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The role of Pax8 in Pancreatic Islet Physiology

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RESUMEN

Motivation: Currently, there are 347 million patients suffering Diabetes Mellitus (DM), raising the obvious need for more effective DM treatments. In this sense, the study of mechanisms that would allow the regeneration and protection of pancreatic insulin producing cells (β-cells) represents a promising strategy to generate novel therapies to treat DM.

Recently, a genome wide analysis showed that a specific polymorphism in the transcription factor Pax8 is associated with increased incidence of type II DM (1). In parallel, Riecket et al. determined that this gene was robustly induced in murine pancreatic islets during pregnancy, a situation of high metabolic demand (2). Interestingly, Pax8 is crucial for thyroid development and thyroxine (T4) production. Remarkably, a low concentration of circulating T4 is associated with gestational DM, which suggests that T4 may be required for the adaptation of pancreatic islets to pregnancy (3). These evidences indicate that alterations in Pax8 expression may be involved in the development of DM.

Methods: In order to asess the physioloigcal role of Pax8 in islet physiology, isolated islets were transduced using lentiviral vectors harbouring GFP (MOCK) or Pax8. A microarray was performed to determine the genetic networks affected by Pax8 overexpressionin pancreatic islets. In addition, apoptosis was measured using a Cell death kit and immunohistochemical studies were conducted in order to determine the transduction efficiency (GFP), islets' morphology (insulin/glucagon) and apoptosis (cleaved caspase 3). In parallel, oral glucose tolerance tests (OGTT) and insulin tolerance tests (ITT) were performed in non-pregnant and pregnant Pax8 heterozygous and wild type mice to determine the role of Pax8 in glucose homeostasis during pregnancy.

Results: Microarray data revealed that the transcriptional profile of pancreatic islets overexpressing Pax8 is associated with diabetogenesis and that interferon signalling is dramatically modulated. Moreover, our results indicate that Pax8 overexpression protects β-cells from apoptosis. The results for in vivo studies cannot be shown since they are under consideration for a patent.

Conclusions: Our results indicate that Pax8 protects pancreatic islets from apoptosis in vitro, suggesting that Pax8 may modulate genetic pathways involved in the maintainance of islets integrity.

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