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Review

CXC chemokine ligand 12 (CXCL12) in atherosclerosis: An underlying therapeutic target

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ABSTRACT

CXC chemokine ligand 12 (CXCL12) is a specific chemokine ligand and plays a significant role in cell chemotaxis. Upon binding to CXC chemokine receptor 4 (CXCR4) or CXCR7, CXCL12 can activate different signaling cascades to regulate cell proliferation, migration, and metabolism. CXCL12 exerts a pro-atherogenic action by aggravating multiple pathogenesis of atherogenesis, including dyslipidemia, inflammation, neointima hyperplasia, angiogenesis, and insulin resistance. Serum CXCL12 levels are also markedly increased in patients with atherosclerosis-associated disease. The present review focuses on recent advances in CXCL12 research in the pathogenesis of atherosclerosis together with its clinical values. This may provide insight into potential novel therapies for atherosclerosis.

1. Introduction

Atherosclerosis is the leading etiology of cardiovascular disease, including myocardial infarction, and ischemic stroke [1]. The formation of atherosclerotic lesions is a long-term process that involves intricate etiology and various regulatory molecules. Dyslipidemia, inflammatory response, neointima hyperplasia, angiogenesis, and insulin resistance are identified as the pathogenesis of atherosclerosis [2–6]. Given atherosclerotic plaques are constantly detected in cardiovascular events such myocardial infarction and ischemic stroke, the seek for biomarkers of subclinical atherosclerosis stills a popular research focus, although stains or combination of it with other drugs has obtained effective improvement in CAD patients [7,8].

Chemokines (8~12KD) are mainly responsible for the recruitment and movement of cells and involved in various vasculopathy. Cell chemotaxis has been implicated in atherogenesis by recruiting pro-atherogenic cells such as leukocytes and vascular smooth muscle cells (VSMCs) to the site of injured arterial wall, expediting the proceeding of atherosclerosis [9,10]. Chemokines and their receptors are extensively expressed in vascular cells, such as endothelial cells (ECs), SMCs and leukocytes. It shares a similar structure with other chemokines, consisting of four cysteine residues. According to the different interval between cysteine residues, the chemokine family is classified into four types: C-, CXC-, CC-, and CX_3C- [11]. CXCL12 is also known as SDF-1 (stromal cell-derived factor-1) and belongs to CXC- subclass of the chemokine family. CXCL12 regulates cellular activity by binding to CXC chemokine receptor 4 (CXCR4) or CXCR7, two receptor proteins located in cytomembrane, leading to the activation of various intracellular signaling pathways [12–19]. Several studies showed that the elevation of serum CXCL12 levels contributes to increased CAD risk, indicating that an association between CXCL12 and cardiovascular disease [20,21]. CXCL12 is also involved in multiple pathogenesis of atherosclerosis, including the regulation of blood lipid profile, activation of vascular inflammatory response, promotion of neointima hyperplasia, stimulation of angiogenesis, and exacerbation of insulin resistance [22–26]. In addition, CXCL12 serves a prognostic and diagnostic indicator, and it is related to the morbidity and mortality of myocardial infarction and ischemic stroke [27,28]. Therefore, CXCL12 appears to be an important target for the treatment of atherosclerosis. The present review focuses on recent advances in CXCL12 research in the pathogenesis of atherosclerosis together with its clinical value. This may provide a novel insight into potential therapies for atherosclerosis.

2. The CXCL12 receptor and signaling

CXCL12 contains two receptors: CXCR4 and CXCR7, that belong to G protein-coupled receptor family but exert an opposite effect on CXCL12. Several clinical trial measured an ample expression of

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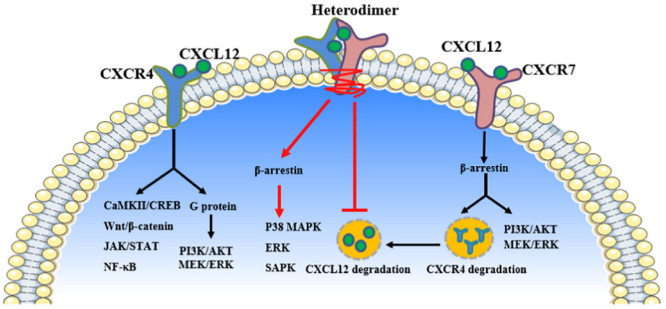

Fig. 1. The CXCL12-regulated signaling cascades. CXCL12 includes two distinct receptors, CXCR4 and CXCR7. The stimulation of CXCR4 triggers G protein to activate PI3K, NF-κB, Wnt, JAK, and MEK signaling, whereas activation of CXCR7 induces PI3K and MEK pathway dependent on β-arrestin. Furthermore, the CXCR4/CXCR7 heterodimer enlargers the signaling directly transduced by β-arrestin, including P38 MAPK-, CaMKII-, and SPAK-mediated signaling. Specifically, upon binding to CXCR7, CXCL12 is internalized and subjected to degradation. However, the CXCR4/CXCR7 heterodimer is responsible for inhibition of CXCL12 degradation. PI3K, phosphoinositide 3-kinase; AKT, Protein kinase B; MEK, mitogen-activated protein kinase kinase; P38 MAPK, P38 mitogen-activated protein kinase; ERK, extracellular signal–regulated kinases; CaMKII, Ca2+/calmodulin-dependent protein kinase II; CREB, cAMP-response element binding protein; SAPK, ste20-related proline/alanine-rich kinase; NF-κB, nuclear factor kB.

CXCL12, CXCR4 and CXCR7 in human carotid atherosclerotic plaques [29]. A body of studies have reported that after binding to its receptor, CXCL12 can activate a variety of downstream molecules (Fig.1), and is involved in many pathological and physiological processes.

2.1. The receptor of CXCL12

CXCR4, a specific receptor for CXCL12, serves as an enhancer to enlarge CXCL12-associated signaling. Unlike CXCR4 exclusively couples with CXCL12 and augments CXCL12-transducted signals, CXCR7 is a non-specific receptor and exerts an inhibitory effect on CXCL12 action. It has a high mortality at birth with ventricular septal defects and semilunar heart valve malformation in CXCR7 deficiency mice, suggesting that CXCR7 is an important factor for cardiac development [30]. Intriguingly, CXCL12 binds to CXCR7 with 10-fold affinity than CXCR4. Furthermore, CXCR7 is identified to be a scavenger for modulation of CXCL12 degradation [31]. The C-terminal serine and threonine site of CXCR7 is primarily contributor during the decomposition of CXCL12 [32,33]. These may partly explain the reason for CXCL12 can not induce atherogenesis in healthy people. Interestingly, the formation of CXCR4/CXCR7 heterodimer is an impetus for augment of CXCL12-mediated signal, implying CXCR4 that effectively prevents the degradation of CXCL12 by CXCR7 [34].

2.2. The signal transduction cascades of CXCL12/CXCR4 axis

CXCL12/CXCR4 axis appears to be correlated with multiple downstream molecules that are involved in the pathological and physiological change of different diseases, including vasculopathy, local inflammation, and pathological cell migration and proliferation [35–37]. Upon binding to CXCR4, CXCL12 can induce the activation of PI3K/Akt (phosphoinositide 3-kinase/ potein kinase B), MEK/ERK (mitogen-activated protein kinase kinase/extracellular signal–regulated kinases) and NF-κB (nuclear factor κB) signaling in G protein-dependent manner [13,14,38]. However, other signaling pathways that are independent of G protein, such as, Wnt/β-catenin, CaMKII/CREB (Ca^{2+}/calmodulin-dependent protein kinase II /AMP-response element binding protein) and JAK/STAT ((The janus kinase/signal transducer and activator of tran-ions) pathways can be also activated by CXCL12/ CXCR4 axis [12,15,17].

2.3. The signal transduction cascades of CXCL12/CXCR7 axis

CXCR7 serves as a participant in CXCL12-induced cell activities. Whereas the downstream signaling of CXCR7 were irrelevant to G protein [39]. The phosphorylated activation of PI3K/Akt and MEK/ERK signaling pathway also initiated by CXCL12/CXCR7 axis, but these were dependent on β-arrestin-mediated [18,19,40]. Additionally, the formation of CXCR4/CXCR7 heterodimer may be a stimulus to enhance β-arrestin-depended cell signaling pathways, including ERK1/2, p38 MAPK (P38 mitogen-activated protein kinase), and SAPK (ste20-related proline/alanine-rich kinase) [41].

