Perspective

Molecular Defects in Insulin Action

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THE TERM DIABETES MELLITUS DESCRIBES A HETEROGENEOUS group of disorders characterized by elevated blood glucose and metabolic abnormalities. These disorders may result from decreased circulating insulin or ineffective insulin action in target cells. Diabetes is classified as being either insulin-dependent (type I) or noninsulin-dependent (type II) and affects 5% of the U.S. population. Target cell resistance to the action of insulin occurs in both forms of diabetes but is a central feature of type II diabetes.

Molecular studies of the insulin receptor and its effector systems, including three reports in this issue of *Science*, have provided further insight into the molecular defects associated with insulin-resistant forms of diabetes. Insulin action in target cells requires the transmembrane signaling activity of the insulin receptor (*1*), a plasma membrane glycoprotein consisting of two α subunits, which bind insulin, and two β subunits, which possess tyrosine-specific protein kinase activity. Insulin binding to the α subunits stimulates the tyrosine kinase activity of the β subunits, which in turn results in receptor autophosphorylation, conformational changes in the β subunit, and activation of the receptor kinase toward other substrates. Receptor activation is followed by rapid phosphorylation and dephosphorylation of intermediary substrates on serine residues, elaboration of secondary mediators of insulin action, modulation of metabolic enzyme activity, and changes in gene expression.

Two rare clinical syndromes of extreme resistance to insulin (type A syndrome and leprechaunism) have provided insights into the role of receptor defects in diabetes (*2*). Cultured cells from individuals with these syndromes have revealed genetic defects in the insulin receptor (*3, 4*), including one which affects receptor mRNA expression, a point mutation that alters processing of the receptor precursor, a point mutation that blocks the insertion of the mature receptor into the plasma membrane, and others that result in reduced insulin binding. Genetic defects in the receptor tyrosine kinase domain also occur. An individual with the type A syndrome had a point mutation in the β subunit resulting in the substitution of a serine residue for tryptophan in the kinase domain (*4*), and two type A individuals described in this issue of *Science* show new mutations in the kinase domain. Odawara *et al.* (*5*) describe an individual heterozygous for a point mutation that alters the Gly-X-Gly-X-X-Gly sequence of the receptor, which is essential for the binding of adenosine triphosphate. Taira *et al.* (*6*) describe an individual heterozygous for a rearrangement of the insulin receptor gene that deletes the entire kinase domain. These individuals are interesting not only because they provide insight into structure-function relations of the receptor that may not have been otherwise subject to analysis, but also because many of them are heterozygous for their receptor defects, and thus express mixed populations of normal and mutant receptors. The presence of mutant receptors appears to have negative effects on the activity of the normal receptor (*6*). Studies with kinase-deficient insulin receptors transfected into cultured cells show that such receptors function as dominant-negative mutations and suppress the function of the endogenous insulin receptors (*7*).

One of the cellular effects of insulin is the stimulation of glucose transport. Although most tissues have glucose transport systems, insulin stimulation of glucose transport occurs primarily in muscle and adipose tissue. At least six presumed glucose transport proteins have been cloned (*8*) including a glucose transporter expressed in HepG2 hepatoma cells and rat brain, one expressed in liver and kidney, one isolated from a fetal skeletal muscle cDNA library, and one expressed primarily in insulin target tissues (fat and skeletal muscle). This latter protein has been called "insulin-responsive" on the basis of its translocation from an intracellular pool to the plasma membrane in adipocytes in response to insulin stimulation. It is not clear, however, if this is a function of the cell type or the transporter, as the HepG2 transporter is also translocated in an insulin-dependent manner when expressed in insulin-responsive cells (*9*).

Although no genetic defects in insulin-sensitive glucose transport have been described, overall glucose transport activity and transporter number are reduced in several diabetic states (*10*). Garvey *et al.* in this issue of *Science* (*11*), and others (*12*), provide a molecular basis for this observation by showing that in experimental diabetes there is a decrease in adipocyte and muscle-type glucose transporter mRNA and protein, which is reversed by insulin treatment. Although this effect appeared to be specific to the "insulin-sensitive" glucose transporter, alterations in expression of mRNA for the HepG2-type transporter occur in animal models of insulin-treated diabetes and insulin resistance (*13*), and insulin increases HepG2-type transporter mRNA in human fibroblasts (*14*). Thus, insulin-resistant states may be associated with an altered number and distribution of several glucose transport species.

As more molecular tools become available, we get closer to an understanding of the pathways of insulin action and disorders of these cellular mechanisms that may lead to clinical insulin resistance. This should ultimately lead to a detailed understanding of the molecular defects underlying diabetes mellitus, many of which may lie in parts of the pathway not yet discovered.

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