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PCSK9 directly stimulates Syk, PKC δ , and NF- κ B, leading to the activation of cytokines in monocytes and atherosclerosis progression independently of LDL receptor

Proprotein convertase subtilisin/kexin type-9 (PCSK9), which degrades low-density lipoprotein receptor (LDLR) and elevates LDL-cholesterol (LDL-C) levels, is used for atherosclerosis treatment. Recently, we demonstrated that PCSK9 interacts with adenyl cyclase-associated protein 1 (CAP1) that mediates endocytosis and degradation of LDLR. Here, we investigated whether PCSK9 binding to CAP1 induces inflammation directly or independently of LDLR. The direct inflammatory action of PCSK9 is examined in vitro in monocytes and endothelial cells, as well as via an in vivo atherosclerosis animal model. PCSK9 exacerbates atherosclerosis in LDLR^{-/-} mice independently of the LDLR pathway. Here we show that CAP1 is the main binding partner of PCSK9 and indispensable for the inflammatory action of PCSK9, including induction of cytokines, Toll like receptor 4 (TLR4), and scavenger receptors, enhancing the uptake of oxidized LDL. We find spleen tyrosine kinase (Syk) and protein kinase C delta (PKC δ) to be the key mediators of inflammation after PCSK9-CAP1 binding. In human peripheral blood mononuclear cells (PBMCs), serum PCSK9 levels are positively correlated with Syk, PKC δ , and p65 phosphorylation. The CAP1-fragment crystallizable region (CAP1-Fc) shows superior efficacy in mitigating PCSK9-mediated inflammatory signal transduction when compared with the PCSK9 inhibitor, evolocumab.

Keywords: Proprotein convertase subtilisin/kexin type-9 (PCSK9), adenyl cyclase-associated protein 1 (CAP1), low-density lipoprotein receptor, LDL-cholesterol (LDL-C), inflammation, atherosclerosis.

Publication

Shin D, Kim S, Lee H, Lee HC, Lee J, Park HW, Fukai M, Choi E, Choi S, Koo BJ, Yu JH, No G, Cho S, Kim CW, Han D, Jang HD*, Kim HS. PCSK9 stimulates Syk, PKC δ , and NF- κ B, leading to atherosclerosis progression independently of LDL receptor. Nat Commun. 2024 Mar 30;15 (1):2789.

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Biography

Dr. Hyun-Duk Jang, PhD, is an Associate Professor at the Biomedical Research Institute, Seoul National University Hospital, where he has been serving since 2012. Prior to this, he was a Research Professor in Molecular Biopharmaceuticals at Ewha Womans University from 2008 to 2011. She completed his postdoctoral fellowship in Hematology-Oncology at UCLA (2005–2007) and was a visiting student in Immunology at the University of Pennsylvania from 2003 to 2005. His research focuses on biomedical science, with particular interest in translational research and clinical applications.