3. The pro-atherogenic role of CXCL12

Atherosclerosis is a chronic vascular disease with complicated pathogenesis. Genome-wide association studies (GWAS) from about 100,000 people have revealed that CXCL12 becomes a new atherosclerosis locus both in mouse and human [42]. CXCL12 is also highly induced in some pro-atherogenic pathological conditions, including hyperlipidemia, pro-inflammatory response, EC and VSMC proliferation and migration, and insulin resistance [25,43–46]. Hence, it is required for considering the roles of CXCL12 in the pathological processes of atherosclerosis so as to make way for the prevention and treatment of atherosclerosis.

3.1. CXCL12 involves dyslipidemia

Dyslipidemia is identified as the key pathological mechanism of atherosclerosis. The accumulation of over-laden lipid in macrophages contributing to foam cell formation, an obvious hallmark of atherogenesis [47]. ABCA1mediates the efflux of cholesterol from macrophages to apolipoprotein A-I (apoA-I) to form high destiny lipoprotein (HDL), which is called reverse cholesterol transport (RCT), a major approach to prevent excess lipid accumulation in macrophages [48,49]. Our laboratory reported an army of regulators for cholesterol efflux by targeting ABCA1, including heat shock protein (HSP70), apolipoprotein A-1 binding protein (AIBP), visceral adipose tissue-derived serine protease inhibitor (vaspin), pregnancy-associated plasma protein-A (PAPP-A) and interferon-stimulated gene 15 (ISG15) [50–54]. Merckelbach et.al showed that CXCL12 is higher expressed, but only in macrophages within carotid plaques [29]. Meanwhile, serum CXCL12 levels were higher in patients with hyperlipidemia, suggesting that CXCL12 may be act as a biomarker for dyslipidemia [55]. However, the role of CXCL12 in lipid metabolism has not been clearly explored. Recent study observed that platelet derived-CXCL12 induces the formation of foam cells, implying a potent possibility that CXCL12 functions in lipid metabolism [24]. Statins is used to treat dyslipidemia disease and preventing cardiovascular disease, especially in the alleviation of atherosclerotic lesions [56]. High-dose of HMG-CoA reductase inhibitor treatment has been reported to decrease circulating CXCL12 levels under the condition of hyperlipidemia. This further supports that CXCL12 acts a target to improve the abnormal blood lipid profile in patients with cardiovascular disease [43].

HDL, a cholesterol transporter, exerts an anti-atherogenic action through transferring cholesterol into liver for biosynthesis of bile acid and steroid hormone [48]. Subramanian et.al analyzed the effects of CXCL12 on cardiovascular outcomes, including cardiovascular-related mortality, myocardial infarction and heart failure in Framingham Heart Study participants containing 3359 patients. They found that CXCL12 levels were negatively correlated with HDL-C levels, but they were positively associated with heart failure and all-cause mortality [22]. Low-destiny lipoprotein (LDL) exerts a pro-atherogenic effect and easier to accumulate in macrophages to form foam cells after oxidized modification [57,58]. After a 30-day high-cholesterol feeding trial, CXCL12 expression is upregulated with the increase of LDL-C levels in mice with hypercholesterolemia [23]. Further analysis also showed that

rs1746048, a CXCL12 variant, is linked with the upregulation of LDL-C concentration in intracranial Aneurysm (IA) patients [59]. Taken together, these data suggest that CXCL12 is closely related to aberrant lipid profile by regulating the levels of HDL and LDL. Therefore, it is urgent needed to further evaluate the effect of CXCL12 on lipid metabolism both in vivo and *vitro*, which may beneficial to the development of new therapeutics for atherosclerosis.

3.2. CXCL12 triggers vascular inflammatory response

Inflammatory cell infiltration serves as the major player in the inflammatory response of the arterial wall [60]. A variety of leukocytes including monocyte, macrophage, dendritic cell (DC), and T cell have been reported to be involved in atherogenesis that continuously drive the progression of atherosclerotic lesions, [61]. During atherogenesis, circulating monocytes migrate into the subintima where they differentiate into macrophages and secret pro-inflammatory cytokines, which is predominantly mediated by intracellular adhesion molecule-1 (ICAM-1), vascular cellular adhesion molecule-1 (VCAM-1) and monocyte chemoattractant protein-1 (MCP-1). ECs treatment with CXCL12 upregulates MCP-1 by activating PI3K and p38-dependent signaling, leading to the adhesion of monocyte to ECs [24,62]. In addition, Schiraldi et.al reported that HMGB1 (high mobility group box 1) and CXCL12 form a heterocomplex that leads to the recruitment of macrophages arrived in injured endothelium via CXCR4 [44]. These data show that CXCL12 mediates not only monocyte differentiation but also macrophage infiltration, thereby exerting pro-inflammatory effect on vascular endothelium and accelerating atherogenesis.

DC infiltration in the arterial wall with atherosclerotic lesions that is positively associated with the plaque vulnerability and inflammatory response, resulting from DCs secrete several pro-inflammatory biological agents [63]. CXCL12 acts as a stimulus to induce DCs maturation then activates T cells by presenting antigen, by which leading to inflammatory cytokine IFN-γ secreted [64,65]. IFN-γ initiates the activation and recruitment of T cells into vascular endothelium that causes local inflammation [66].

3.3. CXCL12 induces neointimal hyperplasia

Neointimal hyperplasia is an undue vascular repair process that occurs in the injured vessel wall. It acts an important morphological characteristic for atherosclerosis and leads to vascular restenosis [67,68]. Most studies have been identified that this process is characterized by the proliferation and migration of VSMCs [69,70]. VSMCs refer to multifarious cardiovascular disease, also as a stimulus for atherosclerosis. During tunica media migrates to intima, the phenotypic transition and proliferation of VSMCs also occurred [71–73]. Schober et.al discovered that circulating CXCL12 levels are closely related to a significant increase in VSMC counts and vasculopathy in cardiac allograft patients [25]. NOX-A12, a CXCL12 inhibitor, has been found to obviously inhibit VSMC proliferation [74]. Consistently, lentivirus vectors-transfected CXCL12 antagonist decreased SMC counts and neointimal hyperplasia in apoE−/− mice [75]. These studies reveal an aggravate role for CXCL12 in atherosclerotic lesions, although it is incompletely understood the exact mechanism of CXCL12-recruited SMCs. Targeting this chemokine may provide a novel strategy to alleviate vascular restenosis after angioplasty.

3.4. CXCL12 induces angiogenesis

Increasing evidence indicate that a distinct association between the new vessel density and atherosclerotic plaque vulnerability [76]. Angiogenesis is one of causes of thrombus formation and detachment [77]. The recruitment of ECs or EPCs is a major cause of angiogenesis and CXCL12 can induce these two types cell recruited to injured arterial, leading to the aggravation of atherosclerotic lesions [78,79]. Doring ei.al recently revealed that the specific deletion of CXCL12 in ECs lead to the marked reduction of atherosclerotic lesions, while the exact mechanisms have not been expounded [80]. eNOS (endothelial nitric oxide synthase) elicits an anti-atherogenic role under normal physiological conditions, but it can promote the progression of atherosclerosis once occurred vascular injure by inducing angiogenesis [81,82]. The binding of CXCL12 to CXCR4 results in the proliferation of ECs and EPCs by stimulating PI3K/Akt pathway to increase eNOS expression [38,83]. Similarly, CXCR4 knockdown blocks CXCL12-mediated angiogenesis in human umbilical vein endothelial cells (HUVECs) by inhibiting the PI3K/Akt, MAPK/ERK and Wnt/β-Catenin pathways [12]. In addition, CXCR7 has been found to participate in CXCL12-induced the directional migration of HUVECs and tube formation [45]. However, it is unclear about the interaction of CXCR4 with CXCR7 in HUVECs-mediated angiogenesis. The general idea is that ECs grow from the existing neovascularization triggered by VEGF (vascular endothelial cell growth factor). Liang et,al implicated that CXCL12/CXCR4 axis activates PI3K/Akt pathway to increase the expression of VEGF in tumor cells [84]. Whether CXCL12-upregulated VEGF also occurs in ECs and EPCs remain to be determined.

