cysteine structural motif. Different chemokine classes tend to exhibit different ranges of leukocyte specificity, and the chemokines produced during the inflammatory process are expected to determine the extent, quality, and duration of the cellular infiltrate.[5–7] However, inappropriately elevated expression of inflammatory chemokines may result in extensive tissue damage caused by activated leukocytes.[8,9] Because fractalkine is expressed on ECs activated by proinflammatory cytokines[10] and has both chemoattractive and adhesive functions,[11–13] it is likely that fractalkine is involved in the extravasation of leukocytes into inflamed tissues in the inflammatory conditions such as rheumatic diseases.[13,14]

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Fractalkine (CX3C chemokine)

Unique structure and function

Fractalkine, a large protein of 373 amino acids containing multiple domains, is the first CX3C-chemokine to be described and is structurally distinct from other chemokines.[10,13–15] Importantly, fractalkine is a transmembrane molecule expressed on the cell surface. Beginning with its extracellular domain, the first 76 amino acids of

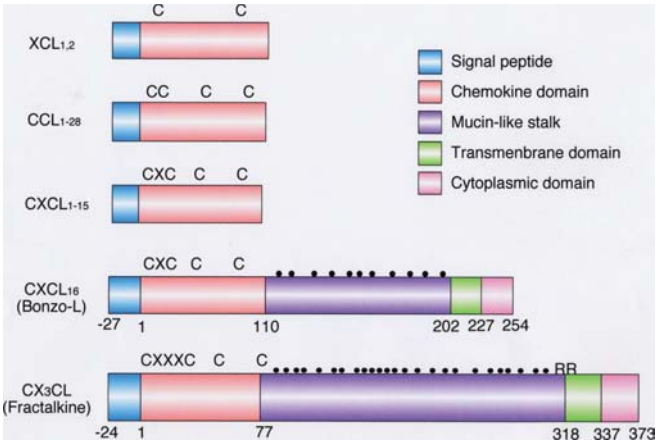

Fig. 1. Schematic structure of fractalkine.[13,14] CX3C-chemokine, fractalkine is a large protein of 373 amino acids containing multiple domains and structurally distinct from other chemokines, i.e., CXCLs, CCLs, and CLs. Beginning with the predicted signal peptide, it contains an N-terminal chemokine domain (residues 1–76) with the unique three-residue insertion between cysteines (CX3C), mucin-like stalk (residues 77–317) with predicted *O*-glycosylated serine and threonine (●), transmembrane domain (residues 318–336), and intracellular domain (residues 337–373). *RR* indicates a membrane-proximal dibasic motif similar to a dibasic cleavage site in syndecans. CXCL16 (Bonzo ligand) has a structure similar to that of of fractalkine

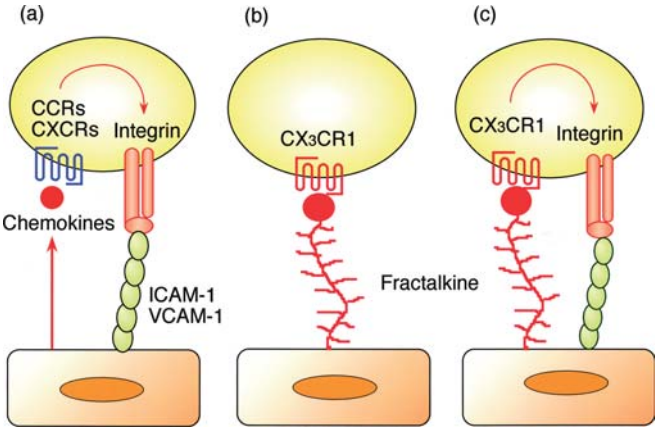

Fig. 2a–c. Dual functions of fractalkine as an adhesion molecule and chemokine.[13,14] **a** Soluble chemokines bind to specific receptors (CCRs or CXCRs) and trigger integrin activation. Integrins with high avidity bind to their ligands (ICAM-1 or VCAM-1) and support cell adhesion. **b** Fractalkine, consisting of chemokine domain and mucin-like stalk, are expressed as the membrane-bound form on activated endothelial cells. Interaction between fractalkine and CX3CR1 can suppose cell adhesion without involvement of integrins. **c** In addition to the intrinsic adhesion function of fractalkine, CX3CR1 can also transduce signals for integrin activation. Therefore, fractalkine and integrins cooperatively mediate cell adhesion. *ICAM-1*, intercellular adhesion molecule-1; *VCAM-1*, vascular cell adhesion molecule-1

