Journal of Clinical and Nursing Research, 2025, Volume 9, Issue 7
http://ojs.bbwpublisher.com/index.php/JCNR
Online ISSN: 2208-3693
Print ISSN: 2208-3685

Research Advances in the CX3CL1/CX3CR1 Signaling Pathway: Implications for Atherosclerosis

Sha Cheng, Zhiling He, Guiying Qian, Guilan Huang, Quanfu Chen*

The Affiliated Traditional Chinese Medicine Hospital, Guangzhou Medical University, Guangzhou 510000, Guangdong, China

**Corresponding author: Quanfu Chen, sdcqf@163.com*

Abstract: The CX3CL1/CX3CR1 signaling axis is established as a pivotal regulator in the pathogenesis of atherosclerosis, with well-documented roles in orchestrating inflammatory responses, mediating immune cell recruitment, and influencing vascular remodeling. This review provides a comprehensive synthesis of current knowledge regarding the structural characteristics and functional properties of the CX3CL1/CX3CR1 pathway. This study delves into its specific mechanistic contributions to atherosclerosis, placing particular emphasis on its regulatory influence across diverse cell types, including arterial endothelial cells, smooth muscle cells, and macrophages. Furthermore, the pathway's integral involvement in both the initiation and progression of atherosclerotic plaques is dissected, highlighting its critical impact on plaque stability and susceptibility to rupture. The review also extends to the pathogenic significance of CX3CL1/CX3CR1 signaling in atherosclerosis-related comorbidities, incorporating the latest advancements in understanding its roles in coronary heart disease, stroke, and other cardiovascular disorders. By critically integrating findings from the extant literature, this review constructs a foundational framework to guide future investigations and underscores the substantial translational potential of targeting this pathway for therapeutic intervention in clinical settings.

Keywords: CX3CL1; CX3CR1; Atherosclerosis; Coronary heart disease; Cardiovascular and cerebrovascular diseases

Online publication: August 4, 2025

1. Introduction

Atherosclerosis is a multifaceted chronic inflammatory condition marked by the development of lipid plaques in artery walls. The accumulation of these plaques causes luminal narrowing and arterial wall rigidity, which in turn triggers serious cardiovascular events like myocardial infarction and stroke [1]. Atherosclerosis has a complex etiology that includes, among other things, aberrant lipid metabolism, arterial endothelial cell dysfunction, immune cell involvement, and chronic inflammatory reactions [2]. Lesion formation and progression are significantly

influenced by the inflammatory response in the arterial wall, in which the immune system and its signaling pathways are essential [3].

One class of small-molecule cytokines called chemokines guides immune cell migration to inflammatory sites. By attaching to specific chemokine receptors, they control immune cell migration, activation, and distribution. In atherosclerotic lesions, the recruitment of monocytes, macrophages, and lymphocytes as well as the start of inflammatory responses depend critically on the interaction between chemokines and their receptors [4]. It has been shown that the chemokine axis, which includes CCL2-CCR2, CXCL1-CXCR2, and CX3CL1-CX3CR1, is substantially linked to the development of atherosclerotic lesions [5].

Fractalkine, or CX3CL1, is the only chemokine in the family that has two roles [6]: it can function as a transmembrane adhesion molecule to encourage cell-cell interactions and as a soluble chemokine to provide a guiding effect. Natural killer (NK) cells, monocytes, and macrophages are immune cells that primarily express the CX3CL1 receptor, CX3CR1, which is involved in the adhesion, migration, and activation of these cells [7]. Numerous studies have demonstrated the significance of the CX3CL1/CX3CR1 signaling pathway in a number of inflammatory diseases, particularly in the pathophysiological process of atherosclerosis [8]. Research has indicated that the binding of CX3CL1 to CX3CR1 is crucial for cell survival, proliferation, and inflammatory regulation in atherosclerotic plaques, in addition to encouraging the recruitment of monocytes and macrophages [9].

