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Leukocyte Chemoattractant Receptor FPR2 May Accelerate Atherogenesis

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Abstract

Atherosclerosis is a chronic inflammatory disease and the number one cause of mortality worldwide. The fundamental causes of atherosclerosis have not been precisely delineated, although pathogenesis clearly involves endothelial dysfunction and both innate and adaptive immunity. Recent evidence suggests that formyl peptide receptor 2 (FPR2), a G protein-coupled receptor (GPCR), mediates a range of inflammatory responses including superoxide production in neutrophils, chemotaxis of monocytes and neutrophils, CCL2 production in endothelial cells (ECs) and monocytes, and increased CXCL8 expression in neutrophils, which are all related with atherogenesis. Therefore, we propose that FPR2 may play a pathogenic role in atherogenesis.

Introduction

Atherosclerosis is a disorder of large and medium-sized arteries and mortality data showed that it accounted for 1/3 of the deaths in the United States in 2008 [1]. The earliest stage of atherosclerosis is thought to involve endothelial dysfunction/activation due to oxidized low-density lipoprotein (oxLDL) stimulation or disturbed blood flow at arterial branching points. This is followed by the adhesion and infiltration of activated platelets and different subsets of leukocytes, including monocytes, neutrophils, dendritic cells, B cells and T cells [2]. Monocytes/macrophages are the predominant cell types that have been identified in atherosclerotic lesions and their uptake of oxLDL leads to the formation of foam cells [3]. Eventually, the atherosclerotic plaque formed in the intimal vessel wall narrows the artery and the rupture of unstable plaques results in myocardial infarction, stroke and other vascular syndromes [1].

Although many risk factors and gene polymorphisms have been identified for atherosclerosis by classical epidemiology and recent genome wide association studies (GWAS), additional work is needed to identify new targets for more effective therapies. FPR2 is a member of the formyl peptide receptor (FPR) family of seven- transmembrane domain, G protein-coupled receptors. FPR2 is expressed mainly by phagocytic leukocytes such as monocytes and neutrophils and is known to be important in both host defense and inflammation [4], thus making it an appealing candidate in promoting atherosclerosis development.

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Conflicts of interest statement
The authors have no conflict of interest.

Hypothesis

We hypothesize that FPR2 triggers the pathogenesis of atherosclerosis and it may serve as a potential target for atherosclerosis treatment.

Supporting Evidences

Several recent studies have shown that activation of FPR2 is potentially proatherogenic (Figure 1). The first evidence is that FPR2 activation may contribute to superoxide production when neutrophils are stimulated with *N*-formyl-Met–Leu–Phe (fMLF), a potent chemoattractant for phagocytes (5). This effect is mediated by NADPH oxidase (NOX) activation and it was found that reactive oxygen species (ROS) production result from NOX activation might accelerate atherogenesis [6].

The second evidence is that several agonists for FPR2 are associated with chronic inflammation (e.g. serum amyloid A [SAA] and amyloid β peptide 42 [$A\beta_{42}$]), which is the major cause of atherosclerosis [2, 4]. For example, SAA is an excellent marker for inflammation and is positively associated with prevalent cardiovascular diseases in humans [7]. A recent study showed that elevated plasma levels of SAA directly accelerate disease progression in a mouse model of atherosclerosis, indicating that it is also an active participant in atherogenesis [8]. FPR2 activation by SAA results in a range of inflammatory responses: chemotaxis of monocytes, neutrophils, mast cells and T lymphocytes, production of proinflammatory cytokines such as TNFα and IL-1β, and increased expression of matrix metalloproteinases (MMPs), which may all accelerate the progression of atherosclerosis (Figure 1) [4, 9].