fractalkine comprise a chemokine domain with a novel arrangement of cysteines (CXXXC: three amino acids separate the first two cysteines), an extended mucin-like stalk, a transmembrane domain, and an intracellular domain of 37 amino acids. Membrane-bound fractalkine can be markedly induced on primary ECs by inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1, and soluble fractalkine can be released, presumably by proteolysis at a membrane-proximal dibasic cleavage site similar to those of syndecans, and exhibits an efficient chemotactic activity for monocytes and T cells (Fig. 1).[10]

Following the original report that fractalkine receptor (CX3CR1)-expressing cells adhered to immobilized fractalkine,[11] transfection studies with chimeric proteins revealed that the mucin domain provides a stalk which extends the chemokine domain away from the endothelial cell surface enabling presentation of the chemokine domain to leukocytes and supporting cell adhesion.[16,17] In addition to the intrinsic adhesion function of fractalkine, we found that soluble-fractalkine enhanced the binding of CX3CR1-expressing THP-1 cells to immobilized fibronectin and intercellular adhesion molecule-1 (ICAM-1). This enhancement was efficiently inhibited by a G_i inhibitor, pertussis toxin, suggesting that CX3CR1 transduces signals to increase integrin avidity through G protein activation (Fig. 2).[12] Furthermore, THP-1 cells adhered to a fractalkine transfected-ECV304 cells or TNF-α-activated human umbilical vein endothelial cells (HUVECs) more efficiently than to control cells.[12] Moreover, we observed that co-immobilization of fractalkine with integrin ligands, including either fibronectin or ICAM-1, enhanced cell adhesion compared with that observed for the fractalkine interaction with CX3CR1 or each integrin system alone.[18] Taken together, these findings suggest that fractalkine can function as an adhesion molecule between fractalkine-expressing ECs and CX3CR1-expressing cells rather than a chemotactic factor.[13]

Fractalkine receptor (CX3CR1) and leukocyte subset

$CD4^+$ helper T cells (Th) as well as $CD8^+$ cytotoxic T cells (Tc) are subdivided into two distinct populations based on the profile of cytokine production. Th1 and Tc1 cells secret interferon (IFN)-γ, TNF-β, and IL-2, mediate immune responses against intracellular pathogens, and are associated with pathological process such as organ-specific autoimmune diseases. Conversely, Th2 and Tc2 cells produce IL-4, IL-5, IL-6, and IL-13, mediate immune responses against extracellular pathogens, and are associated with allergic immune responses.[19,20] Recent studies have shown that various lymphocyte subsets with differential tissue tropism, in accordance with their particular developmental stages and/or functional properties, express specific chemokine receptors.[21,22] It has been reported that Th1 cells preferentially express CCR5 and CXCR3 (Th1-associated chemokine receptors), while Th2 cells preferentially express CCR4, possibly CCR3 and CCR8 (Th2-assocaited chemokine receptors). Helper T cells are further subdivided into two distinct subsets according to the expression of CCR7; $CCR7^+$ naïve cells, $CCR7^+$ lymph-node homing memory cells, and $CCR7^-$ tissue-homing effector memory cells. Memory T cells lacking CCR7 produce the effector cytokine IFN-γ with rapid kinetics (effector memory T cells:

T_{EM}), whereas T cells expressing CCR7 represent a pool of central memory T cells (T_{CM}).[22]

$CD8^+$ cytotoxic T cells start to express lytic mediators, perforin and granzymes, during differentiation to memory/effector stages after antigenic stimulation.[23] Terminally differentiated effector $CD8^+$ T cells do not express CD27, CD28 (costimulatory molecules), and CD62L (L-selectin), and possess high cytolytic activity producing IFN-γ and TNF-α.[24,25]