3.5. CXCL12 aggravates insulin resistance

Insulin resistance is crucial etiology of type 2 diabetes (T2DM) that is characterized by promotion of glucose uptake and reduction of insulin utilization. T2DM is recognized to be a risk factor for atherosclerosis [85]. Clinical study suggested that T2DM patients showed strikingly increased in serum CXCL12 levels, suggesting CXCL12 may as a potential blood marker for T2DM [46]. Several animal studies also displayed an underlying association of CXCL12 with insulin resistance. Adipose tissue macrophages (ATMs) are a prominent source of pro-inflammatory cytokines that can block insulin action and cause systemic insulin resistance [86]. It has been showed an upregulated trend of CXCL12 expression in white adipose tissue of diet-induced obese (DIO) mice. Further studies have shown that adipocyte-derived CXCL12 contributed to the recruitment of ATMs and promotion of pro-inflammatory cytokines secretion that led to adipose tissue inflammation and insulin resistance in DIO mice [26]. Consistently, the antibody of CXCL12 was injected into female mice with non-obese diabetic (NOD) by Matin et.al, they found that it decreased by 30% of diabetes for 30 weeks and improved insulin resistance [87]. These data suggest that CXCL12 plays a key role in insulin resistance, although the exactly regulatory mechanisms are poorly understood. In addition, CXCL12-alleviated insulin resistance only occurs in female NOD mice, whether this phenomenon is involved in estrogen-regulated yet to be confirmed. Furthermore, it needs to further define CXCL12-regulated insulin resistance whether affected by gender difference in clinical research.

4. The clinical value of CXCL12 in cardiovascular diseases

Apart from direct regulation of atherosclerosis occurrence, the single nucleotide polymorphisms (SNPs) and levels of CXCL12 were changed during cardiovascular events, CXCL12 therefore serves as a prognosis and diagnostic markers of atherosclerosis-associated cardiovascular disease.

4.1. The clinical value of CXCL12 in myocardial infarction

The increasing amount and size of plaque may result in reduced vascular elasticity and altered the blood pressure. Myocardial infarction (MI) is an acute complication of CAD, resulting from the exfoliation and rupture of oversize atherosclerotic plaque that causes thrombosis formation and vascular occlusion [88,89]. Mehta et.al measured that common variant rs1746048 and rs501120 at the chromosome 10q11 locus is associated with higher plasma CXCL12 levels and that markedly increased CAD risk in age and gender adjusted models [90].

Consistently, Wang et.al also found that rs1746048 was significantly associated with MI in Chinese populations after adjusting age, sex, and BMI [91]. Lately, Mehta et.al further analyzed study-entry plasma CXCL12 levels in 3687 participants of the Chronic Renal Insufficiency Cohort Study and follow-up was 6 years for incident MI or death. Higher study-entry CXCL12 was correlated with increasing risk of incident MI, death, and combined MI/death after adjusting for all other possible co-variates [27]. In addition, serum CXCL12 levels were significantly increased in CAD patients, with the increase of serious degree of coronary artery occlusion [21]. Furthermore, atherosclerosis patients who have a higher CXCL12 level easier to develop thrombosis through PI3K-induced platelet aggregation [92]. However, Stellos et.al recruit 492 patients with symptomatic CAD and determined plasma CXCL12 levels before percutaneous coronary intervention, plasma CXCL12 levels were significantly decreased in patients with ST-elevation myocardial infarction (NSTEMI) [93]. This discrepancy may be attributed to the fact that subjects in the previous study were not matched for ethnic groups, genetic backgrounds, diseases, age, and sample sizes, or plasma CXCL12 level plays a different role during various type of MI. Furthermore, the reported association of plasma CXCL12 levels with MI could be confused by other CAD risk factors, but none of that changes the fact that CXCL12 acts as a clinical marker for MI.

4.2. The clinical value of CXCL12 in ischemic stroke

Ischemic stroke (IS) patients are detected atherosclerotic plaques in cerebral arterial, atherogenesis thereby becomes a risk factor for IS [94,95]. Duan et.al screened 288 patients with first-ever IS and examined serum CXCL12 level, confirmed that elevation of serum CXCL12 level is a common manifestation for ischemic stroke [28]. Subsequently, Gu et.al further found that serum CXCL12 levels have a positive correlation with stroke recurrence ($P < .0001$), infarct volume ($r = 0.307$, $P < .0001$) and stroke severity ($r = 0.288$, $P < .0001$) in Chinese patients [96–98]. In addition, Zhu et.al discovered that the CXCL12 variants rs1746048 CT/TT genotypes and rs501120 CT/CC genotypes were associated with a significantly increased risk of IS in the northern Chinese Han population, even after adjusting for confounding factors [99]. However, T allele of rs1746048 is a risk factor, while that of rs501120 may act a protector for IS in Chinese men. These results indicated gender specificity for the effect of genetic variation of CXCL12 on IS. The mechanism underlying the different gender-associated effects of the two SNPs remains to be further investigated. Therefore, elevation of serum CXCL12 levels as an indicator for assessing IS, and it may be an effective auxiliary prognosis marker that attributed to its role in stroke recurrence, infarct volume and stroke severity.

5. The therapeutic strategies to inhibit CXCL12 production and activity

CXCL12 is secreted by various types of cells and regulates multiple cell activity. Given its pro-atherogenic properties, reduction of circulating CXCL12 levels or inhibition of CXCL12 action were novel and promising therapeutic approach for prevention or alleviation of atherosclerosis-associated disease.

The modification of structure is a major reason for altering protein activity. Proteolysis, a common post-translational modification, frequently occurs in various proteins. The hydrolysis of the N- or C-terminal amino acids lead to a decrease in CXCL12 activity. Leukocyte elastase, cathepsin G and some members of matrix metalloproteinase family (MMP-1,2,3,9,13, and 14) can cleave CXCL12 N-terminus first three or five residues [100–102]. Similarly, carboxypeptidase N (CPN), CPM and cathepsin X can cleave the lysine of CXCL12 C-terminus [103–105]. Actually, the monomeric CXCL12 is more easily hydrolyzed compared to dimeric state, indicating that inhibition of dimeric formation may be beneficial for reduction of CXCL12 levels [106]. In addition, citrullination of arginine residues and nitration of tyrosine residues are contributed to reduction of CXCL12 activity [107]. However, whether the pro-atherogenic role of CXCL12 involves the anti-hydrolysis that remains worthy to be discussed.

The overwhelming majority of CXCL12-regulated signaling are associated with its receptor. Thus, the CXCR4 antagonist may be an effective measure to limit CXCL12 action. AMD3100 showed an inhibitory effect on CXCL12 function through binding to the its N-terminal [108]. Meanwhile, AMD3465 and POL551 directly inhibit the action of CXCL12-damaged vascular wall. AMD3465 treated with apoE−/− mice presented the amelioration of neointimal lesion and reduction of SMC counts. Whereas POL551 treatment reduced, not only SMC counts, but also macrophage contents [109,110]. CXCR7, the non-classical CXCL12 receptor and also found to negatively regulate CXCL12 expression and function, therefore its agonist may be as a inhibitory target for CXCL12. Berahovich et.al discovered that genetic deletion and pharmacological inhibition of CXCR7 upregulated circulating CXCL12 levels, while CXCR7 agonist exerts an inhibitory effect on CXCL12-induced cell chemotaxis [33,111]. However, AMD3100 and TC14012 also as an allosteric agonist of CXCR7 that is opposite to CXCR4, indicating that part of CXCR antagonists inhibit CXCL12 action involving the activation of CXCR7 [112,113]. Therefore, it is needed to be more cautious in the use of these two compounds as a media to identify the effects of CXCL12 on the respective receptors. Besides, some other chemokine family members, such as CXCL14 acts a direct agonist for CXCL12 via binding the C-terminal [114]. This provides another possible explain for the production of pro-atherogenic action by CXCL12.

