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Review

PCSK9: A potential regulator of apoE/apoER2 against inflammation in atherosclerosis?

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ABSTRACT

Atherosclerosis is characterized by chronic inflammation and lipid accumulation in arterial walls, resulting in several vascular events. Proprotein convertase subtilisin kexin 9 (PCSK9), a serine protease, has a pivotal role in the degradation of hepatic low-density lipoprotein receptor (LDLR). It can increase plasma concentrations of low-density lipoprotein cholesterol and affect lipid metabolism. Recently, PCSK9 has been found to accelerate atherosclerosis via mechanisms apart from that involving the degradation of LDLR, with an emerging role in regulating the inflammatory response in atherosclerosis. Apolipoprotein E receptor 2 (apoER2), one of the LDLR family members expressed in macrophages, can bind to its ligand apolipoprotein E (apoE), exhibiting an anti-inflammatory role in atherosclerosis. Evidence suggests that apoER2 is a target of PCSK9. This review aims to discuss PCSK9 as a potential regulator of apoE/apoER2 against inflammation in atherosclerosis.

1. Introduction

Atherosclerosis is a chronic disease that is mainly driven by inflammation of the arterial walls [1]; inhibiting inflammation could therefore be expected to potentially reduce the extent of atherosclerosis. In 2003, Abifadel et al. [2] discovered that proprotein convertase subtilisin kexin 9 (PCSK9) causes autosomal dominant hypercholesterolemia. The underlying critical mechanism involves promotion of PCSK9 induced hepatic low-density lipoprotein receptor (LDLR) degradation in lysosomes, preventing recycling of the receptor to the cell surface [3]. This results in reduced levels of LDLR protein in the hepatic plasma membrane, as well as increased serum lipid levels. PCSK9 has been thought to indirectly participate in atherogenesis owing to its role in increasing serum lipids; however, the potential direct roles of PCSK9 in atherosclerosis, such as its role in vascular inflammation, are gaining attraction. This article mainly focuses on the relationship between PCSK9 and its pro-inflammatory properties in atherosclerosis.

Earlier studies revealed that apolipoprotein E (apoE) can reduce lipid accumulation in macrophages and inhibit foam cell formation [4,5]. Recent researches have focused on its anti-inflammatory properties [6,7]. For example, it has been reported that apoE exerts anti-inflammatory activity by switching macrophages from the M1 phenotype to M2 phenotype in a process involving signaling via the apoE receptor-2 (apoER2) [8]; this implies that apoE exhibits an anti-inflammatory role by binding to apoER2. In addition, studies have demonstrated that PCSK9 induces the degradation of apoER2 in lysosomes, which may imply that PCSK9 is involved in the apoE/apoER2 anti-inflammatory mechanism by degradation of apoER2. This review focuses on the latest advances in this field and provides insight into the impact of PCSK9 on atherosclerosis via pro-inflammatory pathways.

2. Chronic inflammation mechanisms in atherosclerosis

Atherosclerosis, a chronic multifactorial inflammatory disease [9], is a major cause of death worldwide. The earliest changes that eventually result in the formation of atherosclerotic lesions occur in the endothelium. Under normal conditions, endothelial cells provide a structural barrier between the circulating blood and the surrounding tissue. When endothelial cells are activated by the perturbation of different components (such as hypercholesterolemia, hypertension, infection), they upregulate the expression of various leukocyte adhesion molecules. The initiation of atherosclerosis is characterized by the expression of adhesion proteins, chemokines, cytokines, and growth

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factors, which are responsible for the adherence, migration, and accumulation of peripheral blood mononuclear cells, including monocytes and T lymphocytes [10,11]. After migrating into the subendothelial space, the monocytes differentiate into tissue macrophages [1]. The macrophages scavenge cell debris, lipoproteins, and/or oxidatively modified lipoproteins via various scavenger receptors on the cell membrane surface, forming foam cells [12], which are believed to be the hallmark of arterial lesion. The activated macrophages secrete an array of growth factors and cytokines that are involved in lesion progression and complication.

T lymphocytes similarly enter the intima in response to lymphocyte chemoattractants. On residing in the arterial intima, the T lymphocytes may be activated by endogenous or exogenous antigens; they then produce cytokines, such as γ-interferon and lymphotoxin [tumor necrosis factor (TNF)-β], which, in turn, can stimulate macrophages as well as vascular endothelial cells and smooth muscle cells (SMCs). T lymphocytes may regulate the innate inflammatory response in atherosclerosis, mediated by macrophages within the atherosclerotic lesions.

The early vascular lesion is the so-called “fatty streak.” This is a purely inflammatory lesion, consisting of a large number of monocyte-derived macrophages and T lymphocytes. Further inflammation results in the emigration of multiplied SMCs from the medial layer of the artery wall to the lesion, where they proliferate and take up modified lipoproteins to form foam cells. At the same time, monocytes and T lymphocytes continue to enter the lesion. Together, these processes may lead to an expanded, intermediate fibrous lesion. As the lesion progresses, a fibrous cap may form, consisting of numerous SMCs, proliferated macrophages, T lymphocytes, growing mass of extracellular lipids, and potential amounts of new connective tissue.

Advanced lesions may ultimately result in ischemic symptoms due to vessel lumen stenosis, plaque rupture, and thrombosis. Thus, atherosclerotic lesions result from a series of highly specific cellular and molecular responses, and atherosclerosis can thus be regarded as an inflammatory disease [13].