Imai et al. have identified CX3CR1 and have demonstrated that it is expressed on most $CD16^+$ NK cells, the majority of $CD14^+$ monocytes, and a substantial fraction of $CD3^+$ T cells.[11] Recently, we characterized the phenotypes of lymphoid cells expressing CX3CR1. The majority of CX3CR1-expressing $CD4^+$ and $CD8^+$ T cells co-express CCR5, but not CXCR3, suggesting that CX3CR1-expressing T cells partly overlap with Th1 and Tc1 cells, respectively.[26] In addition, CX3CR1-expressing cells including $CD4^+$ T cells, $CD8^+$ T cells, γδ T cells, and NK cells, express CD57 and CD11b (good markers for cytotoxic lymphocytes) and possess cytoplasmic granules containing perforin and granzyme B.[26] Collectively, these data suggest that CX3CR1 is a highly selective chemokine receptor and surface marker for cytotoxic effector lymphocytes including NK cells, cytotoxic T lymphocytes (CTLs), and γδ T cells.[13,14] Fractalkine is also known to exert an effect on monocytes. Bazan et al. reported that fractalkine induces the migration of monocytes,[10] and Imai et al. demonstrated that $CD14^+$ monocytes express CX3CR1.[11] Profiles of CX3CR1-expressing cells are summarized in Table 1.

Table 1. Profiles of CX3CR1+ cells

	Expression of CX3CR1	
CD4 T cell	5%	
CD8 T cell	40%	
γδ T cell	70%	
NK cell	90%	
Monocytes	80%	
B cell	<1%	
T cells (CD3+)		
Naive	Central memory	Cytotoxic effector
(CD45RA+/CD27+)	(CD45RA–/CD27–)	(CD45RA± /CD27±) CX3CR1+
	Perforin+ Granzyme+ CD57+	
	CCR4+	CD11b+
CCR7+	CCR7–	CCR7–
CD62L+	CD62L–	CD62L–
CD28+	CD28–	CD28–
NK cells (CD16+)		
CX3CR1+, CXCR1+, Perforin+, Granzyme+		
Macrophages (CD14+)		
Immature	Mature	
CX3CR1+	CX3CR1++	
CCR2+	CCR2–	
CD62L+	CD62L–	
Gr1+	Gr1–	

Unique roles in cell transmigration

In the classical pathway of leukocyte migration, the first step involves transient, selectin-mediated interactions between rolling leukocytes and the endothelium (rolling or tethering). Next, integrins on leukocytes are activated by chemokines that have been produced locally and presented on glycosaminoglycans (triggering), resulting in firm adhesion between leukocytes and endothelial cells (firm adhesion). Leukocytes then extravasate through the vascular wall and into the tissue (transmigration).[1,2,27] Prior to the identification and description of fractalkine, chemokines had been perceived to be secreted as the soluble molecule and associate with the tissue matrix such as glycosaminoglycan to retain themselves on the cell surface. Following this binding, the interaction between chemokines and their specific receptors on leukocytes triggers activation of members of the integrin family through a G protein-dependent mechanism.[27]

In the case of fractalkine, the chemokine domain is presented at the top of a cell-bound extended mucin-like stalk and fractalkine itself functions as an adhesion molecule,[10,15,11] thereby obviating the need for both the association with proteoglycans and other adhesion molecules. Indeed, CX3CR1-expressing cells bind rapidly and with high affinity to immobilized fractalkine or fractalkine-expressing cells in both static and physiologic flow conditions.[11,12,28] Video microscopy revealed that CX3CR1-expressing cells adhere more rapidly to immobilized fractalkine than to vascular cell adhesion molecule-1 (VCAM-1) without cell tethering and dislodging in flow conditions.[29] Thus, fractalkine may facilitate extravasation of circulating leukocytes by mediating cell adhesion through the initial tethering and the final transmigration steps (Fig. 3).[13] In addition, we found that engagement of both CX3CR1 and integrins through co-expression of fractalkine and integrin ligands, such as intercellular adhesion molecule-1 (ICAM-1) and VCAM-1, results in greatly enhanced cell adhesion compared with each system alone.[13,18]

