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Role of PCSK9 in lipid metabolism and atherosclerosis

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ABSTRACT

Elevated plasma low-density lipoprotein cholesterol (LDL-C) is an important risk factor for cardiovascular diseases. Statins are the most widely used therapy for patients with hyperlipidemia. However, a significant residual cardiovascular risk remains in some patients even after maximally tolerated statin therapy. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a new pharmacologically therapeutic target for decreasing LDL-C. PCSK9 reduces LDL intake from circulation by enhancing LDLR degradation and preventing LDLR recirculation to the cell surface. Moreover, PCSK9 inhibitors have been approved for patients with either familial hypercholesterolemia or atherosclerotic cardiovascular disease, who require additional reduction of LDL-C. In addition, PCSK9 inhibition combined with statins has been used as a new approach to help reduce LDL-C levels in patients with either statin intolerance or unattainable LDL goal. This review will discuss the emerging anti-PCSK9 therapies in the regulation of cholesterol metabolism and atherosclerosis.

1. Introduction

Increased low density lipoprotein (LDL)-cholesterol is a significant risk factor for atherosclerosis. LDL-cholesterol (LDL-C) reduction is an important target in reducing cardiovascular disease (CVD) risk. Currently, treatment with statins remains one of the main therapy for patients with hypercholesterolemia [1]. However, statin therapy is still inadequate to achieve LDL-C target in some high-risk patients [2]. In addition, more than 30% of patients are unable to tolerate statin therapy [3,4]. Furthermore, the residual cardiovascular risk remains high despite maximal statin therapy [5]. Therefore, additional potent LDL-lowering agents are frequently needed for patients who need further LDL-C reduction.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease involved in the regulation of hepatic apoB lipoprotein uptake and cholesterol metabolism via the LDL receptor (LDLR) [6,7]. Plasma LDL-C are cleared from the plasma mainly through the LDLR pathway. After LDL binds to LDLR, LDL and LDLR are internalized into clathrin-coated pits and degraded in the lysosome [8] (Fig. 1). Afterward, LDLR is recirculated back to the cell membrane. PCSK9 binds to LDLR and mediates LDLR internalization and degradation in the lysosome, and subsequently reduces LDLR recycling and decreases LDL-C cleared from the plasma [8,9]. Very low-density lipoprotein (VLDL) and chylomicron remnants are cholesterol-dense apoB lipoprotein remnants and are considered atherogenic lipoproteins [10,11]. PCSK9 regulates apoB lipoprotein degradation and cholesterol metabolism [12]. Therefore, PCSK9 is also a novel target for decreasing plasma concentrations of apoB lipoproteins [13,14]. Interventions targeting PCSK9 may lead to significant reduction in plasma LDL-C, total apoB, and possibly, cardiovascular risk [15]. PCSK9 inhibitors are recommended for patients with persistently high LDL-C despite treatment with maximally tolerated statin doses [16,17]. This review will discuss PCSK9 as a novel promising drug target for lipid-lowering therapy and in associated atherosclerosis.

2. PCSK9 and LDLR

PCSK9 is mainly expressed in the liver and degrades the LDLR independently of its catalytic activity [18]. PCSK9 can degrade LDLR via an external route and might work in a post-endoplasmic reticulum compartment where it mediates the degradation of LDLR [19]. Secreted PCSK9 binds to epidermal growth factor-like repeat of LDLR and then increases lysosomal degradation [20]. The binding affinity of PCSK9 and LDLR is enhanced at the acidic pH [18,21].