3. ApoE/apoER2: intrinsic anti-inflammatory molecules that protect against atherosclerotic inflammatory response

3.1. Role of apoE in atherosclerosis

ApoE is a 34-kD arginine-rich glycoprotein, produced in various organs including the liver, brain, kidneys, and adrenal glands. Many cell types can synthesize and secrete apoE both in vivo and in vitro; these include parenchymal cells, differentiated macrophages, astrocytic glial cells, and SMCs [14]. ApoE is one of the major apolipoproteins in the human plasma lipoproteins; it mainly mediates the clearance of chylomicrons, very low-density lipoproteins, and their residues in the liver, and it plays an important role in the metabolism of triglyceride-rich lipoproteins [15]. Human apoE is a polymorphic apolipoprotein encoded by three alleles (ε2, ε3, and ε4), which result from single nucleotide substitution within codons 112 and 158 [16]. ApoE2 has cysteines at positions 112 and 158, apoE3 has a cysteine at position 112 and an arginine at position 158, and apoE4 has arginines at positions 112 and 158. These determine six apoE phenotypes (ε3/3, ε4/4, ε2/2, ε3/2, ε4/2, and ε4/3) in the population [17], of which the ε3/3 genotype is the most common. The ε2 allele is associated with recessive inheritance of hyperlipoproteinemia in patients with type III hyperlipidemia [18], and the ε4 allele is strongly associated with cardio-cerebrovascular diseases and Alzheimer's disease [19]. The establishment of apoE knockout animals has greatly helped in clarifying the events through which apoE plays its important, protective role in atherosclerosis. Compared with wild-type mice, the apoE-deficient mice have high plasma cholesterol levels due to an impaired clearance of the remnant lipoproteins. The apoE-deficient mice can develop severe, spontaneous, premature atherosclerotic lesions. ApoE is best known for its role in the transport of cholesterol and other lipids between peripheral tissues and liver. However, it has direct effects on the vessel wall, which may contribute to arterial protection. ApoE has been found to protect from atherogenesis in the absence of significant changes in plasma lipoproteins via four mechanisms [20]. First, it facilitates the efflux of cellular cholesterol from macrophage foam cells in the arterial wall. Evidence suggests that, under normal circumstances, both apolipoprotein AI and apoE on HDL particles act in concert to mediate this protective efflux [21]. Second, apoE regulates the chronic inflammatory response. Its expression is modified, which in turn modifies both T lymphocyte and macrophage cytokine production; therefore, apoE appears to have a direct influence on both the innate and the acquired immune responses that contribute to atherosclerosis. Third, apoE inhibits platelet aggregation and stimulates platelet nitric oxide synthease activity. Fourth, it blocks the proliferation of lymphocytes and endothelial cells. Additionally, apoE also presents allele-specific antioxidant activity in atherosclerosis. Thus, apoE has numerous functions that protect against atherosclerosis.

3.2. Role of apoER2 in atherosclerosis

ApoER2 [22] (gene name: LDL receptor-related protein-8, LRP8) is a type 1 transmembrane protein with an extracellular domain composed of multiple cysteine-rich ligand binding repeats, an epidermal growth factor (EGF) domain with three cysteine-rich repeats, an O-linked glycosylation domain, a single transmembrane domain, and a short cytoplasmic tail that includes several adaptor protein-binding motifs. As a member of the LDLR family [23], apoER2 recognizes extracellular ligands (for example,apoE) and internalizes them for degradation in lysosomes via a process of receptor-mediated endocytosis. ApoER2 is expressed in the brain, testes, and heart, and it is also present in cells that participate in atherogenesis including platelets, endothelial cells, and monocytes/macrophages [24]. Riddell et al. have shown that apoE exerts its impact by increasing the production of platelet-derived nitric oxide, which has been found to be a potent inhibitor of platelet activation. They demonstrated a link between apoE and nitric oxide in platelets that is mediated by apoER2. In endothelial cells, the binding of apoE to apoER2 also stimulates nitric oxide synthesis and inhibits the expression of vascular cell adhesion molecule-1 [25]. ApoER2 on platelets and endothelial cells also interacts with the β2-glycoprotein I–antibody complex and mediates leukocyte–endothelial cell adhesion and thrombosis by antiphospholipid antibodies via the inhibition of endothelial nitric oxide synthase [26,27]. It is also thought that platelet apoER2 modulates adhesion and bleeding time [28]. A strong experimental evidence suggests that antiphospholipid antibodies and dimeric β-2GPI have thrombogenic properties through apoER2 expressed on the endothelial cells and monocytes. In addition, the binding of apoE to apoER2 may reduce atherosclerosis by suppressing the inflammatory function of macrophages [29]. ApoER2 expression in macrophages reduces lipid accumulation and cell death, and this can retard the development of atherosclerotic plaques and necrosis in vivo [30]. Taken together, these findings show that apoER2 has an important impact in protection against atherosclerosis.

3.3. Potent anti-inflammatory effects of ApoE/apoER2 in atherosclerosis

As described earlier, atherosclerosis is a chronic and complex inflammatory disease. Thus, inhibiting inflammation can reduce the extent of atherosclerosis. Macrophages, the main source of inflammatory cytokines in atherosclerotic lesions and the main immune cells in the innate immune response, play a key role in the progression of atherosclerotic plaque. The aggregation of inflammatory macrophages and the formation foam cells accelerated the rupture of the plaque. Macrophages are a heterogeneous cell that can be divided into two polarities after entering the subendothelial cells: classically activated macrophages (M1) that express high levels of pro-inflammatory cytokines; and alternatively activated macrophages (M2) that express high

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