6. Conclusion and future directions

The pro-atherogenic action of CXCL12 is multi-aspect, including its effect on lipid metabolism, vascular inflammation, neointima hyperplasia, angiogenesis, and insulin resistance (Fig. 2). However, the exact role of CXCL12 in atherosclerosis are still needed to be addressed. Ongoing studies of full spectrum of CXCL12 actions to avoid later surprises. For example, although inhibition of CXCL12 may be desirable in preventing atherogenesis, it could have serious implications for

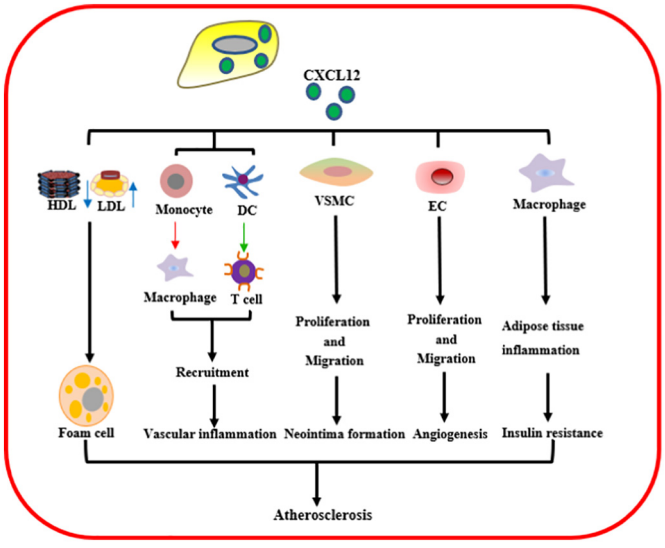

Fig. 2. The underlying molecular mechanisms for the simulative effect of CXCL12 on atherogenesis. CXCL12 accelerates atherosclerosis by promoting macrophage foam cell formation, inflammatory response, neointima formation, angiogenesis, and insulin resistance. DC, dendritic cell; EC, endothelial cell. Red arrow: differentiation; Green arrow: activation; Blue arrow: level upregulated or downregulated. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

another, it might be bad for the embryonic development [115,116]. Batchu et.al recently revealed that CXCL12 has inverse cardiac effects on different age group diabetic mice, suggesting age acts an variable factor during CXCL12-regulated cardiovascular system [117]. Merckelbach et.al also found that CXCL12 and its receptors are highly expressed in human carotid atherosclerotic plaque and are closely associated with the progression of atherosclerosis [29,118,119]. However, the pro-atherogenic mechanisms of CXCL12 and its receptors were little to known, therefore, the further investigation in order to definite molecular signaling network. This may beneficial to prevention and treatment of atherosclerosis and improve cardiovascular diseases in future.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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References