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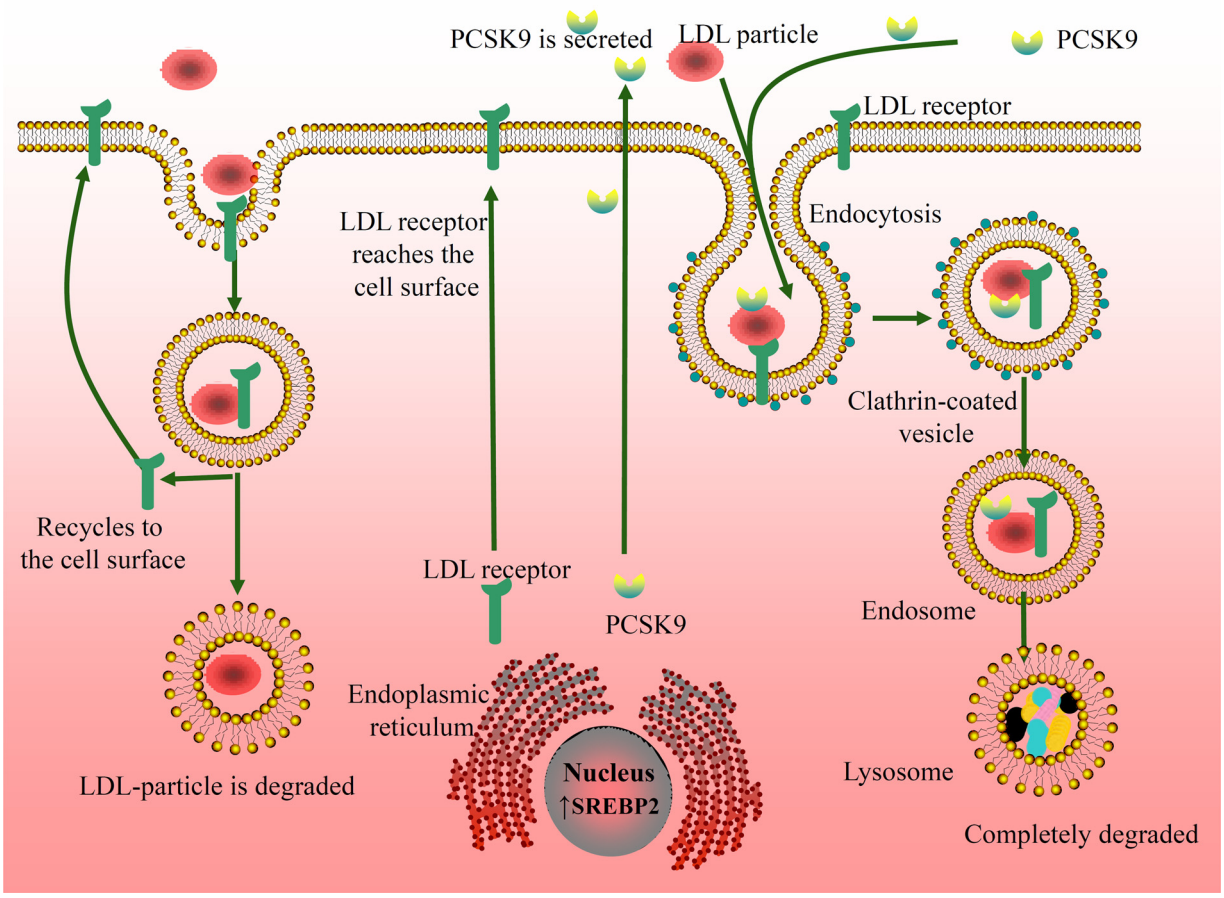

Fig. 1. Schematic representation of the intracellular and extracellular pathways of PCSK9 induced degradation of the LDLR. When PCSK9 levels are high, PCSK9 will enhance the degradation of LDLR in acidic lysosomes and then increased serum LDL levels. In absence of PCSK9, LDLR exists at the cell surface and delivery of LDL particles to degradation in acidic endosomes, and then LDLR recycled back to the cell surface.

3. PCSK9 and other receptors

3.1. VLDL-R

VLDL receptor (VLDLR) is expressed in the brain, heart, and adipocytes. VLDLR has a highly preserved EGF-A domain, and the VLDLR sequences are similar to LDLR. PCSK9 promotes degradation of VLDLR in hepatic cells, fibroblasts, and neurons [22]. PCSK9 binds several receptors (apoE-R2, LDLR, and VLDLR) via its EGF-A-binding domain and degradation of these receptors, which can be inhibited by an EGF-A peptide [23]. In addition, endogenous PCSK9 regulates VLDLR protein levels in adipose tissue and limits visceral adipogenesis likely via adipose VLDLR regulation [24].

3.2. LOX-1

Lectin-like oxLDL receptor-1 (LOX-1) is expressed in monocytes and smooth muscle cells [25]. Tumor necrosis factor α and interleukin-1 (IL-1) promote the expression of LOX-1[26]. During an inflammatory state, PCSK9 promotes the activation of LOX-1[27]. LOX-1 plays an important role in foam cell formation and migration of smooth muscle cells [28]. Deletion of LOX-1 reduces arterial wall inflammation, macrophage trafficking [29], and atherosclerosis [30].

3.3. LRP1 and CD36

LDLR-related protein 1 (LRP1) is a member of the LDL receptor family. The structure of LRP1 is similar to that of LDLR [31]. LRP1 facilitates bacterial toxins and apoptotic cell debris internalization and degradation [32]. In addition, Canuel et al. reported that PCSK9 mediates degradation of LRP1 in multiple cell lines [33]. Moreover, the uptake of apoB remnants is mediated by LRP1 [33]. PCSK9 is associated with the degradation of LRP1 in the absence of LDLR or at least in melanoma cell lines [33]. PCSK9 modulates lipid transport and metabolism via a cholesterol transporter, CD36 [7]. PCSK9-mediated CD36 degrades and inhibits fatty acid uptake and triglyceride accumulation in liver PCSK9-knockout mice [34].

4. Regulation of PCSK9 expression

4.1. Dietary regulation, diurnal rhythm and gender

Sterol deprivation and high-fructose diet increases the expression of PCSK9 in HepG2 cells [35,36]. Plasma PCSK9 concentration is significantly reduced in the Mediterranean diet [37] and in n-6 polyunsaturated fatty acids [38]. Fasting decreases the expression of PCSK9 in healthy volunteers [39,40] via SREBP1 and HNF1α [41]. PCSK9 has a marked diurnal rhythm, in that serum PCSK9 is lowest at 4:00 p.m. and peaks at midnight [42]. PCSK9 levels are higher in women than men [43]. In addition, growth hormones induce PCSK9 synthesis [44,45]. Thus, PCSK9 is associated with age, gender, and fasting insulinemia [46].

4.2. Chinese traditional drugs

Xuezhikang and berberine are traditional Chinese drugs [47]. Xuezhikang increases PCSK9 levels through SREBP-2 in rats and humans [48]. Berberine reduces serum LDL-C and increases hepatic LDLR