2. Structure and function of the CX3CL1/CX3CR1 axis

The only membrane-bound chemokine in the chemokine family, CX3CL1 has special dual roles in adhesion and chemotaxis. An N-terminal chemokine domain, a linker domain, a transmembrane domain, and an intracellular tail are among the several functional domains that make up the structure of CX3CL1. The CX3CR1 receptor is bound by the N-terminal chemokine domain, which also controls downstream signal transduction. The intracellular tail facilitates intracellular signal transduction, while the transmembrane domain binds CX3CL1 to the cell membrane. Intracellular signaling pathways are activated by the intracellular tail region's interactions with different signaling proteins [10]. Several inflammatory factors, such as TNF-α, IL-1β, and interferon-γ (IFN-γ), regulate the expression of CX3CL1, a membrane-bound molecule that is primarily expressed on vascular endothelial cells, neurons, smooth muscle cells, and dendritic cells. CX3CL1 plays a crucial role in controlling inflammatory responses, as evidenced by the fact that its expression is typically markedly elevated in inflammatory environments [11]. Additionally, ADAM17 and ADAM10 can cleave CX3CL1 through proteolysis, releasing it in a soluble form. This soluble form of CX3CL1 has a strong chemotactic ability to direct the migration of monocytes, macrophages, and NK cells [12].

The G protein-coupled receptor (GPCR) family includes CX3CR1, the sole receptor for CX3CL1. With its typical GPCR structure and seven transmembrane helical domains, CX3CR1 can activate several downstream signaling pathways via G proteins. Monocytes, macrophages, NK cells, and certain T cells all have high levels of CX3CR1 expression, which is controlled by inflammatory status and markedly elevated in atherosclerotic plaques [13]. Gαi proteins, which can inhibit adenylate cyclase, lower intracellular cAMP levels, and activate phosphatidylinositol 3-kinase (PI3K)/Akt and MAPK signaling pathways, mediate the signal transduction of CX3CR1. Cell migration, proliferation, and survival all depend on these signaling pathways [14]. According to research, the CX3CR1 signaling pathway can improve monocyte and macrophage survival, prevent apoptosis, and be crucial in the early stages of plaque development [15]. Furthermore, the recruitment of inflammatory cells,

the activation of vascular endothelial cells, and the control of local immune responses in atherosclerosis are all intimately linked to CX3CR1 activation [16].

When CX3CL1 binds to CX3CR1, intricate downstream signal transduction pathways are triggered. These pathways control not only cell adhesion and migration but also cell survival, proliferation, and inflammatory responses. After CX3CL1 binds to CX3CR1 via its chemokine domain, CX3CR1 uses Gαi protein coupling to activate several signaling pathways, such as the PI3K/Akt, ERK/MAPK, and NF-κB pathways [17–19]. By blocking the PI3K/Akt pathway, CX3CR1 activation can increase monocyte and macrophage survival and prevent apoptosis. This process is essential for the inflammatory cells' ongoing existence in atherosclerotic plaques. Overexpression of CX3CR1 has been demonstrated to increase macrophage survival, which in turn promotes the development and advancement of atherosclerotic plaques [9]. The ERK/MAPK signaling pathway allows CX3CR1 to control cell migration and proliferation. ERK1/2 activation is important for smooth muscle cell proliferation, which is directly linked to the growth and stability of atherosclerotic plaques, in addition to promoting macrophage migration [20]. Via the NF-κB signaling pathway, CX3CR1 can also control cellular inflammatory responses. TNF-α and IL-6 are two pro-inflammatory cytokines whose expression is controlled by NF-κB, a crucial transcription factor. Atherosclerosis progression can be exacerbated by activation of CX3CL1/CX3CR1, which can increase local inflammatory responses via this pathway [21]. Furthermore, research has indicated that CX3CL1-CX3CR1 binding influences systemic immune responses in addition to local inflammation. Research shows that whereas elevated expression of CX3CL1 is linked to the activation of local inflammatory responses, macrophages' directional migration in plaques is correlated with their expression of CX3CR1 [22]. In addition to causing vascular damage and exacerbation of atherosclerosis, activation of this axis is linked to oxidative stress responses and the activation of vascular endothelial cells [13].

