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Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9): A Promising Therapeutic Target for Cardiovascular Diseases

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Abstract

Cardiovascular disease (CVD) is one of the major diseases which causing premature death in the world. It has been estimated that over 23.3 million people globally will die annually from CVD by 2030. There are two types of cholesterol-protein carriers in the plasma: the low-density lipoprotein (LDL) cholesterol and the high-density lipoprotein (HDL) cholesterol. The former is referred as bad cholesterol and the latter as good cholesterol. The 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors, also known as statins, are the most effective class of drugs for lowering serum LDL cholesterol. It is now most widely prescribed medicine to treat cardiovascular disease with high level of LDL-cholesterol worldwide. However, there are some known side effects such as muscle pain in taking statins in some people and some even cannot tolerate it. Recently, a new therapy called PCSK9 inhibitor has been emerged from the horizon for treatment of hypercholesterolemia with real possibility of combining with statins or stands alone to improve the patient outcome with high level of LDL cholesterol.

Keywords: Proteinase; Population; Zymogen; Cholesterol; Hypercholesterolemia

Introduction

PCSK9 is a secretory serine proteinase; belong to pro-protein convertase (PCs) family [1]. It was initially discovered by a French group investing a rare genetic disorder of autosomal dominant hypercholesterolemia [2]. PCSK9 has a wide spectrum of mutations in human population. PCSK9 gain-of-function variations are associated with hypercholesterolaemia, whereas loss-of-function variations are associated with hypocholesterolaemia [3]. Due to its direct binding to and degradation of LDLR [1], PCSK9 is regarded as a valid and novel target for the treatment of hypercholesterolemia. Indeed, PCSK9-knock-out mice exhibit higher levels of liver LDLR and reduced serum cholesterol [4], while over expression of PCSK9 reduces LDLR and increases serum cholesterol [5]. Interestingly, those individuals with loss of function mutations of PCSK9 have lower levels of LDL cholesterol and are protected from cardiovascular diseases [6]. PCSK9 is emerging as one of the best genetically validated targets for treatment of heart disease.

Pro-PCSK9 is a 73 kDa zymogen, which is undergoes autocatalytic cleavage in the endoplasmic reticulum and then secreted as a 63 kDa mature protein which forms a complex with the N-terminal predomain. The secreted PCSK9 binds specifically to the epidermal growth factor (EGF)-like repeat A of the LDLR at the cell surface [1]. PCSK9 post-translationally regulates the number of the cell-surface LDLR, although the exact mechanism by which PCSK9 chaperones LDLR to the lysosomes degradation remains unknown. Recently, we have used shotgun proteomic approach to find that a cellular inhibitor of apoptosis 1 (C-IAP1) protein binds and processes PCSK9 [7]. We found that there is a dramatic decrease in secreted mature PCSK9 protein accompanied by a significant increase in LDLR protein levels In C-IAP1 null mouse embryonic fibroblasts (MEFs), in comparison with matched wild-type MEF cells [7]. C-IAP1 also acts as an E3 ligase for ubiquitination of PCSK9 at lysine residue K27 in ubiquitin, leading to its lysosomal degradation [7]. Recently, in a study investigating of the role of hepatitis C virus (HCV) in LDLR regulation, Syed et al. found there was PCSK9 ubiquitination after HCV infection, accompanied by moderated increase of c-IAP protein, suggesting HCV targeting PCSK9 ubiquitiantion probably through upregulating c-IAP E3 activity [8].

The further evidence to show that C-IAP1 being involved in the maturation and secretion of PCSK9 came from a recent study by Haas et al. [9]. In their recent study of the role of PCSK9 in nephrotic syndrome-associated hypercholesterolemia, the plasma PCSK9 level has been found to increase up to 24-fold in the mouse model of nephrotic syndrome on the mice treated with nephrotoxic serum. The level of PCSK9 changes is based on a posttranscriptional mechanism. This mechanism may involve cIAP1, because both NTS-treated and Pod-ATTAC mice showed an increase in hepatic C-IAP1, which promotes PCSK9 secretion. These data suggest that anti-PCSK9 antibody inhibitors could be used to explore its potential for treatment of patients with nephrotic syndrome–associated hypercholesterolemia [9]. Given both LDLR and C-IAP1 binding PCSK9 in acidic lysosome/endosome environment [10], this PCSK9-C-IAP1 novel pathway may pave a new avenues for explore cholesterol regulation.

PCSK9 inhibition is currently a “hot drug target” for developing new therapy for reduction of cholesterol in plasma. A race to bring a PCSK9 inhibitor to market among pharmarceutical companies has yield tremendous and rapid success [11-13]. In fact, two anti-PCSK9 antibody drugs (Evolocumab from Amgen and Alirocumab from Sanofi/Regeneron) have already gained the approvals in US and European drug regulatory authorities and both drugs have been widely used in the numerous drug trials for reductions in LDL cholesterol in patient populations [13]. Alirocumab has been shown to be more effective than Evolocumab in patients with high cardiovascular risk, whereas Evolocumab has been shown to be stronger in patients with heterogeneous familial hypercholesterolemia and patients with varied

cardiovascular risk [13]. A long-term cardiovascular benefit for these drug treatment remains to be further explored.

Other developments on PCSK9 inhibitions include therapeutic RNAi targeting PCSK9 gene [14] and small molecule compound inhibitors. A method for high-throughput screening of PCSK9 inhibitors has been developed by us recently using human liver cell HepG2 and a compound library of National Institute of Neurological Disorders and Stroke (NINDS) compound library, which is a collection of known drugs and pharmacologically active compounds of 1041 compounds [15]. One of the lead compounds, colchicine, has been validated by both cell-based LDL uptakes assay and the Western blot assay for PCSK9-mediated LDLR degradation in dose-responsive assay [15]. Colchicine has been known previously for acute gout treatment. Further work needs to be done to show if this compound has some usage for cardiovascular disease treatment.

It should be noted that, despite the very promising clinical outcomes of PCSK9 inhibitors have been achieved so far, there are several side effects and risks emerging from these trials. For examples, in both Alirocumab [16] and Evolocumab [17] trials, there were significant reduction of LDL cholesterol (over 50%) in the treatment groups than that of control group and better cardiovascular outcomes in over one year's period. But both trials also detected some adverse neurocognitive issue and injection-site swelling issue. The much significant reduction of LDL cholesterol treatment by PCSK9 inhibitors could also have some unforeseen consequences. The other problem is the relative high cost of using the anti-PCSK9 antibody which could cost of $14,000 per year at full retails preventing it being used widely so far. The long term cardiovascular outcome of PCSK9 inhibitors should be clear in coming two or three years' time to establish whether or not PCSK9 inhibitors are the truly new cholesterol-lowing blockbuster drug.

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