Non-insulin-dependent diabetes mellitus (NIDDM) is characterized by peripheral insulin resistance and insulin secretory dysfunction (1, 2). These abnormalities are either genetically defined or augmented by hyperglycemia itself, and may interact in a complex manner to cause and sustain hyperglycemia. Previous prospective studies have demonstrated that both insulin resistance/hyperinsulinemia and low insulin secretory response to glucose are predictors of NIDDM in humans (3–7). The notion that either peripheral insulin resistance or an insulin secretory defect alone would be sufficient for the development of NIDDM has been tested in several knockout mouse models. Mice lacking the insulin receptor exhibit severe insulin resistance and die from ketoacidosis within 3–7 days after birth. Mice lacking insulin receptor substrate (IRS)-1 are growth retarded in addition to being insulin resistant, but are not diabetic, because of compensatory hyperinsulinemia. Glucokinase-deficient mice are diabetic as a result of defective glucose sensing in the pancreatic β cell and consequently disturbed insulin secretion, but do not present with peripheral insulin resistance, which is characteristic of NIDDM. Heterozygous animals of the first two models do not exhibit any obvious clinical phenotype. Heterozygous glucokinase-deficient mice have decreased glucose tolerance as a result of reduced insulin secretory capacity. These mouse models with single genetic defects represent rare diabetic syndromes found in humans, but do not serve as models for the most abundant form of diabetes: NIDDM. Thus the hypothesis that has emerged from these observations is that an accumulation of several genetic defects (and/or variants), each of which in isolation would not lead to frank NIDDM, together may be the basis for the development of NIDDM. The most plausible combination would be a defect leading to peripheral insulin resistance, plus an insulin secretory defect.

Two important studies have now tested this hypothesis and have established polygenic models of NIDDM (8, 9). The first model involved the crossing of homozygous IRS-1-deficient mice with heterozygous-glucokinase deficient mice. Thus peripheral insulin resistance, together with disturbed glucose sensing and insulin secretion in the pancreatic β cell, leads to an animal model having a close resemblance to NIDDM (8). In the second model (9), double heterozygotes of animals lacking one allele each of IRS-1 and the insulin receptor were developed. The mice presented with profound peripheral insulin resistance. These animals could be further divided into two distinct groups: those that would (approximately 40%) and those that would not develop NIDDM. It may be assumed that an as yet unknown genetic factor is the cause of the stratification, and, in conformity with the first model, this defect may be hypothesized to cause β cell dysfunction.

Both mouse models have a remarkable resemblance to NIDDM in humans. First, they are polygenic and inheritable; secondly, they bear the major metabolic hallmarks of NIDDM: insulin resistance, fasting hyperglycemia and hyperinsulinemia, and β cell dysfunction; and thirdly, the development of NIDDM is age-dependent and appears in older (begins at 4 months of age) and not young animals. Why age is a factor in the development of NIDDM is not clear from these studies. The authors do not mention in detail the results of glucose tolerance tests in young animals. However, it may be speculated that insulin secretory dysfunction requires some time to develop (perhaps when β cell regenerative capacity is exhausted or β cells fail as a result of ‘glucose toxicity’). Notably, both studies have revealed increased β cell mass and altered islet architecture in the diabetic animals, suggesting that a proliferative stress has been placed on the islets. The results are consistent with the concept that increased insulin resistance and decreased insulin secretion are independent yet co-operative risk factors for the development of NIDDM. It must be stated, however, that knocking out an element in the pathway of intracellular glucose metabolism or insulin signaling is expected to interfere with glucose metabolism, therefore these new mouse models may reflect NIDDM at the metabolic, but not at the genetic, level.

An inverse approach to elucidating the genetic basis of NIDDM – searching for trait loci in established NIDDM animal models – has also resulted in the observation that NIDDM is most probably attributable to the coincidence of several genetic traits. The (patho-)physiologically well characterized spontaneously diabetic Goto-Kakizaki (GK) rat model is one of the best animal models for studying genetic susceptibility to NIDDM. The GK rat manifests the main features of the metabolic, hormonal and vascular disorders described in NIDDM, having mild basal hyperglycemia, marked glucose intolerance and both hepatic and peripheral insulin resistance. Moreover, GK rats exhibit basal hyperinsulinemia and impaired insulin response to glucose. A major difference between the GK rat model (and the above mentioned mouse models) and human NIDDM is, however, the lack of obesity in the animals.

Two recent articles reported on the combined use of physiological and genetic studies to identify quantitative trait loci responsible for the control of glucose homeostasis and insulin secretion (10, 11). The loci, which in...
some instances overlap as reported in the two articles, are independently responsible for the control of fasting concentrations of blood glucose and insulin, and for glucose response and insulin secretion during glucose challenges. Indeed, the conclusion the authors draw is that NIDDM is a polygenic disease that becomes overt when several trait loci and their respective phenotypes appear in combination. It is certainly exciting to await the identification of the genes present on these various loci that are responsible for the different facets of metabolic disturbances of NIDDM.

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