During atherosclerosis, a critical step is the recruitment of leukocytes by chemokines [10]. CCL2 is one of the best-studied chemokines in this regard and is a key mediator of monocyte migration into early atherogenic lesions [3]. Genetic inactivation of either CCL2 or its receptor CCR2 has been reported to significantly reduce the development of atherosclerosis in mouse models [10]. Moreover, there is a significant correlation in humans of CCL2 plasma levels with peripheral arterial disease and acute coronary syndrome [11]. Recently it has been reported that SAA can induce CCL2 production in human monocytes in a time- and concentration-dependent manner, and the induction is mediated by FPR2 since a FPR2 antagonist can dramatically inhibit this process [12]. Also, SAA can induce CCL2 production in human endothelial cells through FPR2 and FPR2 knockdown by short interfering RNA almost completely blocked the induction [13]. Both endothelial cells and monocytes play important roles in atherosclerosis because endothelial dysfunction is considered the trigger of atherogenesis, whereas monocyte recruitment is critical for both the initiation and progression of atherosclerosis. FPR2 activation by SAA in endothelial cells may increase expression of CCL2, which can recruit monocytes to the endothelium and promote transendothelial migration. Monocytes can then secrete additional CCL2 through FPR2 activation, recruiting more circulating monocytes into the atherosclerotic lesions, thus form a pro-atherogenic positive feedback loop in the vessel wall.

Another important chemokine involved in atherogenesis is CXCL8, which targets monocytes and neutrophils [10]. CXCL8 has been reported to induce firm adhesion of rolling monocytes to endothelial cells but the receptors for CXCL8, CXCR1 and CXCR2, are mainly expressed on neutrophils [3, 11]. Mice depleted of neutrophils or transferred with $CXCR2^{-/-}$ bone marrow are protected from atherosclerotic lesion development, suggesting that the CXCL8-CXCR2 axis may play a pro-atherogenic role [10, 14]. In neutrophils, SAA can induce rapid secretion of CXCL8 through activation of FPR2; moreover, overexpression of FPR2 increased CXCL8 secretion while an antibody against FPR2 inhibited CXCL8 expression [15]. Considering that SAA can also induce chemotaxis of neutrophils through

FPR2 [4], it is possible that FPR2 is an important bridge between SAA and CXCL8 during the recruitment of neutrophils into atherosclerotic plaques (Figure 1).

The role of FPR2 in inflammation is complicated by the fact that some of its agonists (e.g. LXA4 and its analogs) also exert anti-inflammatory effects [16]. The deletion of FPR2 in mice resulted in either increased inflammatory response or reduced inflammation depending on the specific animal model [17, 18]. Thus, it is still not clear how FPR2 can respond to both pro-inflammatory and anti-inflammatory ligands, but it suggests at least that FPR2 is critical in the modulation of immune and inflammatory responses.

Testing the hypothesis

In order to test the hypothesis, we suggest the following research directions:

1. Compare the development of atherosclerosis in wild type and FPR2 knockout mice. Considering that normal mice do not develop atherosclerosis spontaneously, those mice may need to be backcrossed with $ApoE^{-/-}$ or $Ldlr^{-/-}$ mice, which are prone to atherosclerosis.
2. Test the effect of FPR2 agonists/antagonists on the development of atherosclerosis in mouse models.
3. Check the function of FPR2 on other human leukocytes such as T cells and dendritic cells to see whether they play similar roles as in monocytes and neutrophils.
4. Identify FPR2 polymorphisms in humans and test their associations with cardiovascular disease.

Implications of the hypothesis

Although atherosclerosis has been studied for decades, and there has been major progress in the diagnosis and treatment of patients, there is still only a limited range of treatment options. New targets are necessary for more effective therapies and here we propose FPR2 as a potential target worth studying. Agonists and antagonists are already available for FPR2 and if it can be validated as a pro-atherogenic factor in mouse models and in humans, there will be a rationale for moving them forward in clinical trials of atherosclerotic cardiovascular disease.