Cytotoxic function

Natural killer (NK) cells, which express cytolytic activity without known prior antigenic stimulation, are thought to mediate immunity against viruses and surveillance for protection against neoplastic transformation.[30] NK cells are stimulated through NK activating receptors such as CD2, CD16 and NKG2D, and can mediate target cell lysis through several pathways including exocytosis of granules containing lytic mediators, such as perforin and granzymes, and CD95(Fas)–CD95L(FasL) interaction.[31,32]

Almost all NK cells express CX3CR1,[11,33] suggesting that they are important effectors of the biological functions of

fractalkine, i.e., chemotaxis and cellular activation. Certainly, soluble fractalkine can induce NK cell transmigration[11] and enhance granule exocytosis and cytolytic function of NK cells.[33] In addition, fractalkine-expressing ECV304 cells or HUVECs showed increased interaction with NK cells and susceptibility to NK cell-mediated cytolysis, indicating that fractalkine on ECs actually functions as a triggering molecule for NK cell activation.[33]

Similar to NK cells, CX3CR1-expressing $CD8^+$ and $CD4^+$ T cells, but not those without surface CX3CR1, showed terminally differentiated effector phenotypes with cytotoxic granules. We found that $CD8^+$ T cells sorted into CX3CR1-positive population indeed possess much greater cytotoxic activity than presorted or CX3CR1-negative $CD8^+$ T cells by CD3 monoclonal antibody-mediated redirected cytotoxicity assay.[26] These findings suggest that the expression of fractalkine at the site of inflammation can attract and activate NK cells through CX3CR1, and that NK cells, once activated under such conditions, can lyse neighboring ECs despite MHC class I expression.[13,33]

Roles in inflammation

Nishimura et al. have reported that transmigration of $CD8^+$ T cells ($CX3CR1^+/CCR5^+$) and NK cells ($CX3CR1^+/CXCR1^+$) to secondary chemokines, macrophage inflammatory protein (MIP)-1β or IL-8, was significantly increased in the presence of membrane-bound fractalkine.[26] Thus, fractalkine expressed on inflamed endothelium may play a role as vascular gateway for cytotoxic effector cells (CX3CR1-expressing cells) by rapidly capturing them from the blood, and by promoting their migration into tissue, where Th1 polarization may be occurring through IFN-γ production.

NK cells are important in innate immunity through production of cytokines, including IFN-γ, TNF-α, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-3, IL-5, IL-10, and IL-15.[34] Interferon-γ, produced by NK cells and γδ T cells as well as Th1 cells, has also been shown to be Th1 cell polarization.[35,36] Recently, Yoneda et al. reported that stimulation of NK cells with immobilized fractalkine, but not with soluble fractalkine, or coculture of NK cells with fractalkine-expressing cells, markedly induced IFN-γ production,[37] suggesting a role for fractalkine expressed on ECs in developing Th1 responses.[13,14] Interferon-γ also enhances expression of fractalkine on ECs,[10,11] indicating existence of a paracrine feedback loop system in which ECs may be activated to produce more fractalkine (Fig. 4).[14]

Fractalkine in rheumatoid arthritis and allied conditions

Inflammation is caused by proinflammatory cytokines produced by activated immune-potent cells. Inflammatory cytokines, such as TNF-α and IFN-γ, increase expression of adhesion molecules and production of chemokines including fractalkine, leading to leukocyte transmigration into tissues. Therefore, inappropriately elevated expression of inflammatory chemokines may result in extensive tissue damage and/or chronic inflammation. Since fractalkine promotes cell transmigration and activates CX3CR1-positive cells to produce IFN-γ, it is likely that fractalkine is involved in the immunopathogenesis of autoimmune diseases through chronic inflammation.[13,14]

