Abstract: 1441
LRP5 and PCSK9 in inflammatory cells immunomodulation

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Background: Atherosclerosis, the leading cause of cardiovascular diseases, is driven by high blood cholesterol levels and chronic inflammation. The disruption of the hepatic interaction between Proprotein Convertase Subtilisin/Kexin 9 (PCSK9) and Low-Density Lipoprotein Receptor (LDLR) downregulates blood cholesterol levels and reduces cardiovascular events. Recent data suggest that other members of the LDLR superfamily may be targets of PCSK9.

Purpose: The aim of this work is to determine if LDLR-related protein 5 (LRP5) is a PCSK9 target, and to study the role of PCSK9 and LRP5 in foam cell formation and hence, in the mechanism of lipid accumulation and atherosclerotic plaque formation.

Methods: Intracellular protein and lipid localization, cholesteryl esters (CE) accumulation; quantification of structural and inflammatory proteins expression and immunoprecipitation analyses were performed in primary cultures of human inflammatory cells (monocytes and macrophages) silenced for LRP5 or PCSK9 and challenged with modified LDLs.

Results: We first show that LRP5 is needed for macrophage lipid uptake since LRP5-silenced macrophages have less intracellular CE accumulation. In LDL treated macrophages internalization of LRP5-bound LDL starts after 30 minutes of incubation and lasts up to 24 hours. The SREBP-2 promoter is not involved in LRP5 regulation but it does regulate macrophage PCSK9 expression. Immunoprecipitation experiments show that LRP5 forms a complex with PCSK9 in lipid-loaded macrophages. Finally we studied the role of PCSK9 and LRP5 in the inflammatory response by TLR4/NFκB signaling pathway. We show decreased TLR4 protein expression levels and decreased nuclear translocation of NFκB in PCSK9 silenced-inflammatory cells after lipid loading indicating a downregulation of the proinflammatory pathway TLR4/NFκB. Increased gene expression is observed in TNF-α and IL1β after lipid-loading that is abolished in PCSK9-silenced macrophages. Furthermore release of the proinflammatory cytokines TNF-α and IL1β is decreased in PCSK9-silenced macrophages. LRP5 protein expression is increased in lipid-loaded macrophages independent of the presence or absence of PCSK9.

Conclusions: These results demonstrate that, in human macrophages, LRP5 is internalized with lipids. Furthermore, PCSK9 and LRP5 can form a complex in the cytoplasm of lipid-loaded macrophages opening the possibility that PCSK9 induces lysosomal LRP5 degradation in a similar manner than it does with LDLR. Finally we also show that PCSK9 gene interference decreases inflammation and supports a role for PCSK9 as an inflammatory mediator in atherosclerosis.