3. Mechanisms of CX3CL1/CX3CR1 signaling in atherosclerotic pathogenesis

One of the early stages of atherosclerosis is the overexpression of CX3CL1 in endothelial cells, which are essential for preserving the structural integrity and functionality of blood vessels. By changing the expression levels of cell adhesion molecules (like VCAM-1 and ICAM-1), CX3CL1 not only encourages CX3CR1-positive immune cells to stick to the endothelial surface but also raises the risk of inflammatory cell migration into the subendothelium [23]. According to reports, endothelial cells' production of reactive oxygen species (ROS) can be greatly increased by activating the CX3CL1/CX3CR1 signal. This oxidative stress response is one of the main causes of atherosclerosis. In addition to harming endothelial cells, oxidative stress encourages low-density lipoprotein (LDL) oxidation, which is a precondition for atherosclerosis [24]. The development of atherosclerotic plaques is significantly influenced by the migration and phenotypic change of smooth muscle cells (SMCs), and the CX3CL1/CX3CR1 signaling pathway serves a number of purposes in this process. According to recent research, through CX3CR1, CX3CL1 can trigger the phenotypic change of smooth muscle cells from the contractile to the synthetic type. This causes the cells to release a lot of extracellular matrix proteins, like collagen and elastin, which exacerbates plaque enlargement and hardening [25]. Changes in intracellular calcium signals also accompany this phenotypic transformation of smooth muscle cells, which encourages their aberrant proliferation in lesion areas. Furthermore, by causing smooth muscle cells to activate the Notch signaling pathway, CX3CL1 further promotes matrix remodeling and cell migration [26].

The function of the CX3CL1/CX3CR1 signaling pathway in the polarization and functional differentiation

of monocytes and macrophages has drawn more attention than their migration. By influencing macrophage polarization, research has shown that CX3CL1 not only attracts monocytes to plaques but also encourages their polarization toward M1-type pro-inflammatory macrophages [27]. In addition to intensifying local inflammatory responses, this pro-inflammatory polarization promotes the formation of foam cells and increased lipid uptake. It is noteworthy that CX3CR1-positive macrophages in plaques have stronger oxidative stress and inflammatory responses, which are brought about by improved STAT3 and NF-κB signaling pathways [28]. Further promoting the long-term survival and functional maintenance of monocytes and macrophages in lesion areas, CX3CL1 also contributes to the metabolic regulation of these cells, particularly controlling the glucose metabolism of macrophages via the mTOR signaling pathway [29].

The CX3CL1/CX3CR1 signaling pathway not only directly attracts inflammatory cells but also indirectly modulates other chemokine networks to enhance immune responses. More immune cells are drawn to lesion areas by CX3CL1's ability to increase the expression of pro-inflammatory chemokines like CCL2 and CXCL10, according to studies [30]. This cascade effect increases local chronic inflammatory responses through various inflammatory pathways, which is especially important in raising the risk of atherosclerotic plaque instability and rupture. The fundamental function of CX3CL1/CX3CR1 in fostering chronic inflammation and hastening the development of atherosclerosis is also explained by the synergistic effect of CX3CR1 with other chemokine receptors (such as CCR5), which further improves the directional migration and long-term retention ability of different immune cells [31].

4. Regulatory dynamics of the CX3CL1/CX3CR1 pathway in atherosclerosis plaque progression

By carefully regulating the migration and activity of monocytes and macrophages, the CX3CL1/CX3CR1 signaling pathway directly promotes the formation of plaque during the initial stage of atherosclerosis. In order to promote monocyte adhesion and endothelium infiltration, this process involves the interaction of CX3CL1 with CX3CR1, which activates specific G protein-coupled signaling pathways, including the PI3K/Akt and Rac1 pathways [9]. According to research, the PI3K/Akt pathway activates integrin family members, such as α4β1 integrin, to facilitate adhesion between immune cells and vascular endothelial cells [32]. Together with the overexpression of molecules involved in cell adhesion (e.g. G. Immune cell infiltration through the vascular wall is facilitated by endothelial cells' VCAM-1 and ICAM-1. Additionally, the downstream Rac1 small GTPase pathway, which is necessary for macrophage migration, is promoted by CX3CL1/CX3CR1 signaling. By reorganizing the cytoskeleton, Rac1 increases cell motility, promoting macrophage migration to lesion sites quickly, and escalating inflammatory reactions in the surrounding inflammatory milieu [33]. This molecular regulatory mechanism describes how CX3CL1 carefully controls macrophage orientation and movement to promote the formation of early atherosclerotic plaques.