[1] T.S. Polonsky, H. Ning, M.L. Daviglus, K. Liu, G.L. Burke, M. Cushman, J. Eng, A.R. Folsom, P.L. Lutsey, J.A. Nettleton, W.S. Post, R.L. Sacco, M. Szklo, D.M. Lloyd-Jones, Association of cardiovascular health with subclinical disease and incident events: the multi-ethnic study of atherosclerosis, J. Am. Heart Assoc. 6 (2017) e004894.
[2] E. Brandsma, N.J. Kloosterhuis, M. Koster, D.C. Dekker, M.J.J. Gijbels, S. van der Velden, M. Rios-Morales, M.J.R. van Faassen, M.G. Loreti, A. de Bruin, J. Fu, F. Kuipers, B.M. Bakker, M. Westerterp, M.P.J. de Winther, M.H. Hofker, B. van de Sluis, D.P.Y. Koonen, A proinflammatory gut microbiota increases systemic inflammation and accelerates atherosclerosis, Circ. Res. 124 (2019) 94–100.
[3] A. Gorur, A. Celik, D.D. Yildirim, A. Gundes, L. Tamer, Investigation of possible effects of microRNAs involved in regulation of lipid metabolism in the pathogenesis of atherosclerosis, Mol. Biol. Rep. 46 (2019) 909–920.
[4] M. Guo, Y. Cai, C. He, Z. Li, Coupled modeling of lipid deposition, inflammatory response and intraplaque angiogenesis in atherosclerotic plaque, Ann. Biomed. Eng. 47 (2019) 439–452.
[5] V.P. Menezes, C. Cohen, J. Del-Rei, W. Oigman, M.F. Neves, F.J. Medeiros, Evaluation of endothelial function and arterial stiffness in obese individuals with insulin resistance, Nutr. Health (2019), https://doi.org/10.1177/0260106018819374 (260106018819374) Epub ahead of print.
[6] M. Satish, D.K. Agrawal, Pro-resolving lipid mediators in the resolution of neointimal hyperplasia pathogenesis in atherosclerotic diseases, Expert. Rev. Cardiovasc. Ther. 17 (2019) 177–184.
[7] X. Guo, L. Wang, X. Xia, P. Wang, X. Li, Effects of atorvastatin and/or probucol on recovery of atherosclerosis in high-fat-diet-fed apolipoprotein E-deficient mice, Biomed. Pharmacother. 109 (2019) 1445–1453.
[8] Y. Xu, W. Zhu, T. Wang, L. Jin, T. Liu, X. Li, Z. Guan, Z. Jiang, X. Meng, J. Wang, Y. Guo, Low molecule weight fucoidan mitigates atherosclerosis in ApoE (−/−) mouse model through activating multiple signal pathway, Carbohydr. Polym. 206 (2019) 110–120.
[9] A. Zernecke, E. Shagdarsuren, C, Chemokines in atherosclerosis: an update, Arterioscler. Thromb. Vasc. Biol. 28 (2008) 1897–1908.
[10] E.P. van der Vorst, Y. Doring, C. Weber, Chemokines and their receptors in atherosclerosis, J. Mol. Med. (Berlin, Germany) 93 (2015) 963–971.
[11] E.P. van der Vorst, Y. Doring, C. Weber, Chemokines, Arteriosclerosis, Thrombosis, and Vascular Biology, vol. 35, (2015), pp. e52–e56.
[12] Z.Y. Song, F. Wang, S.X. Cui, X.J. Qu, Knockdown of CXCR4 inhibits CXCL12-induced angiogenesis in HUVECs through downregulation of the MAPK/ERK and PI3K/AKT and the Wnt/beta-catenin pathways, Cancer Investig. 36 (2018) 10–18.
[13] T.J. LaRocca, F. Fabris, J. Chen, D. Benhayon, S. Zhang, L. McCollum, A.D. Schecter, J.Y. Cheung, E.A. Sobie, R.J. Hajjar, D. Lebeche, Na+/Ca2+ exchanger-1 protects against systolic failure in the Akitains2 model of diabetic cardiomyopathy via a CXCR4/NF-kappaB pathway, Am. J. Physiol. Heart Circ. Physiol. 303 (2012) H353–H367.
[14] Y. Tian, H. Yin, X. Deng, B. Tang, X. Ren, T. Jiang, CXCL12 induces migration of oligodendrocyte precursor cells through the CXCR4activated MEK/ERK and PI3K/AKT pathways, Mol. Med. Rep. 18 (2018) 4374–4380.
[15] A.J. Vila-Coro, J.M. Rodriguez-Frade, A. Martin De Ana, M.C. Moreno-Ortiz, A.C. Martinez, M. Mellado, The chemokine SDF-1alpha triggers CXCR4 receptor dimerization and activates the JAK/STAT pathway, FASEB J. 13 (1999) 1699–1710.
[16] Y. Zhang, C.Q. Yang, Y. Gao, C. Wang, C.L. Zhang, X.H. Zhou, Knockdown of CXCR7 inhibits proliferation and invasion of osteosarcoma cells through inhibition of the PI3K/Akt and beta-arrestin pathways, Oncol. Rep. 32 (2014) 965–972.
[17] X.M. Hu, H. Zhang, H. Xu, H.L. Zhang, L.P. Chen, W.Q. Cui, W. Yang, W. Shen, Chemokine receptor CXCR4 regulates CaMKII/CREB pathway in spinal neurons that underlies cancer-induced bone pain, Sci. Rep. 7 (2017) 4005.
[18] R. Kumar, V. Tripathi, M. Ahmad, N. Nath, R.A. Mir, S.S. Chauhan, K. Luthra, CXCR7 mediated Gialpha independent activation of ERK and Akt promotes cell survival and chemotaxis in T cells, Cell. Immunol. 272 (2012) 230–241.
[19] F. Torossian, A. Anginot, A. Chabanon, D. Clay, B. Guerton, C. Desterke, L. Boutin, S. Marullo, M.G. Scott, J.J. Lataillade, M.C. Le Bousse-Kerdiles, CXCR7 participates in CXCL12-induced CD34+ cell cycling through beta-arrestin-dependent Akt activation, Blood 123 (2014) 191–202.
[20] J. Sjaarda, H. Gerstein, M. Chong, S. Yusuf, D. Meyre, S.S. Anand, S. Hess, G. Pare, Blood CSF1 and CXCL12 as causal mediators of coronary artery disease, J. Am. Coll. Cardiol. 72 (2018) 300–310.
[21] V.T. Ferdousie, M. Mohammadi, G. Hassanshahi, H. Khorramdelazad, S.K. Falahati-Pour, M. Mirzaei, M.A. Tavakoli, Z. Kamiab, Z. Ahmadi, R. Vazirinejad, Serum CXCL10 and CXCL12 chemokine levels are associated with the severity of coronary artery disease and coronary artery occlusion, Int. J. Cardiol. 233 (2017) 23–28.
[22] S. Subramanian, C. Liu, A. Aviv, J.E. Ho, P. Courchesne, P. Muntendam, M.G. Larson, S. Cheng, T.J. Wang, N.N. Mehta, D. Levy, Stromal cell-derived factor 1 as a biomarker of heart failure and mortality risk, Arterioscler. Thromb. Vasc. Biol. 34 (2014) 2100–2105.
[23] A.L. Gomes, T. Carvalho, J. Serpa, C. Torre, S. Dias, Hypercholesterolemia promotes bone marrow cell mobilization by perturbing the SDF-1:CXCR4 axis, Blood 115 (2010) 3886–3894.
[24] M. Chatterjee, S.N. von Ungern-Sternberg, P. Seizer, F. Schlegel, M. Buttcher, N.A. Sindhu, S. Muller, A. Mack, M. Gawaz, Platelet-derived CXCL12 regulates monocyte function, survival, differentiation into macrophages and foam cells through differential involvement of CXCR4-CXCR7, Cell Death Dis. 6 (2015) e1989.
[25] A. Schober, M. Hristov, S. Kofler, R. Forbrig, B. Lohr, N. Heussen, Z. Zhe, S. Akhtar, U. Schumann, F. Krotz, M. Leibig, A. Konig, I. Kaczmarek, B. Reichart, V. Klauss, C. Weber, H.Y. Sohn, CD34+CD140b+ cells and circulating CXCL12 correlate with the angiographically assessed severity of cardiac allograft vasculopathy, Eur. Heart J. 32 (2011) 476–484.
[26] D. Kim, J. Kim, J.H. Yoon, J. Ghim, K. Yea, P. Song, S. Park, A. Lee, C.P. Hong, M.S. Jang, Y. Kwon, S. Park, M.H. Jang, P.O. Berggren, P.G. Suh, S.H. Ryu, CXCL12 secreted from adipose tissue recruits macrophages and induces insulin resistance in mice, Diabetologia 57 (2014) 1456–1465.
[27] N.N. Mehta, G.J. Matthews, P. Krishnamoorthy, R. Shah, C. Mclaughlin, P. Patel, M. Budoff, J. Chen, M. Wolman, A. Go, Higher plasma CXCL12 levels predict incident myocardial infarction and death in chronic kidney disease: findings from the Chronic Renal Insufficiency Cohort study, Eur. Heart J. 35 (2014) 2115–2122.
[28] X.X. Duan, G.P. Zhang, X.B. Wang, H. Yu, J.L. Wu, K.Z. Liu, L. Wang, X. Long, The diagnostic and prognostic value of serum CXCL12 levels in patients with ischemic stroke, Neurol. Sci. 36 (2015) 2227–2234.
[29] S. Merckelbach, V.D.V. Epc, M. Kallmayer, C. Rischpler, R. Burgkart, Y. Dã Ring, G.J. de Borst, M. Schwaiger, H.H. Eckstein, C. Weber, Expression and cellular localization of CXCR4 and CXCL12 in human carotid atherosclerotic plaques, Thromb. Haemost. 118 (2018) 195–206.
[30] F. Sierro, C. Biben, L. Martinez-Munoz, M. Mellado, R.M. Ransohoff, M. Li, B. Woehl, H. Leung, J. Groom, M. Batten, R.P. Harvey, A.C. Martinez, C.R. Mackay, F. Mackay, Disrupted cardiac development but normal hematopoiesis in mice deficient in the second CXCL12/SDF-1 receptor, CXCR7, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 14759–14764.
[31] U. Naumann, E. Cameroni, M. Pruenster, H. Mahabaleshwar, E. Raz, H.G. Zerwes, A. Rot, M. Thelen, CXCR7 functions as a scavenger for CXCL12 and CXCL11, PLoS One 5 (2010) e9175.
[32] F. Hoffmann, W. Muller, D. Schutz, M.E. Penfold, Y.H. Wong, S. Schulz, R. Stumm, Rapid uptake and degradation of CXCL12 depend on CXCR7 carboxyl-terminal serine/threonine residues, J. Biol. Chem. 287 (2012) 28362–28377.
[33] A. Uto-Konomi, B. McKibben, J. Wirtz, Y. Sato, A. Takano, T. Nanki, S. Suzuki, CXCR7 agonists inhibit the function of CXCL12 by down-regulation of CXCR4, Biochem. Biophys. Res. Commun. 431 (2013) 772–776.
[34] A. Levoye, K. Balabanian, F. Baleux, F. Bachelerie, B. Lagane, CXCR7 heterodimerizes with CXCR4 and regulates CXCL12-mediated G protein signaling, Blood 113 (2009) 6085–6093.
[35] F. Yang, Y. Takagaki, Y. Yoshitomi, T. Ikeda, J. Li, M. Kitada, A. Kumagai, E. Kawakita, S. Shi, K. Kanasaki, D. Koya, Inhibition of dipeptidyl peptidase-4 accelerates epithelial-mesenchymal transition and breast cancer metastasis via the CXCL12/CXCR4/mTOR Axis, Cancer Res. 79 (2019) 735–746.
[36] Y. Doring, L. Pawig, C. Weber, H. Noels, The CXCL12/CXCR4 chemokine ligand/receptor axis in cardiovascular disease, Front. Physiol. 5 (2014) 212.
[37] L. Yu, L. Yu, Q. Pham, T. Wang, Transcriptional and translational-uncoupling in regulation of the CXCL12 and its receptors CXCR4, 7 in THP-1 monocytes and macrophages, Immun. Inflam. Dis. 6 (2018) 106–116.
[38] H. Zheng, G. Fu, T. Dai, H. Huang, Migration of endothelial progenitor cells mediated by stromal cell-derived factor-1alpha/CXCR4 via PI3K/Akt/eNOS signal transduction pathway, J. Cardiovasc. Pharmacol. 50 (2007) 274–280.
[39] N.L. Coggins, D. Trakimas, S.L. Chang, A. Ehrlich, P. Ray, K.E. Luker, J.J. Linderman, G.D. Luker, CXCR7 controls competition for recruitment of beta-arrestin 2 in cells expressing both CXCR4 and CXCR7, PLoS One 9 (2014) e98328.
[40] X.X. Li, H.T. Zheng, L.Y. Huang, D.B. Shi, J.J. Peng, L. Liang, S.J. Cai, Silencing of CXCR7 gene represses growth and invasion and induces apoptosis in colorectal cancer through ERK and beta-arrestin pathways, Int. J. Oncol. 45 (2014)

