18

GENETIC MODELS OF INSULIN RESISTANCE:
ALTERATIONS IN β-CELL BIOLOGY

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INTRODUCTION

One of the essential biological actions of insulin in mammals is the maintenance of euglycaemia. This is a complex process and involves the uptake, storage and oxidation of glucose in skeletal muscle and adipose tissues, as well as the suppression of hepatic glucose production. A significant blunting of these actions in spite of the presence of normal or even high circulating levels of insulin indicates the presence of an “insulin resistant” phenotype. A variety of pathological states including type 2 diabetes, obesity, hypertension, atherosclerosis and polycystic ovary disease are characterized by the presence of insulin resistance (1-6). In the case of type 2 diabetes it is generally accepted that insulin resistance must be accompanied by a β-cell defect for the full development of the disease. Although there is some debate as to which of these two defects is primary, longitudinal studies in several populations suggest that insulin resistance may be the first defect to be detected (2,7,8). The early insulin resistance observed in pre-diabetic individuals is initially compensated by an increase in insulin secretion by the islet β-cells that could represent either an enhanced secretory capacity or an increased islet/β-cell mass or a combination of both. Over a period of time, however, the β-cell compensation fails leading to uncontrolled hyperglycaemia and overt diabetes.

The number of functional β-cells is a critical determinant of the insulin secreting capacity of the pancreas. A notable and consistent feature in several rodent models of type 2 diabetes is the presence of islet hyperplasia ranging from mild to massive increases in β-cell mass (9-15). Several nutrient and hormonal factors including glucose, placental lactogen, prolactin and growth hormone have been suggested to contribute to islet growth in different models (for review see (16)) (17-23). Recently, overexpression of parathyroid hormone-related protein (24), hepatocyte growth factor (25), cyclin-dependent kinase 4 (26) and IGF-II (27,28) in islets/β-cells have also been shown to cause islet hyperplasia. However, the factors contributing to islet/β-cell hyperplasia in states of insulin resistance are not yet known. Although glucose itself has been shown to stimulate β-cell replication (17,29) the presence of islet hyperplasia even in euglycaemic animal models of type 2 diabetes (12,14,15) strongly predicts the presence of a glucose-independent factor. In humans, very few data exist describing alterations in islet/β-cell mass, however, non-diabetic obese individuals with insulin resistance show a significant increase in β-cell volume (30) and macrosomic infants and foetuses of non-diabetic mothers show islet hyperplasia.
that correspond to high insulin levels (31). In patients with long-standing type 2 diabetes, on the other hand, the \(\beta\)-cell mass usually shows no change (32) or a mild reduction (33,34). From these observations, it is conceivable that insulin resistance early in the disease is associated with islet growth and a consequent increase in insulin secretion.

**GENETIC MODELS OF INSULIN RESISTANCE**

Molecular and genetic analysis of complex traits in humans can be limited by the difficulties associated with longitudinal analysis, access to tissues and knowledge of the exact genetic defects. An alternative approach to understanding the pathogenesis of type 2 diabetes has been to create genetically-engineered animal models with specific molecular defects that can be studied longitudinally and at both physiological and molecular levels. To investigate the role of insulin signalling in the pathogenesis of type 2 diabetes, we and others have generated mouse models with global or conditional deletions of one or more proteins in the insulin/IGF-1 signalling pathway (for reviews see (35,36», (12-14,37-41). In addition, there are several naturally occurring rodent models of insulin resistance, obesity and type 2 diabetes including the \(ob/ob\) and \(db/db\) mice and the Zucker fatty rat. For the purposes of this review, however, we will focus on some of the recently created genetic models that develop insulin resistance as an approach to understanding islet hyperplasia and effects of insulin resistance on \(\beta\)-cell function.

**INSULIN/IGF SIGNALLING PATHWAYS**

A schematic overview of the insulin/IGF signalling pathway is shown in Figure 1 and is based on the tyrosine kinase activity of these receptors (for review see (42)). The principal substrates for the insulin and insulin-like growth factor-1 (IGF-1) receptors are a family of cytosolic proteins referred to as insulin receptor substrates -1, -2, -3, and -4. IRS-1 and -2 are expressed in most mammalian tissues (43-45) and tyrosine phosphorylated by the activated insulin receptor, while IRS-3 and -4 have more limited tissue distribution (46,47). In addition to the established role of these substrates and the insulin and IGF signalling pathways in skeletal muscle, liver and adipose tissues, a growing body of evidence suggests that these pathways play an important role in the function and growth of the islet/\(\beta\)-cells. Indeed the insulin and IGF-1 receptors and all four IRS proteins have been detected in islet tissue (15,40,41,48-51), however, the roles of these proteins in islet function has not been fully elucidated.

**\(\beta\)-CELL FUNCTION IN THE INSULIN RECEPTOR SUBSTRATE-1 (IRS-1) KNOCKOUT**

To evaluate the function of IRS-1, our laboratory and that of Kadowaki have used homologous recombination to create IRS-1 deficient (IRS-1\(^{-/-}\)) mice (12,13). The IRS-1\(^{-/-}\) mice are approximately 50% smaller than wild type controls at birth and throughout life. The IRS-1\(^{-/-}\) mice also show mild insulin resistance reflected by elevated plasma insulin levels, a blunted insulin/IGF-1 stimulated glucose uptake, a mildly impaired glucose tolerance in response to intra-peritoneal (IP) injection of glucose, and a \(~50\%\) decrease in circulating leptin levels probably secondary to a decrease in fat mass (12,15). Fasting and fed blood glucose levels are similar