The primary way that the CX3CL1/CX3CR1 signaling pathway contributes to plaque stability and rupture is by controlling molecular processes like cell apoptosis and matrix metalloproteinases (MMPs). MMPs are essential for the thickness and collagen content of the fibrous cap of plaque, which determines how stable the plaque is. MMP-9 and MMP-12 are expressed when macrophages are activated by CX3CL1/CX3CR1 signaling. This can break down collagen and elastin in the fibrous cap, weakening the plaque's structural integrity [34]. Notably, the NF-κB signaling pathway is how CX3CL1 controls MMP expression. CX3CR1-positive macrophages' pro-inflammatory activity is intimately linked to the activation of NF-κB, a transcription factor that promotes

inflammation. CX3CL1 stimulates the classical NF-κB signaling pathway through CX3CR1 in the late stage of atherosclerosis, increases macrophage MMP expression, and further encourages extracellular matrix degradation by causing oxidative stress [35]. This molecular-level process weakens the fibrous cap, raising the risk of plaque rupture and, consequently, cardiovascular events linked to atherosclerosis.

Apart from controlling matrix metalloproteinases, the CX3CL1/CX3CR1 signal is also crucial for smooth muscle cell apoptosis. Studies have shown that by activating the p38 MAPK signaling pathway and causing smooth muscle cell death, CX3CL1 exacerbates plaque instability [36]. In addition to promoting cell death, p38 MAPK also cooperates with MMP overexpression to further weaken the structural integrity of the plaque.

The CX3CL1/CX3CR1 signaling pathway is a major contributor to the chronic inflammatory response of atherosclerosis. It is controlled by the activity of local immune cells as well as by the actions of smooth muscle and endothelial cells, which modify the inflammatory environment of the vascular intima. The production of oxidative stress is greatly increased by endothelial cells overexpressing CX3CL1, and ROS (reactive oxygen species) is a key inflammatory mediator that intensifies the release of local pro-inflammatory cytokines by triggering the NF-κB and JNK signaling pathways [37]. According to studies, ROS not only damages endothelial cells' ability to act as a barrier but also encourages the oxidation of LDL, which forms the basis of foam cells and accelerates the development of atherosclerosis. By controlling Th1-type helper T cell responses, CX3CL1 also intensifies systemic and local inflammatory reactions [38]. By secreting pro-inflammatory cytokines like IFN-γ, CX3CR1-positive T cells directly control the activity of endothelial cells and macrophages, exacerbating the inflammatory response and hastening the development of atherosclerosis. It is important to note that CX3CL1's synergistic interaction with other chemokine receptors, including CXCR3 and CCR5, is crucial for maintaining chronic inflammation and immune cell retention over the long term. The chronic inflammatory state of atherosclerosis is further reinforced by this multi-chemokine network effect [39]. Furthermore, the survival of foam cells in plaques is intimately linked to over-activation of the CX3CL1/CX3CR1 signaling pathway. By controlling the mTOR signaling pathway, CX3CL1 improves the metabolic activity and anti-apoptotic potential of foam cells, which are the main cells of atherosclerotic plaques [40]. This metabolic regulatory mechanism promotes excessive lipid accumulation and increases the survival time of foam cells, both of which accelerate the development of atherosclerosis.

5. CX3CL1/CX3CR1 signaling in atherosclerosis-related comorbidities

The CX3CL1/CX3CR1 signaling pathway is essential to the pathogenesis of coronary artery disease (CAD), a common clinical manifestation of atherosclerosis. Recent research indicates that CX3CL1 activates multiple molecular signaling pathways in coronary endothelial cells through CX3CR1, primarily engaging the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway via G protein-coupled receptors (GPCRs), thereby enhancing immune cell adhesion and inflammatory responses in endothelial cells [41]. Particularly in vascular endothelial cells close to unstable plaques, CX3CL1 expression is markedly elevated in CAD patients. This overexpression is closely linked to the ongoing recruitment of immune cells, which exacerbates local inflammatory responses. Notably, CX3CL1/CX3CR1 controls monocyte migration to the arterial wall and local polarization status, which is a key factor in the persistence of inflammatory responses. CX3CL1 increases monocyte migration capacity by triggering the Rho family GTPase Rac1 [42]. At the same time, CX3CL1 can cause macrophage polarization to the pro-inflammatory M1 type via CX3CR1. These M1-type macrophages can accelerate plaque instability and raise the risk of myocardial infarction in CAD patients by secreting matrix metalloproteinases

