Insulin Promoter Factor-1 Controls Several Aspects of β-Cell Identity

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Insulin promoter factor-1 (IPF-1)/pancreatic duodenal homeobox-containing factor-1 (PDX-1) expression is initiated at stages 10–12 in the somites and is restricted to the dorsal and ventral walls of the primitive foregut endoderm at the positions where the pancreas will eventually form (1). Homozygosity for mutations in the IPF-1/PDX-1 gene in mice results in a complete loss of the pancreas (2,3). Interestingly, loss of function of the human IPF-1 gene also results in complete pancreatic agenesis (4). Although IPF-1 is not required for evagination and initial bud formation, it is required to specify the early epithelium in order to proliferate, branch, and subsequently differentiate.

Around embryonic day 10.5 (E10.5), IPF-1 expression is downregulated in the growing pancreatic buds, then reappears in the differentiating β-cells, where finally, in the adult pancreas, it becomes restricted to the mature β-cells (3), where it has been proposed to regulate the expression of a variety of endocrine genes, including insulin, somatostatin, glucokinase, and Glut2.

OBJECTIVES

To acquire a greater understanding of the role of IPF-1 during development and in the adult β-cell, we focused on two different transgenic strategies that will allow *1*) the characterization of upstream signals required for IPF-1 activation and *2*) the identification of the downstream targets of IPF-1.

IPF-1 IN THE DEVELOPING PANCREAS

To address the first issue, we have generated a transgenic mouse in which the IPF-1 promoter drives the expression of the enhanced green fluorescent protein (EGFP). This system provides an easy and rapid way to screen for the appearance of IPF-1$^+$ cells after culture of early naive endoderm (i.e., before the initiation of pancreas) gut exposed to different inductive factors. Initial characterization of the IPF-1/EGFP transgenic mice have shown that the transgene is expressed in the developing pancreas, thus providing the base for studies concerning candidate molecules. These studies are currently in progress. To be able to identify early IPF-1–target genes, we have in parallel initiated a differential screening analysis between IPF-1$^{-/-}$ and IPF-1$^{+/-}$ early E10 pancreatic buds. Ten novel candidate cDNAs with no match in the databases have at present been identified and are currently being analyzed. This approach will allow the characterization of key target genes involved in early pancreatic growth, differentiation, and morphogenesis.

IPF-1 AND β-CELL FUNCTION

In the adult pancreas, the β-cells sense glucose and control blood glucose levels by secreting active insulin. To address the role of IPF-1 in the adult β-cell, we previously generated transgenic mice in which the IPF-1 gene has been disrupted specifically in the β-cells using the CRE-lox system. This model revealed that IPF-1 was required to maintain correct hormone expression in the β-cell and to maintain high levels of expression of Glut2, the key component in the glucose-sensing machinery (5). More recent work has shown that in these mice, the expression of the proinsulin processing enzymes PC1/3 and PC2 are also affected, leading to partially processed insulin being stored and subsequently secreted from the β-cells. All together, these results show that IPF-1 is necessary to maintain glucose homeostasis by controlling several aspects of β-cell identity, because aberrant IPF-1 expression leads to β-cell dysfunction and consequently type 2 diabetes.

We believe that these approaches will generate data that will expand our understanding of the intrinsic regulatory molecules that act upstream and downstream of IPF-1 during pancreatic development and in the adult β-cell. We hope this knowledge will contribute to the development of improved diabetes therapies.

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EGFP, enhanced green fluorescent protein.