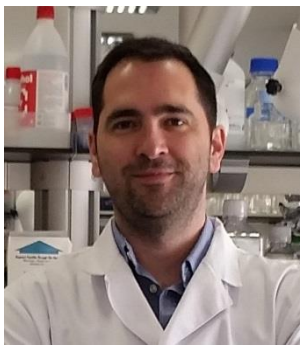
Rescuing pancreatic beta cell function in type 2 diabetes



Dr. Joan-Marc Servitja is an accredited researcher at the Pathogenesis and Prevention of Diabetes group at the Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) and member of the CIBERDEM. In 2003, he joined IDIBAPS with a Ramon y Cajal contract and since then he has been studying transcriptional and signaling networks related to islet biology and diabetes. He is currently leading different research lines focused on the regulation of gene expression and inter-organ cross-talk in pancreatic islets with the ultimate goal to design novel therapeutic strategies for the treatment of type 2 diabetes. He has also received contracts from the pharmaceutical industry in order to test novel applications of existing drugs as potential treatments for type 1 and type 2 diabetes.

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ABSTRACT

Type 2 diabetes is characterized by the failure of insulin-secreting pancreatic beta cells to compensate for insulin resistance. Therefore, there is a medical need for new therapeutic approaches to treat T2D, including the optimization and protection of functional beta cell mass in individuals with T2D.

The first part of the talk will focus on the aggregation of human islet amyloid polypeptide (hIAPP), which has been associated with pancreatic islet inflammation and dysfunction in T2D, and in particular, the potential therapeutic effect of the anti-inflammatory molecule alpha1-antitrypsin (AAT). Mice overexpressing hIAPP (hIAPP-Tg) in pancreatic β-cells are glucose intolerant and exhibit impaired insulin secretion. Interestingly, our results showed that treatment with AAT improves glucose homeostasis in mice overexpressing hIAPP and protects pancreatic β-cells from the cytotoxic actions of hIAPP mediated by macrophages. These results support the use of AAT-based therapies to recover pancreatic β-cell function for the treatment of T2D.

The second part of the talk will focus on the role of β-site APP-cleaving enzyme 2 (BACE2), a protease highly specific of pancreatic beta cells. Accumulating evidence indicates that BACE2 inhibition increases insulin secretion and beta-cell proliferation. Thus, we aimed to investigate the effects of BACE2 suppression in a model of diet-induced obesity. Unexpectedly, after 16 weeks of high fat feeding, BACE2 knock-out (BKO) mice exhibited an exacerbated body weight gain and hyperphagia, in comparison to WT littermates. HFD-induced hyperinsulinemia, insulin resistance, and β-cell expansion were also more pronounced in BKO mice. In turn, leptin-induced food intake inhibition and hypothalamic insulin signaling were impaired in BKO mice, regardless of the diet, in accordance with deregulation of the expression of hypothalamic neuropeptide genes. This study illustrates how an approach aimed to promote insulin secretion may result in the aggravation of the adverse metabolic effects associated with obesity.