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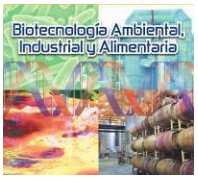

Effect of Epas1 and Pcx inactivation in pancreatic β-cell formation and function

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ABSTRACT

According to the consensus model for GSIS (Glucose-Stimulated Insulin Secretion), glucose is rapidly metabolized and coupled to insulin secretion involving a substantial number of cofactors and metabolites intermediates such as ATP, NADPH and citrate, among many others (1). In particular, pyruvate carboxylase (PC) is a fundamental enzyme in redox cycling between NADH and NADPH and also participates in an intricate process known as “pyruvate cycling” which allows the anaplerotic entry of pyruvate in the krebs cycle (2).

Pancreatic β-cells express abnormally high levels of pyruvate carboxylase (PC) and insignificant levels of phosphoenolpyruvate carboxylase, the enzyme necessary for gluconeogenesis. This implies that PC must play a different role in β-cells, such as insulin secretion, which is required for the "metabolic switch" from glycolytic to aerobic metabolism during β-cell maturation. It is also known that pyruvate carboxylase activity is elevated in mature β-cells but diminished under diabetic conditions. Recent studies have revealed that the Hypoxia Inducible factor (HIF) pathway plays an important role of in β-cell function (cita algun articulo nuestro). Both overexpression and inactivation of HIF-1α in β cells cause defects in insulin secretion. However, the role of HIF-2α in β-cell formation and function has been largely ignored despite been reported to be activated during diabetic conditions.

In this project, we hypothesize that HIF-2α and pyruvate carboxylase activity during late pancreatic HIF-2α formation is critical for the metabolic switch that ocurrs in β-cell during early postnatal development and thus for proper β-cell function.

In this study, we will analyze the expression of Epas1 (the gene encoding HIF-2α and Pcx) at different prenatal and postnatal stages by mRNA TaqMan essay. Using Cre/lox technology in mice, we will inactivate Epas1 and Pcx specifically in β-cells. Immunofluorescence and immunohistochemical assays will be carried out to determine specific markers of cell identity, vascularization, proliferation, and polarity in pancreatic tissue of Epas1- and Pcx-deficient mice. Finally, we will also evaluate the in vivo behavior of pancreatic β-cells in transgenic mice through glucose and insulin tolerance assays (GTT and ITT). This will help us understand the relationship between HIF-2 and PC activity and β-cell development and function, as well as whether HIF-2 and PC activity play a role in β-cell failure during diabetes.

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