UNIVERSITÀ DEGLI STUDI DI PADOVA

PROJECT

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1) Project title
Low density lipoprotein receptor-independent effect of PCSK9: role on ectopic fat accumulation and low-grade inflammation
2) Abstract (max 2000 words)
The wealth of evidence, from epidemiological studies to randomized clinical trials, consistently shows that low-density lipoprotein cholesterol (LDL-C) is causally associated with cardiovascular disease. These studies also show that lowering LDL-C levels reduces the risk of cardiovascular events proportional to the absolute reduction in LDL-C. Blood LDL-C levels are under the control of several metabolic pathways, including the proprotein convertase subtilisin/kexin type 9 (PCSK9). PCSK9 is a plasma protein, mainly of hepatic origin, that mediates the degradation of the LDL receptor (LDLR) and affecting the LDL-C uptake. Nevertheless, experimental evidence supports the role of PCSK9 on insulin resistance, visceral adiposity, ectopic fat accumulation, post-prandial hypertriglyceridemia and low-grade inflammation. These effects are mainly independent from LDLR and are mediated by the very low-density lipoprotein receptor (VLDLR) and the scavenger receptor CD36, additional targets of PCSK9. PCSK9-mediated CD36 degradation was proposed to limit fatty acid uptake and TG accumulation in tissues, such as the liver. In parallel, studies using transgenic animals with the specific inactivation of PCSK9 in the liver further showed that VLDLR expression is regulated by circulating PCSK9. These data suggest the possibility that, by targeting VLDLR and/or CD36, PCSK9 may also modulate the TG uptake by adipose tissue and intestinal absorption. Several observations have also pointed the attention on the role of PCSK9 in inflammation. For instance, i) PCSK9 levels correlate with white blood cells count in patients with stable CAD; ii) PCSK9 inhibition with siRNA inhibits the OxLDL-mediated response in cultured macrophages and reduces vascular inflammation in apoE null mice, fed a HFD; iii) in hypercholesterolemic mice, mAb anti PCSK9 reduces inflammatory monocyte recruitment; iv) PCSK9 induces a pro-inflammatory phenotype in cultured macrophages; v) overexpression of PCSK9 in mice increases vascular inflammation. Based on these observations, the main aim of the present study will be to provide new experimental and clinical insights on the pathological significance of PCSK9-mediated CD36 and VLDLR degradation on triglyceride-rich lipoprotein (TGRL) metabolism, ectopic fat accumulation and inflammation. This action of PCSK9 will be investigated in both clinical and experimental settings.

Subjects with genetic variants on CD36 and VLDLR genes will be first identified and then characterized in for visceral and subcutaneous adipose tissue and inflammatory status. These analyses will be then integrated with ex-vivo studies on human atherosclerotic plaque specimens, plasma levels of PCSK9, and proinflammatory mediators. Finally, in vivo (transgenic and knock-out mice) and in vitro (genetically modified cultured cells) experimental approaches will be utilized in order to define the basic molecular mechanisms underlying the relationship between PCSK9 and low-grade inflammation associated to ectopic fat accumulation.