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Abbreviations

fMLF	N-formyl-Met–Leu–Phe
SAA	serum amyloid A
FPR2	formyl peptide receptor 2
NOX	NADPH oxidase
ROS	reactive oxygen species
ECs	endothelial cells
MMPs	matrix metalloproteinases
TNα	tumor necrosis factor-alpha

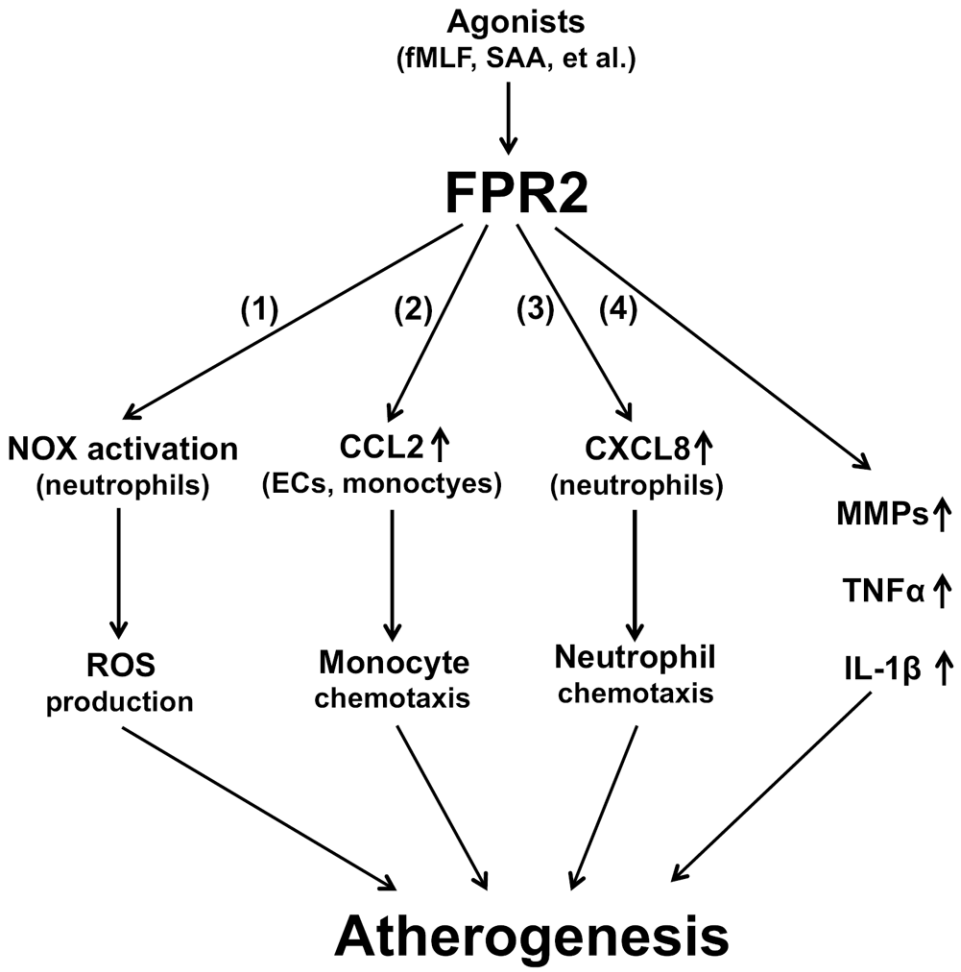

Figure 1. FPR2 may accelerate atherogenesis through different pathways

FPR2 activation by its agonists (e.g. fMLF, SAA) lead to (1) NOX activation and ROS production in neutrophils; (2) increased CCL2 expression in ECs and monocytes, thus inducing monocyte chemotaxis; (3) increased CXCL8 expression in neutrophils, thus inducing neutrophil chemotaxis; and (4) increased levels of MMPs, TNFα and IL-1β. All these factors are proatherogenic and FPR2 will probably promote atherogenesis either by one major pathway or by a synergistic effect of different pathways.