1649–1657.
[41] F.M. Decaillot, M.A. Kazmi, Y. Lin, S. Ray-Saha, T.P. Sakmar, P. Sachdev, CXCR7/CXCR4 heterodimer constitutively recruits beta-arrestin to enhance cell migration, J. Biol. Chem. 286 (2011) 32188–32197.
[42] S.S. Farouk, D.J. Rader, M.P. Reilly, N.N. Mehta, CXCL12: a new player in coronary disease identified through human genetics, Trends Cardiovasc. Med. 20 (2010) 204–209.
[43] W. Camnitz, M.D. Burdick, R.M. Strieter, B. Mehrad, E.C. Keeley, Dose-dependent effect of statin therapy on circulating CXCL12 levels in patients with hyperlipidemia, Clin. Transl. Med. 1 (2012) 23.
[44] M. Schiraldi, A. Raucci, L.M. Munoz, E. Livoti, B. Celona, E. Venereau, T. Apuzzo, F. De Marchis, M. Pedotti, A. Bachi, M. Thelen, L. Varani, M. Mellado, A. Proudfoot, M.E. Bianchi, M. Uguccioni, HMGB1 promotes recruitment of inflammatory cells to damaged tissues by forming a complex with CXCL12 and signaling via CXCR4, J. Exp. Med. 209 (2012) 551–563.
[45] M. Zhang, L. Qiu, Y. Zhang, D. Xu, J.C. Zheng, L. Jiang, CXCL12 enhances angiogenesis through CXCR7 activation in human umbilical vein endothelial cells, Sci. Rep. 7 (2017) 8289.
[46] R. Derakhshan, M.K. Arababadi, Z. Ahmadi, M.N. Karimabad, V.A. Salehabadi, M. Abedinzadeh, H. Khorramdelazad, P. Balaei, D. Kennedy, G. Hassanshahi, Increased circulating levels of SDF-1 (CXCL12) in type 2 diabetic patients are correlated to disease state but are unrelated to polymorphism of the SDF-1beta gene in the Iranian population, Inflammation 35 (2012) 900–904.
[47] X.H. Yu, D.W. Zhang, X.L. Zheng, C.K. Tang, Cholesterol transport system: an integrated cholesterol transport model involved in atherosclerosis, Prog. Lipid Res. 73 (2019) 65–91.
[48] C.E. Kosmas, I. Martinez, A. Sourlas, K.V. Bouza, F.N. Campos, V. Torres, P.D. Montan, E. Guzman, High-density lipoprotein (HDL) functionality and its relevance to atherosclerotic cardiovascular disease, Drugs Context 7 (2018) 212525.
[49] X.H. Yu, D.W. Zhang, X.L. Zheng, C.K. Tang, C1q tumor necrosis factor-related protein 9 in atherosclerosis: mechanistic insights and therapeutic potential, Atherosclerosis 276 (2018) 109–116.
[50] M. Zhang, L. Li, W. Xie, J.F. Wu, F. Yao, Y.L. Tan, X.D. Xia, X.Y. Liu, D. Liu, G. Lan, Apolipoprotein A-1 binding protein promotes macrophage cholesterol efflux by facilitating apolipoprotein A-1 binding to ABCA1 and preventing ABCA1 degradation, Atherosclerosis 248 (2016) 149–159.
[51] M. Zhang, G.J. Zhao, F. Yao, X.D. Xia, D. Gong, Z.W. Zhao, L.Y. Chen, X.L. Zheng, X.E. Tang, C.K. Tang, AIBP reduces atherosclerosis by promoting reverse cholesterol transport and ameliorating inflammation in apoE(−/−) mice, Atherosclerosis 273 (2018) 122–130.
[52] C. Huang, X.H. Yu, X.L. Zheng, X. Ou, C.K. Tang, Interferon-stimulated gene 15 promotes cholesterol efflux by activating autophagy via the miR-17-5p/Beclin-1 pathway in THP-1 macrophage-derived foam cells, Eur. J. Pharmacol. 827 (2018) 13–21.
[53] Z.W. Zhao, M. Zhang, L.Y. Chen, D. Gong, X.D. Xia, X.H. Yu, S.Q. Wang, X. Ou, X.Y. Dai, X.L. Zheng, Heat shock protein 70 accelerates atherosclerosis by down-regulating the expression of ABCA1 and ABCG1 through the JNK/Elk-1 pathway, Biochim. Biophys. Acta 1863 (2018) 806–822.
[54] S.L. Tang, Z.W. Zhao, S.M. Liu, G. Wang, X.H. Yu, J. Zou, S.Q. Wang, X.Y. Dai, M.G. Fu, X.L. Zheng, D.W. Zhang, H. Fu, C.K. Tang, Pregnancy-associated plasma protein-A accelerates atherosclerosis by regulating reverse cholesterol transport and inflammation, Circ. J. vol. 83, (2019) 515–523.
[55] S.L. Li, W. Lin, Y. Zhang, Z.C. Zheng, L.J. Liu, H. Fu, J. Liu, G.D. Wang, S.Y. Chen, L.H. Feng, Stromal cell-derived factor-1alpha as a novel biomarker for hyperlipidemia, Tohoku J. Exp. Med. 228 (2012) 355–363.
[56] R.S. Rosenson, Statins in atherosclerosis: lipid-lowering agents with antioxidant capabilities, Atherosclerosis 173 (2004) 1–12.
[57] L.P. van de Vijver, A.F. Kardinaal, W. van Duyvenvoorde, D.A. Kruijssen, D.E. Grobbee, G. van Poppel, H.M. Princen, LDL oxidation and extent of coronary atherosclerosis, Arterioscler. Thromb. Vasc. Biol. 18 (1998) 193–199.
[58] S. Mitra, T. Goyal, J.L. Mehta, Oxidized LDL, LOX-1 and atherosclerosis, Cardiovasc. Drugs Ther. 25 (2011) 419–429.
[59] J. Zhang, H. Shen, M. Wang, S. Nie, X. Wu, Y. Huang, X. Gao, Significant association of CXCL12 rs1746048 with LDL-C level in intracranial aneurysms, Curr. Neurovasc. Res. 15 (2018) 26–33.
[60] I. Hilgendorf, F.K. Swirski, C.S. Robbins, Monocyte fate in atherosclerosis, Arterioscler. Thromb. Vasc. Biol. 35 (2015) 272–279.
[61] M.Y. Wu, C.J. Li, M.F. Hou, P.Y. Chu, New insights into the role of inflammation in the pathogenesis of atherosclerosis, Int. J. Mol. Sci. 18 (2017) e2034.
[62] T.M. Calderon, E.A. Eugenin, L. Lopez, S.S. Kumar, J. Hesselgesser, C.S. Raine, J.W. Berman, A role for CXCL12 (SDF-1alpha) in the pathogenesis of multiple sclerosis: regulation of CXCL12 expression in astrocytes by soluble myelin basic protein, J. Neuroimmunol. 177 (2006) 27–39.
[63] H. Ait-Oufella, A.P. Sage, Z. Mallat, A. Tedgui, Adaptive (T and B cells) immunity and control by dendritic cells in atherosclerosis, Circ. Res. 114 (2014) 1640–1660.
[64] T. Nanki, P.E. Lipsky, Cutting edge: stromal cell-derived factor-1 is a costimulator for CD4+ T cell activation, J. Immunol. (Baltimore, Md. : 1950) 164 (2000) 5010–5014.
[65] M. D'Apuzzo, A. Rolink, M. Loetscher, J.A. Hoxie, I. Clark-Lewis, F. Melchers, M. Baggiolini, B. Moser, The chemokine SDF-1, stromal cell-derived factor 1, attracts early stage B cell precursors via the chemokine receptor CXCR4, Eur. J. Immunol. 27 (1997) 1788–1793.
[66] K.K.Y. Liu, K. Dorovini-Zis, Regulation of CXCL12 and CXCR4 expression by human brain endothelial cells and their role in CD4+ and CD8+ T cell adhesion and transendothelial migration, J. Neuroimmunol. 215 (2009) 49–64.