Rheumatoid arthritis

Recently, several papers indicate that fractalkine may be involved in pathogenesis of rheumatoid arthritis. Ruth et al. have reported that increased expression of fractalkine and CX3CR1 on synovial tissue macrophages, fibroblasts, endothelial cells and dendritic cells in rheumatoid arthritis (RA) patients as well as in an adjuvant-induced arthritis model in rats.[38,39] Furthermore, they observed that expression of fractalkine on $CD14^+$ monocytes and CX3CR1 on $CD3^+$ T cells in synovial fluids correlated positively with morning stiffness and swollen joint count, respectively.[39] Nanki et al. have reported that CX3CR1 expression on $CD4^+$ and $CD8^+$ T cells was up-regulated in RA patients and that these T cells in RA patients produced IFN-γ and TNF-α.[40] Similar results have been reported by Sawai et al., namely that fractalkine expression on fibroblast-like synoviocytes co-stimulated T-cell-activating signals and amplified proliferation and IFN-γ production.[41] Volin et al. have reported that fractalkine in synovial fluid from RA patients promotes angiogenic activity in vitro.[42] It has been reported that antifractalkine monoclonal antibody ameliorates arthritis by inhibiting infiltration of inflammatory cells into the synovium in collagen-induced arthritis mouse model.[43]

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by multiorgan damage with infiltration and sequestration of various immune potent cells. A variety of diffuse and focal neuropsychiatric symptoms often occur in SLE patients. Originally, fractalkine has been reported as neurotactin to be expressed in brain inflammation.[15] Yajima et al. have reported that serum fractalkine levels were significantly elevated in patients with SLE than in healthy controls and correlated well with the SLE damage index, titers of anti-DNA and anti-Sm antibodies, immune complex, and serum complement levels.[44] They also reported that fractalkine levels were significantly higher in cerebrospinal fluid from SLE patients with neuropsychiatric involvement that those without involvement.

Autoimmune diseases in MRL/lpr mice resemble human SLE and are characterized by the dysregulation of both cellular and humoral immunity. MRL/lpr mice spontaneously develop lethal glomerulonephritis in association with an increase in circulating immune complexes, autoantibody production, and abnormalities of cytokines and chemokines. There are a number of reports suggesting a