like MMP-9, which break down the extracellular matrix in plaques [43]. Additionally, research has shown that CX3CL1 can improve the expression of endothelial cell adhesion molecules (like VCAM-1 and ICAM-1) in order to increase the interaction between monocytes and endothelial cells [44]. A possible therapeutic target, these molecular-level mechanisms highlight the central regulatory roles of CX3CL1/CX3CR1 in the development of CAD. Particularly, the V249I and T280M variants of the CX3CR1 gene have been the subject of much research in recent years. These gene variants have been linked to a lower affinity of CX3CR1 for CX3CL1, which weakens monocyte adhesion and migration ability and lowers the risk of coronary heart disease [45]. Intervention in the CX3CL1/CX3CR1 signal may offer new targets for the treatment of coronary heart disease, as this finding indicates the possible protective effect of CX3CR1 gene regulation in coronary heart disease.

The CX3CL1/CX3CR1 signaling pathway is associated with coronary heart disease and is also significant in other cardiovascular disorders. Research indicates that CX3CL1 modulates macrophage activation and chemotaxis in peripheral artery disease (PAD), promoting macrophage viability in affected arteries via the PI3K/Akt/mTOR pathway and stimulating matrix metalloproteinases (MMPs) to degrade the extracellular matrix, resulting in arterial wall structural instability [46]. Mechanistic investigations in peripheral artery disease (PAD) reveal that CX3CL1 not only modulates local inflammation but also facilitates disease advancement by perpetuating vascular wall damage. Moreover, CX3CL1 is significantly associated with conditions such as myocardial fibrosis and heart failure. In patients with heart failure, CX3CL1 stimulates the proliferation and activation of cardiac fibroblasts via the CX3CR1-activated signaling pathway, hence exacerbating cardiac fibrosis [47]. This signifies that CX3CL1 is implicated in vascular inflammatory responses and is crucial in the clinical progression of cardiac insufficiency through the modulation of myocardial fibrosis.

The pathogenic association between stroke, particularly ischemic stroke, and atherosclerosis is more evident. The CX3CL1/CX3CR1 signaling pathway is significant in both coronary heart disease and cerebrovascular disorders. CX3CL1, by the activation of CX3CR1, facilitates the recruitment of inflammatory cells and reactions in the brain, engaging several intracellular signaling pathways, particularly associated with blood-brain barrier impairment and ischemia injury [48]. Research indicates that CX3CL1 activates the RhoA/ROCK signaling pathway in the cerebrovascular system via the CX3CR1 receptor, resulting in the rearrangement of the endothelial cell cytoskeleton, increased permeability of the blood-brain barrier, and enhanced infiltration of immune cells and pro-inflammatory factors into the brain parenchyma, thereby exacerbating the pathological damage associated with stroke [49]. Furthermore, CX3CL1 promotes macrophage survival and pro-inflammatory activities via the PI3K/Akt and mTOR signaling pathways, allowing CX3CR1-positive macrophages to endure in the local inflammatory microenvironment and perpetually aggravate tissue damage.

The CX3CL1/CX3CR1 signaling pathway is significant in ischemia-reperfusion damage associated with cerebrovascular disorders. During reperfusion, CX3CL1 amplifies the generation of reactive oxygen species (ROS) in endothelial cells and macrophages via the CX3CR1 receptor. Excessive formation of reactive oxygen species (ROS) not only directly harms brain tissue but also activates the Nrf2 signaling pathway, hence intensifying oxidative stress responses [50]. The interplay between oxidative stress and inflammatory responses intensifies ischemia injury to cerebral tissue following a stroke.

6. Conclusion

The CX3CL1/CX3CR1 signaling pathway serves as a crucial regulatory element in atherosclerosis and associated

cardiovascular and cerebrovascular illnesses, exhibiting intricate functions in modulating inflammatory responses, immune cell recruitment, and vascular remodeling, as evidenced by recent investigations. Nonetheless, despite considerable advancements in current research, prospective research avenues remain replete with problems and potential. The CX3CL1/CX3CR1 signaling pathway has recently been identified as a possible therapeutic target for atherosclerosis. However, more medication development and clinical study are required. Optimizing CX3CL1/CX3CR1 targeted therapy in clinical practice to mitigate immunosuppressive adverse effects from systemic inhibition is a crucial avenue for future study. Investigating the influence of various CX3CR1 gene variants on therapeutic responses may facilitate the development of individualized targeted therapies for the clinical prevention and treatment of atherosclerosis and coronary heart disease. The advancement of technologies like single-cell sequencing, genomics, transcriptomics, and proteomics has rendered multi-omics studies an efficient approach for elucidating the intricate regulatory network of the CX3CL1/CX3CR1 signaling pathway. Integrating data at various levels will enable future studies to elucidate the dynamic alterations and regulatory mechanisms of the CX3CL1/CX3CR1 signaling pathway across many cell types and pathological conditions.

