PCSK9 (PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9) DEFICIENCY REDUCES INSULIN SECRETION AND PROMOTES GLUCOSE INTOLERANCE: THE ROLE OF THE LDL RECEPTOR

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Background: PCSK9 (proprotein convertase subtilisin/kexin type 9) is mainly synthesized and secreted by the liver and regulates the levels of circulating LDL-C by enhancing the degradation of the hepatic LDLR. Pre clinical evidences suggest a biological role for PCSK9 in extra-hepatic organs specifically on adipose tissue and pancreas. Furthermore, PCSK9 genetic variants not only are associated to lower LDL cholesterol but result in higher plasma glucose levels and increased risk of type 2 diabetes mellitus. In this study, we investigated the molecular mechanisms beyond this association.

Methods and results: WT and PCSK9 KO mice were fed for 20 weeks with a High Fat Diet (HFD) or Standard Fat Diet (SFD). Glucose clearance was significantly impaired in PCSK9 KO mice fed a standard or a high fat diet for 20 weeks compared to wild type animals with both diet (glucose AUC in PCSK9 KO was 1.42 ± 0.08 folds higher compared to wild type $p<0.05$); insulin sensitivity was not affected as both animals showed a similar decrease in plasma glucose levels following insulin injection. Plasma insulin levels were reduced in PCSK9 KO mice compared to wild type (3.24±0.14 ng/mL vs 4.35±0.43 ng/mL, $p<0.05$) and accordingly fasting and refeeding experiments showed increased plasma glucose in PCSK9 KO compared to wild type (266± 14 mg/dL compared to 217± 3 mg/dL, $p<0.05$). A detailed analysis of pancreas morphology revealed larger islets with insulin accumulation in PCSK9 KO mice compared to controls (10022±2802 um2 vs 5061±1843 um2, $p<0.05$). This phenotype was completely reverted in LDLR/PCSK9 double KO mice implying the LDLR as the PCSK9 target responsible for the phenotype observed. Further studies in albumin CRE+/PCSK9LoxP/LoxP (liver selective PCSK9 knock-out mice), which lack detectable circulating PCSK9, also showed a complete recover of the phenotype, thus indicating that liver-derived circulating PCSK9 does not impact beta cells function and insulin secretion.

Conclusion: The PCSK9/LDLR axis affects beta cell function and control insulin secretion. Our data indicate that this effect is independent of circulating PCSK9, and is probably related to local effects of PCSK9 suggesting the possibility that anti-PCSK9 antibodies or liver specific therapies, such as siRNAs, might have a limited impact on LDLR expression in pancreas and beta cells dysfunction.