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Identification of New Molecule to Mediate Binding of PCSK9 and LDL-Receptor -- New Insight on Action Mechanism of PCSK9 to Degrade LDL-R --

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Atherosclerotic cardiovascular diseases (ACVDs) are the leading cause of death world-widely and excess low-density lipoprotein cholesterol (LDL-C) is the most important causal risk factor. Proprotein convertase subtilisin/kesintype-9 (PCSK9) determines plasma LDL-C levels by regulating internalization and lysosomal degradation of LDL receptor (LDLR) and has been emerged as a promising therapeutic target. Inhibitors of PCSK9 have reduced plasma LDL-C levels and improved cardiovascular outcomes. However, the precise mechanism how PCSK9 determines the fate of LDLR has not been elucidated. Here, we discovered new protein that directly interacted with PCSK9 through CRD of PCSK9. Knock-down of this protein attenuated PCSK9-mediated LDLR degradation both in vitro and in vivo. Homo-knock-out mice were embryo-lethal, while hetero-knock-out mice were viable and showed higher level of LCLR in liver and lower level of plasma LDL-C than litter-mate wild type mice. PCSK9 induced caveolae-dependent endocytosis and lysosomal degradation of LDLR, which relied on this new protein.