Funding

Study on the Protective Mechanism of Safflower Yellow Pigment on Vascular Endothelial Function in Patients with Phlegm-Stasis Syndrome Coronary Heart Disease and Stable Angina Pectoris(Project No. 20222A010012); Single-Cell Immune Panorama Study on Neiguan (PC6) Acupoint Injection for Improving Pyroptosis in Chronic Heart Failure (Project No. 2025A03J3499); The study on the effect and mechanism of Guanxinning Tablets on vascular homeostasis and remodeling in populations with early vascular aging (Project No. 2024QC-B1007); Guangzhou Key Laboratory of Traditional Chinese Medicine Rehabilitation (Project No. 2024A03J0790).

Disclosure statement

The authors declare no conflict of interest.

References

[1] Libby P, Ridker PM, Maseri A, 2002, Inflammation and Atherosclerosis. Circulation, 105(9): 1135–1143.

[2] Björkegren JL, Lusis AJ, 2022, Atherosclerosis: Recent Developments. Cell, 185(10): 1630–1645

[3] Hansson GK, Hermansson A, 2011, The Immune System in Atherosclerosis. Nature Immunology, 12(3): 204–212.

[4] Weber C, Schober A, Zernecke A, 2004, Chemokines: Key Regulators of Mononuclear Cell Recruitment in Atherosclerotic Vascular Disease. Arteriosclerosis, Thrombosis, and Vascular Biology, 24(11): 1997–2008.

[5] Zernecke A, Shagdarsuren E, Weber C, 2008, Chemokines in Atherosclerosis: An Update. Arteriosclerosis, Thrombosis, and Vascular Biology, 28(11): 1897–1908.

[6] Imaizumi T, Yoshida H, Satoh K, 2004, Regulation of CX3CL1/Fractalkine Expression in Endothelial Cells. Journal of Atherosclerosis and Thrombosis, 11(1): 15–21.

[7] Lee M, Lee Y, Song J, et al., 2018, Tissue-Specific Role of CX3CR1 Expressing Immune Cells and Their Relationships with Human Disease. Immune Network, 18(1).

[8] Combadière C, Potteaux S, Rodero M, et al., 2008, Combined Inhibition of CCL2, CX3CR1, and CCR5 Abrogates Ly6Chi and Ly6Clo Monocytosis and Almost Abolishes Atherosclerosis in Hypercholesterolemic Mice. Circulation,

117(13): 1649–1657.

[9] Landsman L, Bar-On L, Zernecke A, et al., 2009, CX3CR1 Is Required for Monocyte Homeostasis and Atherogenesis by Promoting Cell Survival. Blood, 113(4): 963–972.

[10] Imai T, Hieshima K, Haskell C, et al., 1997, Identification and Molecular Characterization of Fractalkine Receptor CX3CR1, Which Mediates Both Leukocyte Migration and Adhesion. Cell, 91(4): 521–530.

[11] Bazan JF, Bacon KB, Hardiman G, et al., 1997, A New Class of Membrane-Bound Chemokine with a CX3C Motif. Nature, 385(6617): 640–644.

[12] 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(4): 1186–1195.

[13] Geissmann F, Jung S, Littman DR, 2003, Blood Monocytes Consist of Two Principal Subsets with Distinct Migratory Properties. Immunity, 19(1): 71–82.

[14] Zhang X, Feng X, Cai W, et al., 2015, Chemokine CX3CL1 and Its Receptor CX3CR1 Are Associated with Human Atherosclerotic Lesion Vulnerability. Thrombosis Research, 135(6): 1147–1153.

[15] Tacke F, Alvarez D, Kaplan TJ, et al., 2007, Monocyte Subsets Differentially Employ CCR2, CCR5, and CX3CR1 to Accumulate Within Atherosclerotic Plaques. The Journal of Clinical Investigation, 117(1): 185–194.

