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

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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.

He secreted PCSK9 binds spiccatol 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 quant increase in LDLR protein levels In C-IAP1 null mouse embryonic browbeats (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 ubiquitination probably through upregulating c-IAP E3 activity [8].

REFERENCES


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