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PCSK9 is a cholesterol lowering agent with a role in cancer progression

Abstract:

There are numerous evidences that Proprotein Convertase Subtilisin/Kexin 9 (PCSK9) inhibitors combat cancer. These cholesterol lowering agents, together with lipid receptors have a deep impact on the development of atherosclerosis. The role between PCSK9 inhibitors, lipid receptors and cancer progression is not fully studied. The disruption of the hepatic interaction between 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. In this presentation I will show that LDLR-related protein 5 (LRP5) is a PCSK9 target, and both proteins participate in foam cell formation and hence, in the mechanism of lipid accumulation and cancer progression. I will first show that LRP5 is needed for macrophage lipid uptake since LRP5-silenced macrophages have less intracellular cholesterol accumulation. Immunoprecipitation experiments will show that LRP5 forms a complex with PCSK9 in lipid-loaded macrophages opening the possibility that PCSK9 induces lysosomal LRP5 degradation in a similar manner than it does with LDLR. We have also studied the role of PCSK9 and LRP5 in the inflammatory response by TLR4/NFkB signaling pathway and show that PCSK9 gene interference decreases inflammation supporting a role for PCSK9 as an inflammatory mediator in cancer progression. We then validated our results in an in vivo mice model. We analyzed the differential expression of cholesterol and inflammation related genes in wildtype (Wt) and LRP5 knock-out (Lrp5-/-) mice fed a normocholesterolemic (NC) or a hypercholesterolemic (HC) diet. Results show that cholesterol accumulates differently in livers of Wt and Lrp5-/- mice and a that cholesterol accumulation play a role in inflammation and cancer progression

Biography

Borrell is a senior investigator at the Research Institute of the Santa Creu i Sant Pau Hospital in Barcelona. Prior appointments include a postdoctoral position in the Neurology Department of the Curie Institut, Paris, France studying Huntington's disease. She leads a project based in lipoprotein receptors role in cholesterol metabolism. In recent years she has been developing a project that analyzes the function of PCSK9 beyond its function in cholesterol lowering. These results have been published in different journals including EHJ, BRIC or CVR and lead to the concession of projects financed by both, the government and the industry.