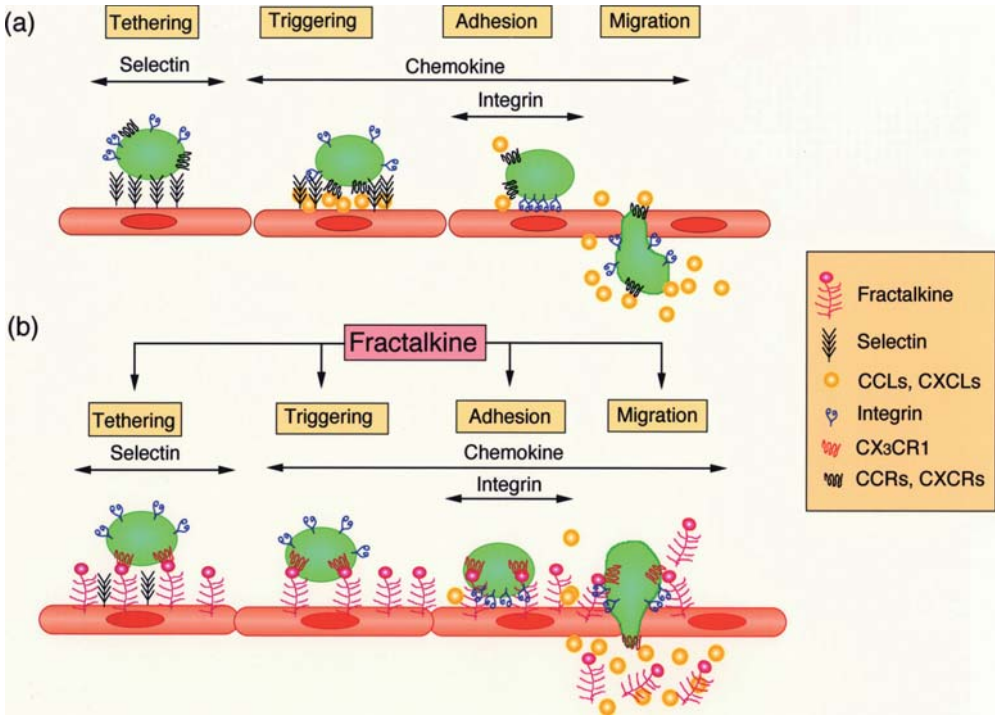

Fig. 3a,b. Schematic model of classical and fractalkine-mediated pathways in the adhesion cascade.[13,14] Leukocyte migration from the circulation into the peripheral tissue is a stepwise process. **a** The classical pathway. The first step involves transient, weak, selectin-mediated binding (*Tethering*). Next, integrins on leukocytes are activated by chemokines that have been presented on glycosaminoglycans (*Triggering*), resulting in firm adhesion between leukocytes and endothelial cells (*Adhesion*). Finally, leukocytes migrate through the endothelial layer in response to a chemokine gradient (*Migration*). **b** Fractalkine-mediated pathway. Fractalkine is expressed on endothelial cells as the membrane-bound form and captures leukocytes in a selectin- and integrin-independent manner. Interaction between fractalkine and CX3CR1 can also increase integrin avidity, resulting in firmer adhesion. Leukocytes then extravasate through the vascular wall and into the tissue to a chemokine gradient. Fractalkine may facilitate extravasation of circulating leukocytes by mediating cell adhesion through the initial tethering and the final transmigration steps

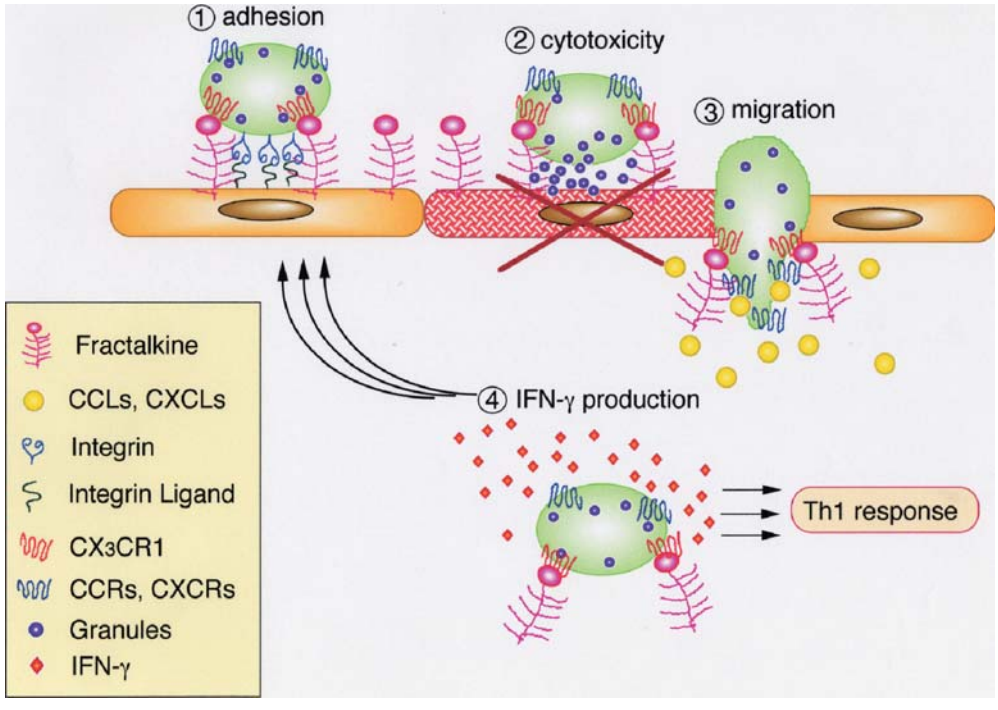

Fig. 4. Biological functions of fractalkine.[14] *1*, Engagement of CX3CR1 and integrins through coexpression of fractalkine and integrin ligands results in firm adhesion. *2*, CX3CR1-expressing cytotoxic effector cells including NK cells, $CD8^+$ T cells and γδ T cells containing cytoplasmic granules. When these cells are activated by membrane-bound fractalkine or activating receptors, they may damage neighboring endothelial cells. *3*, Membrane-bound fractalkine enhanced the effect of other chemokines on migration of CX3CR1-expressing cells into tissue. *4*, Transmigrated CX3CR1-expressing cells, activated by fractalkine, produce interferon-gamma (*IFN-γ*), leading to Th1 response. IFN-γ also enhances expression of fractalkine on endothelial cells, indicating a paracrine feedback loop system