[16] Lesnik P, Haskell CA, Charo IF, 2003, Decreased Atherosclerosis in CX3CR1–/– Mice Reveals a Role for Fractalkine in Atherogenesis. The Journal of Clinical Investigation, 111(3): 333–340.

[17] Wang K, Jiang L, Hu A, et al., 2021, Vertebral-Specific Activation of the CX3CL1/ICAM-1 Signaling Network Mediates Non-Small-Cell Lung Cancer Spinal Metastasis by Engaging Tumor Cell–Vertebral Bone Marrow Endothelial Cell Interactions. Theranostics, 11(10): 4770.

[18] Korbecki J, Simińska D, Kojder K, et al., 2020, Fractalkine/CX3CL1 in Neoplastic Processes. International Journal of Molecular Sciences, 21(10): 3723.

[19] Popiolek-Barczyk K, Mika J, 2016, Targeting the Microglial Signaling Pathways: New Insights in the Modulation of Neuropathic Pain. Current Medicinal Chemistry, 23(26): 2908–2928.

[20] Lee SG, Oh J, Bong SK, et al., 2018, Macrophage Polarization and Acceleration of Atherosclerotic Plaques in a Swine Model. PloS One, 13(3): e0193005.

[21] Poupel L, Boissonnas A, Hermand P, et al., 2013, Pharmacological Inhibition of the Chemokine Receptor, CX3CR1, Reduces Atherosclerosis in Mice. Arteriosclerosis, Thrombosis, and Vascular Biology, 33(10): 2297–2305.

[22] Apostolakis S, Spandidos D, 2013, Chemokines and Atherosclerosis: Focus on the CX3CL1/CX3CR1 Pathway. Acta Pharmacologica Sinica, 34(10): 1251–1256.

[23] Liu H, Jiang D, 2011, Fractalkine/CX3CR1 and Atherosclerosis. Clinica Chimica Acta, 412(13–14): 1180–1186.

[24] Imaizumi T, Yoshida H, Satoh K, 2004, Regulation of CX3CL1/Fractalkine Expression in Endothelial Cells. Journal of Atherosclerosis and Thrombosis, 11(1): 15–21.

[25] Gomez D, Owens GK, 2012, Smooth Muscle Cell Phenotypic Switching in Atherosclerosis. Cardiovascular Research, 95(2): 156–164.

[26] Liu ZJ, Tan Y, Beecham GW, et al., 2012, Notch Activation Induces Endothelial Cell Senescence and Pro-Inflammatory Response: Implication of Notch Signaling in Atherosclerosis. Atherosclerosis, 225(2): 296–303.

[27] Woollard KJ, Geissmann F, 2010, Monocytes in Atherosclerosis: Subsets and Functions. Nature Reviews Cardiology, 7(2): 77–86.

[28] Zernecke A, Weber C, 2010, Chemokines in the Vascular Inflammatory Response of Atherosclerosis. Cardiovascular

Research, 86(2): 192–201.

[29] Zhang H, Guo C, Wu D, et al., 2012, Hydrogen Sulfide Inhibits the Development of Atherosclerosis with Suppressing CX3CR1 and CX3CL1 Expression. PloS One, 7(7): e41147.

[30] Altara R, Manca M, Brandão RD, et al., 2016, Emerging Importance of Chemokine Receptor CXCR3 and Its Ligands in Cardiovascular Diseases. Clinical Science, 130(7): 463–478.

[31] Combadière C, Potteaux S, Rodero M, et al., 2008, Combined Inhibition of CCL2, CX3CR1, and CCR5 Abrogates Ly6Chi and Ly6Clo Monocytosis and Almost Abolishes Atherosclerosis in Hypercholesterolemic Mice. Circulation, 117(13): 1649–1657.

[32] Tsou CL, Peters W, Si Y, Slaymaker S, et al., 2007, Critical Roles for CCR2 and MCP-3 in Monocyte Mobilization from Bone Marrow and Recruitment to Inflammatory Sites. The Journal of Clinical Investigation, 117(4): 902–909.

[33] Damås JK, Boullier A, Wæhre T, et al., 2005, Expression of Fractalkine (CX3CL1) and Its Receptor, CX3CR1, Is Elevated in Coronary Artery Disease and Is Reduced During Statin Therapy. Arteriosclerosis, Thrombosis, and Vascular Biology, 25(12): 2567–2572.