[67] S. Weibin, P. Hong, J.J. Fischer, J.C. James, J.F. Angle, A.H. Matsumoto, G.A. Helm, I.J. Sarembock, Neointimal formation in two apolipoprotein E-deficient mouse strains with different atherosclerosis susceptibility, J. Lipid Res. 45 (2004) 2008–2014.
[68] V.J. Dzau, R.C. Braun-Dullaeus, D.G. Sedding, Vascular proliferation and atherosclerosis: new perspectives and therapeutic strategies, Nat. Med. 8 (2002) 1249–1256.
[69] A. Rudijanto, The role of vascular smooth muscle cells on the pathogenesis of atherosclerosis, Acta Med. Indonesiana 39 (2007) 86–93.
[70] A. Saiura, M. Sata, Y. Hirata, R. Nagai, M. Makuuchi, Circulating smooth muscle progenitor cells contribute to atherosclerosis, Nat. Med. 7 (2001) 382–383.
[71] M.C. Clarke, N. Figg, J.J. Maguire, A.P. Davenport, M. Goddard, T.D. Littlewood, M.R. Bennett, Apoptosis of vascular smooth muscle cells induces features of plaque vulnerability in atherosclerosis, Nat. Med. 12 (2006) 1075–1080.
[72] M. Clarke, M. Bennett, The emerging role of vascular smooth muscle cell apoptosis in atherosclerosis and plaque stability, Am. J. Nephrol. 26 (2006) 531–535.
[73] M.R. Bennett, S. Sinha, G.K. Owens, Vascular smooth muscle cells in atherosclerosis, Circ. Res. 118 (2016) 692–702.
[74] M.N. Thomas, A. Kalnins, M. Andrassy, A. Wagner, S. Klussmann, M. Rentsch, A. Habicht, S. Pratschke, M. Stangl, A.V. Bazhin, B. Meiser, M. Fischereder, J. Werner, M. Guba, J. Andrassy, SDF-1/CXCR4/CXCR7 is pivotal for vascular smooth muscle cell proliferation and chronic allograft vasculopathy, Transpl. Int. 28 (2015) 1426–1435.
[75] A. Zernecke, A. Schober, I. Bot, P. von Hundelshausen, E.A. Liehn, B. Mopps, M. Mericskay, P. Gierschik, E.A. Biessen, C. Weber, SDF-1alpha/CXCR4 axis is instrumental in neointimal hyperplasia and recruitment of smooth muscle progenitor cells, Circ. Res. 96 (2005) 784–791.
[76] J.C. Sluimer, M.J. Daemen, Novel concepts in atherogenesis: angiogenesis and hypoxia in atherosclerosis, J. Pathol. 218 (2009) 7–29.
[77] M.L. Bochenek, K. Schafer, Role of endothelial cells in acute and chronic thrombosis, Hamostaseologie (2019), https://doi.org/10.1055/s-0038-1675614 (Epub ahead of print).
[78] Y. Yin, X. Zhao, Y. Fang, S. Yu, J. Zhao, M. Song, L. Huang, SDF-1alpha involved in mobilization and recruitment of endothelial progenitor cells after arterial injury in mice, Cardiovasc. Pathol. 19 (2010) 218–227.
[79] J. Deshane, S. Chen, S. Caballero, A. Grochot-Przeczek, H. Was, S. Li Calzi, R. Lach, T.D. Hock, B. Chen, N. Hill-Kapturczak, G.P. Siegal, J. Dulak, A. Jozkowicz, M.B. Grant, A. Agarwal, Stromal cell-derived factor 1 promotes angiogenesis via a heme oxygenase 1-dependent mechanism, J. Exp. Med. 204 (2007) 605–618.
[80] Y. Doring, E.P.C. van der Vorst, J. Duchene, Y. Jansen, S. Gencer, K. Bidzhekov, D. Atzler, D. Santovito, D.J. Rader, D. Saleheen, C. Weber, CXCL12 derived from endothelial cells promotes atherosclerosis to drive coronary artery disease, Circulation 139 (2019) 1338–1340.
[81] S. Kawashima, M. Yokoyama, Dysfunction of endothelial nitric oxide synthase and atherosclerosis, Arterioscler. Thromb. Vasc. Biol. 24 (2004) 998–1005.
[82] S. Park, C.M. Sorenson, N. Sheibani, PECAM-1 isoforms, eNOS and endoglin axis in regulation of angiogenesis, Clin. Sci. (London, England : 1979) 129 (2015) 217–234.
[83] Z. Zhao, X. Ma, J. Ma, X. Sun, F. Li, J. Lv, Naringin enhances endothelial progenitor cell (EPC) proliferation and tube formation capacity through the CXCL12/CXCR4/PI3K/Akt signaling pathway, Chem. Biol. Interact. 286 (2018) 45–51.
[84] Z. Liang, J. Brooks, M. Willard, K. Liang, Y. Yoon, S. Kang, H. Shim, CXCR4/CXCL12 axis promotes VEGF-mediated tumor angiogenesis through Akt signaling pathway, Biochem. Biophys. Res. Commun. 359 (2007) 716–722.
[85] M. Pansuria, H. Xi, L. Li, X.F. Yang, H. Wang, Insulin resistance, metabolic stress, and atherosclerosis, Front. Biosci. (Scholar edition) 4 (2012) 916–931.
[86] H. Xu, G.T. Barnes, Q. Yang, G. Tan, D. Yang, C.J. Chou, J. Sole, A. Nichols, J.S. Ross, L.A. Tartaglia, H. Chen, Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance, J. Clin. Invest. 112 (2003) 1821–1830.
[87] K. Matin, M.A. Salam, J. Akhter, N. Hanada, H. Senpuku, Role of stromal-cell derived factor-1 in the development of autoimmune diseases in non-obese diabetic mice, Immunology 107 (2002) 222–232.
[88] N.M. De Jesus, L. Wang, A.W. Herren, J. Wang, F. Shenasa, D.M. Bers, M.L. Lindsey, C.M. Ripplinger, Atherosclerosis exacerbates arrhythmia following myocardial infarction: role of myocardial inflammation, Heart Rhythm. 12 (2015) 169–178.
[89] P. Dutta, G. Courties, Y. Wei, F. Leuschner, R. Gorbatov, C.S. Robbins, Y. Iwamoto, B. Thompson, A.L. Carlson, T. Heidt, M.D. Majmudar, F. Lasitschka, M. Etzrodt, P. Waterman, M.T. Waring, A.T. Chicoine, A.M. van der Laan, H.W. Niessen, J.J. Piek, B.B. Rubin, J. Butany, J.R. Stone, H.A. Katus, S.A. Murphy, D.A. Morrow, M.S. Sabatine, C. Vinegoni, M.A. Moskowitz, M.J. Pittet, P. Libby, C.P. Lin, F.K. Swirski, R. Weissleder, M. Nahrendorf, Myocardial infarction accelerates atherosclerosis, Nature 487 (2012) 325–329.
[90] N.N. Mehta, M. Li, D. William, A.V. Khera, S. DerOhannessian, L. Qu, J.F. Ferguson, C. McLaughlin, L.H. Shaikh, R. Shah, P.N. Patel, J.P. Bradfield, J. He, I.M. Stylianou, H. Hakonarson, D.J. Rader, M.P. Reilly, The novel atherosclerosis locus at 10q11 regulates plasma CXCL12 levels, Eur. Heart J. 32 (2011) 963–971.
[91] Y. Wang, L. Wang, X. Liu, Y. Zhang, L. Yu, F. Zhang, L. Liu, J. Cai, X. Yang, X. Wang, Genetic variants associated with myocardial infarction and the risk factors in Chinese population, PLoS One 9 (2014) e86332.
[92] S. Abi-Younes, A. Sauty, F. Mach, G.K. Sukhova, P. Libby, A.D. Luster, The stromal cell-derived factor-1 chemokine is a potent platelet agonist highly expressed in atherosclerotic plaques, Circ. Res. 86 (2000) 131–138.
[93] K. Stellos, M. Ruf, K. Sopova, A. Kilias, A. Rahmann, K. Stamatelopoulos,