role for fractalkine in human renal diseases (glomerulonephritis, renal tumor, and renal transplants) and in kidney disease in animal models. For example, viral chemokine similar to macrophage inflammatory protein II (vMIP-II), with antagonistic activity for CC-, CXC- and CX3C-chemokine receptors, reduced the infiltration of leukocytes significantly and attenuated proteinuria in the rat crescent glomerulonephritis model.[45] Feng et al. have reported that anti-CX3CR1 antibody treatment dramatically blocked leukocyte infiltration into the glomeruli, prevented crescent formation, and improved renal function.[46] In SLE model mice, Inoue et al. have reported that fractalkine antagonist (fractalkine analogs truncated by >4 amino acid residues from N-terminus) significantly reduced glomerular hypercellularity, glomerulosclerosis, crescent formation, and vasculitis compared with control mice.[47]

Systemic sclerosis

Systemic sclerosis (SSc) is an autoimmune disease with disorders of connective tissue characterized by excessive fibrosis and vascular abnormality in the skin and internal organs. Perivascular cellular infiltration is often observed in affected lesions, and may promote endothelial damage and fibrosis through the production of soluble mediators in patients with SSc. Hasegawa et al. have reported that expression of CX3CR1 on monocytes and T cells were increased in lesions of skin and lungs, and that levels of soluble fractalkine in SSc patients were higher than controls and correlated well with erythrocyte sedimentation rates, digital ischemia, and severity of pulmonary fibrosis.[48]

Myositis

Idiopathic inflammatory myopathy such as polymyositis or dermatomyositis is characterized by chronic inflammation of the voluntary muscles associated with infiltration of immune competent cells, including $CD4^+$ and $CD8^+$ T cells and monocytes, in the skeletal muscle. Infiltrated T cells express cytotoxic molecules, such as granzyme and perforin, and produce TNF-α and IFN-γ. Nanki et al. have reported fractalkine expression on mononuclear cells and endothelial cells, and CX3CR1 expression on the infiltrated $CD4^+$ and $CD8^+$ T cells in an experimental autoimmune myositis mouse model. They also reported that treatment of experimental mice with antifractalkine monoclonal antibody significantly reduced the histopathological myositis score, and infiltration of $CD4^+$ and $CD8^+$ T cells and macrophages.[49]

Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a common complication of systemic inflammatory conditions, such as SLE and SSc, leading to progressive right heart failure and ultimately death. This disease results from chronic obstruction of small pulmonary arteries through endothelial and vascular smooth muscle cell dysfunction accompanied by infiltration of T and B lymphocytes and macrophages. Balabanian et al. have reported that CX3CR1 expression and function are upregulated in circulating T lymphocytes, mostly of the $CD4^+$ T cells, and soluble fractalkine concentrations are elevated in patients with PAH. They also reported that fractalkine mRNA and protein product are expressed in pulmonary artery endothelial cells.[50,51]

Conclusions

The unique chemokine, fractalkine, can fulfill the dual functions of an adhesion molecule and a chemoattractant. Fractalkine is expressed on activated ECs, and functions as a vascular gateway by attracting CX3CR1-expressing NK cells, CTLs, and macrophages with immediate cytolytic function. Inappropriate expression or function of fractalkine might well be involved in inflammatory conditions leading to vascular and tissue damage. Taken together, fractalkine may be expressed in many tissues and be involved in the accumulation of CX3CR1-positive T cells at inflammation sites in rheumatoid arthritis and allied conditions.

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