[34] Clark AK, Staniland AA, Malcangio M, 2011, Fractalkine/CX3CR1 Signalling in Chronic Pain and Inflammation. Current Pharmaceutical Biotechnology, 12(10): 1707–1714.

[35] Lucas AD, Bursill C, Guzik TJ, et al., 2003, Smooth Muscle Cells in Human Atherosclerotic Plaques Express the Fractalkine Receptor CX3CR1 and Undergo Chemotaxis to the CX3C Chemokine Fractalkine (CX3CL1). Circulation, 108(20): 2498–2504.

[36] Li C, He J, Zhong X, et al., 2018, CX3CL1/CX3CR1 Axis Contributes to Angiotensin II-Induced Vascular Smooth Muscle Cell Proliferation and Inflammatory Cytokine Production. Inflammation, 41: 824–834.

[37] Li G, Xu Y, Sheng X, et al., 2017, Naringin Protects Against High Glucose-Induced Human Endothelial Cell Injury via Antioxidation and CX3CL1 Downregulation. Cellular Physiology and Biochemistry, 42(6): 2540–2551.

[38] Ma J, Luo J, Sun Y, et al., 2022, Cytokines Associated with Immune Response in Atherosclerosis. American Journal of Translational Research, 14(9): 6424.

[39] Rowinska Z, Koeppel TA, Sanati M, et al., 2017, Role of the CX3C Chemokine Receptor CX3CR1 in the Pathogenesis of Atherosclerosis After Aortic Transplantation. PloS One, 12(2): e0170644.

[40] Tiwari RL, Singh V, Barthwal MK, 2008, Macrophages: An Elusive Yet Emerging Therapeutic Target of Atherosclerosis. Medicinal Research Reviews, 28(4): 483–544.

[41] Gimbrone MA Jr, García-Cardeña G, 2016, Endothelial Cell Dysfunction and the Pathobiology of Atherosclerosis. Circulation Research, 118(4): 620–636.

[42] Roy-Chowdhury E, Brauns N, Helmke A, Nordlohne J, Bräsen JH, Schmitz J, von Vietinghoff S, 2021, Human CD16+ Monocytes Promote a Pro-Atherosclerotic Endothelial Cell Phenotype via CX3CR1–CX3CL1 Interaction. Cardiovascular Research, 117(6): 1510–1522.

[43] Kasama T, Wakabayashi K, Sato M, et al., 2010, Relevance of the CX3CL1/Fractalkine–CX3CR1 Pathway in Vasculitis and Vasculopathy. Translational Research, 155(1): 20–26.

[44] Combadière C, Potteaux S, Rodero M, et al., 2008, Combined Inhibition of CCL2, CX3CR1, and CCR5 Abrogates Ly6Chi and Ly6Clo Monocytosis and Almost Abolishes Atherosclerosis in Hypercholesterolemic Mice. Circulation, 117(13): 1649–1657.

[45] Moatti D, Faure S, Fumeron F, et al., 2001, Polymorphism in the Fractalkine Receptor CX3CR1 as a Genetic Risk Factor for Coronary Artery Disease. Blood, 97(7): 1925–1928.

[46] Kim KW, Ivanov S, Williams JW, 2020, Monocyte Recruitment, Specification, and Function in Atherosclerosis. Cells,

10(1): 15.

[47] Li R, Frangogiannis NG, 2021, Chemokines in Cardiac Fibrosis. Current Opinion in Physiology, 19: 80–91.

[48] Dénes Á, Humphreys N, Lane TE, et al., 2010, Chronic Systemic Infection Exacerbates Ischemic Brain Damage via a CCL5 (Regulated on Activation, Normal T-Cell Expressed and Secreted)-Mediated Proinflammatory Response in Mice. Journal of Neuroscience, 30(30): 10086–10095.

[49] Tomaszewski M, Bębnowska D, Hrynkiewicz R, et al., 2021, Role of the Immune System Elements in Pulmonary Arterial Hypertension. Journal of Clinical Medicine, 10(16): 3757.

[50] Wong BW, Wong D, McManus BM, 2002, Characterization of Fractalkine (CX3CL1) and CX3CR1 in Human Coronary Arteries with Native Atherosclerosis, Diabetes Mellitus, and Transplant Vascular Disease. Cardiovascular Pathology, 11(6): 332–338.