R. Jorbenadze, T. Geisler, M. Gawaz, B. Bigalke, Plasma levels of stromal cell-derived factor-1 in patients with coronary artery disease: effect of clinical presentation and cardiovascular risk factors, Atherosclerosis 219 (2011) 913–916.
[94] A. Chatzikonstantinou, A.D. Ebert, S.O. Schoenberg, M.G. Hennerici, T. Henzler, Atherosclerosis in intracranial, extracranial, and coronary arteries with aortic plaques in patients with ischemic stroke of undetermined etiology, Int. J. Neurosci. 125 (2015) 663–670.
[95] M. Ghosh, K. Ghosh, A. Chatterjee, A. Bhattacharya, A. Acharya, S. Chakraborty, B. Ghosh, Correlation of intracranial atherosclerosis with carotid stenosis in ischemic stroke patients, Ann. Indian Acad. Neurol. 18 (2015) 412–414.
[96] X.L. Gu, L. Liu, X.D. Lu, Z.R. Liu, Serum CXCL12 levels as a novel predictor of future stroke recurrence in patients with acute ischemic stroke, Mol. Neurobiol. 53 (2016) 2807–2814.
[97] R.C. Schutt, M.D. Burdick, R.M. Strieter, B. Mehrad, E.C. Keeley, Plasma CXCL12 levels as a predictor of future stroke, Stroke 43 (2012) 3382–3386.
[98] P. Liu, J.W. Xiang, S.X. Jin, Serum CXCL12 levels are associated with stroke severity and lesion volumes in stroke patients, Neurol. Res. 37 (2015) 853–858.
[99] R. Zhu, X. Liu, Z. He, Genetic variants on chromosome 10q11.21 are associated with ischemic stroke in the northern Chinese Han population, J. Mol. Neurosci. 51 (2013) 394–400.
[100] A. Valenzuela-Fernandez, T. Planchenault, F. Baleux, I. Staropoli, K. Le-Barillec, D. Leduc, T. Delaunay, F. Lazarini, J.L. Virelizier, M. Chignard, D. Pidard, F. Arenzana-Seisdedos, Leukocyte elastase negatively regulates stromal cell-derived factor-1 (SDF-1)/CXCR4 binding and functions by amino-terminal processing of SDF-1 and CXCR4, J. Biol. Chem. 277 (2002) 15677–15689.
[101] M.B. Delgado, I. Clark-Lewis, P. Loetscher, H. Langen, M. Thelen, M. Baggiolini, M. Wolf, Rapid inactivation of stromal cell-derived factor-1 by cathepsin G associated with lymphocytes, Eur. J. Immunol. 31 (2001) 699–707.
[102] G.A. McQuibban, G.S. Butler, J.H. Gong, L. Bendall, C. Power, I. Clark-Lewis, C.M. Overall, Matrix metalloproteinase activity inactivates the CXC chemokine stromal cell-derived factor-1, J. Biol. Chem. 276 (2001) 43503–43508.
[103] D.A. Davis, K.E. Singer, M. De La Luz Sierra, M. Narazaki, F. Yang, H.M. Fales, R. Yarchoan, G. Tosato, Identification of carboxypeptidase N as an enzyme responsible for C-terminal cleavage of stromal cell-derived factor-1alpha in the circulation, Blood 105 (2005) 4561–4568.
[104] L. Marquez-Curtis, A. Jalili, K. Deiteren, N. Shirvaikar, A.M. Lambeir, A. Janowska-Wieczorek, Carboxypeptidase M expressed by human bone marrow cells cleaves the C-terminal lysine of stromal cell-derived factor-1alpha: another player in hematopoietic stem/progenitor cell mobilization? Stem Cells (Dayton, Ohio) 26 (2008) 1211–1220.
[105] N.D. Staudt, W.K. Aicher, H. Kalbacher, S. Stevanovic, A.K. Carmona, M. Bogyo, G. Klein, Cathepsin X is secreted by human osteoblasts, digests CXCL-12 and impairs adhesion of hematopoietic stem and progenitor cells to osteoblasts, Haematologica 95 (2010) 1452–1460.
[106] P. Ray, S.A. Lewin, L.A. Mihalko, S.C. Lesher-Perez, S. Takayama, K.E. Luker, G.D. Luker, Secreted CXCL12 (SDF-1) forms dimers under physiological conditions, Biochem. J. 442 (2012) 433–442.
[107] R. Janssens, S. Struyf, P. Proost, The unique structural and functional features of CXCL12, Cell. Mol. Immunol. 15 (2018) 299–311.
[108] Y. Kofuku, C. Yoshiura, T. Ueda, H. Terasawa, T. Hirai, S. Tominaga, M. Hirose, Y. Maeda, H. Takahashi, Y. Terashima, K. Matsushima, I. Shimada, Structural basis of the interaction between chemokine stromal cell-derived factor-1/CXCL12 and its G-protein-coupled receptor CXCR4, J. Biol. Chem. 284 (2009) 35240–35250.
[109] E. Karshovska, D. Zagorac, A. Zernecke, C. Weber, A. Schober, A small molecule CXCR4 antagonist inhibits neointima formation and smooth muscle progenitor cell mobilization after arterial injury, J. Thromb. Haemost. 6 (2008) 1812–1815.
[110] K. Hamesch, P. Subramanian, X. Li, K. Dembowsky, E. Chevalier, C. Weber, A. Schober, The CXCR4 antagonist POL5551 is equally effective as sirolimus in reducing neointima formation without impairing re-endothelialisation, Thromb. Haemost. 107 (2012) 356–368.
[111] R.D. Berahovich, B.A. Zabel, S. Lewen, M.J. Walters, K. Ebsworth, Y. Wang, J.C. Jaen, T.J. Schall, Endothelial expression of CXCR7 and the regulation of systemic CXCL12 levels, Immunology 141 (2014) 111–122.
[112] I. Kalatskaya, Y.A. Berchiche, S. Gravel, B.J. Limberg, J.S. Rosenbaum, N. Heveker, AMD3100 is a CXCR7 ligand with allosteric agonist properties, Mol. Pharmacol. 75 (2009) 1240–1247.
[113] S. Gravel, C. Malouf, P.E. Boulais, Y.A. Berchiche, S. Oishi, N. Fujii, R. Leduc, D. Sinnett, N. Heveker, The peptidomimetic CXCR4 antagonist TC14012 recruits beta-arrestin to CXCR7: roles of receptor domains, J. Biol. Chem. 285 (2010) 37939–37943.
[114] T. Kosuke, T. Kohei, S. Kenji, S. Akira, O. Akira, H. Takahiko, Dimeric peptides of the C-terminal region of CXCL14 function as CXCL12 inhibitors, FEBS Lett. 587 (2013) 3770–3775.
[115] J.W. Cheng, Z. Sadeghi, A.D. Levine, M.S. Penn, H.A.V. Recum, A.I. Caplan, A. Hijaz, The role of CXCL12 and CCL7 chemokines in immune regulation, embryonic development, and tissue regeneration, Cytokine 69 (2014) 277–283.
[116] T. Nagasawa, S. Hirota, K. Tachibana, N. Takakura, S. Nishikawa, Y. Kitamura, N. Yoshida, H. Kikutani, T. Kishimoto, Defects of B-cell lymphopoiesis and bone-marrow myelopoiesis in mice lacking the CXC chemokine PBSF/SDF-1, Nature 382 (1996) 635–638.
[117] S.N. Batchu, K. Thieme, F.H. Zadeh, T.A. Alghamdi, V.G. Yerra, M.J. Hadden, S. Majumder, M.G. Kabir, B.B. Bowskill, D. Ladha, A.O. Gramolini, K.A. Connelly, A. Advani, The dipeptidyl peptidase 4 substrate CXCL12 has opposing cardiac effects in young mice and aged diabetic mice mediated by Ca(2+) flux and phosphoinositide 3-kinase gamma, Diabetes 67 (2018) 2443–2455.
[118] Y. Doring, H. Noels, E.P.C. van der Vorst, C. Neideck, V. Egea, M. Drechsler, M. Mandl, L. Pawig, Y. Jansen, K. Schroder, K. Bidzhekov, R.T.A. Megens, W. Theelen, B.M. Klinkhammer, P. Boor, L. Schurgers, R. van Gorp, C. Ries, P.J.H. Kusters, A. van der Wal, T.M. Hackeng, G. Gabel, R.P. Brandes, O. Soehnlein, E. Lutgens, D. Vestweber, D. Teupser, L.M. Holdt, D.J. Rader, D. Saleheen, C. Weber, Vascular CXCR4 limits atherosclerosis by maintaining arterial integrity: evidence from mouse and human studies, Circulation 136 (2017) 388–403.
[119] X. Li, M. Zhu, M.E. Penfold, R.R. Koenen, A. Thiemann, K. Heyll, S. Akhtar, S. Koyadan, Z. Wu, F. Gremse, F. Kiessling, M. van Zandvoort, T.J. Schall, C. Weber, A. Schober, Activation of CXCR7 limits atherosclerosis and improves hyperlipidemia by increasing cholesterol uptake in adipose tissue, Circulation 129 (2014) 1244–1253.