

peripheral target tissues such as skeletal muscle and adipose. Insulin binding to its receptor stimulates intrinsic tyrosine kinase activity, leading to receptor autophosphorylation and the recruitment of intracellular signaling molecules, including the important insulin receptor substrates (IRS). IRS and other adaptor proteins initiate a complex cascade of phosphorylation and dephosphorylation reactions, resulting in the widespread metabolic and mitogenic effects of insulin. As an example, activation of the phosphatidylinositol-3'-kinase (PI-3-kinase) pathway stimulates translocation of a facilitative glucose transporter (e.g., GLUT4) to the cell surface, an event that is crucial for glucose uptake by skeletal muscle and fat. Activation of other insulin receptor signaling pathways induces glycogen synthesis, protein synthesis, lipogenesis, and regulation of various genes in insulin-responsive cells.

PATHOGENESIS

■ TYPE 1 DM

Type 1 DM is the result of interactions of genetic, environmental, and immunologic factors that ultimately lead to immune-mediated destruction of the pancreatic beta cells and insulin deficiency. Type 1 DM can develop at any age. Most, but not all, individuals with type 1 DM have evidence of islet-directed autoimmunity, which is detected by the presence of autoantibodies against beta cell antigens in the blood. The presence of two or more autoantibodies is now designated as stage 1 T1DM (**Fig. 403-6**). The temporal decline of beta cell function and mass preceding the development of type 1 DM is shown schematically in **Fig. 403-6**. In susceptible individuals, the autoimmune process is thought to be triggered by an infectious or environmental stimulus. In the majority of patients, autoantibodies against beta cell antigens appear after this triggering event, followed by progressive loss of insulin secretion. The rate of decline in beta cell function varies widely among individuals, with some patients progressing rapidly to clinical diabetes and others evolving to diabetes more slowly and over a period of several years. Features of diabetes do not become evident until a threshold loss of insulin