

# Types of Diabetes

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Type 1 diabetes has not previously been considered, since it is generally viewed exclusively as an autoimmune disease. However, the pathophysiology of either disease is centered on  $\beta$ -cells, and type 1 and type 2 diabetes share many concerns, especially the goal of preserving or restoring a normal functional  $\beta$ -cell mass. Evidence has accumulated that immune tolerance reflects a permanent cross talk between the different cells involved in immune survey functions and peripheral tissues, as in the case of  $\beta$ -cells in type 1 diabetes. As in most common autoimmune diseases, the problem of the antigenic specificity of the autoimmune reaction that drives the  $\beta$ -cell damage has been one with most unpredictable issues over the past 20 years. Whether the activation of autoimmunity proceeds from intrinsic immune dysregulation or requires the presence of  $\beta$ -cells is now no longer a question. Against all predictions, the search for the “diabetes autoantigen” has resulted in a long list of candidates with rather loose identification criteria. All presently high-ranking  $\beta$ -cell autoantigens are defined as proteins expressed by  $\beta$ -cells, not as  $\beta$ -cell-specific antigens. Indeed, evidence has accumulated to indicate that B- and T-cells recognize many autoantigens, rather than a single autoantigen, during diabetes development and that most autoantigens are not  $\beta$ -cell specific. This makes type 1 diabetes a  $\beta$ -cell disease rather than an antigen-specific immune disease.

As for type 2 diabetes, there is overwhelming evidence that it cannot be considered exclusively from the angle of the  $\beta$ -cell.  $\beta$ -Cells are at the center of multiple physiological loops that send signals and receive information to control energy disposal and storage. A key loop is the one between  $\beta$ -cells and adipocytes, establishing a direct link between metabolic and immune pathways. Many hormones, cytokines, transcription factors, and bioactive lipids are common to metabolic and immune pathways. Macrophages and adipocytes are overlapping cells that establish a functional link between energy storage functions and defense against pathogens. Not unexpectedly, obesity is associated with a state of chronic inflammation that has direct implications for the pathophysiology of type 2 diabetes. The close evolutionary links between immune and metabolic pathways raise the possibility that type 1 and type 2 diabetes may not be as different as initially thought. Moreover, uncommon forms of diabetes, namely latent autoimmune diabetes in adults (LADA), have been considered as possible overlaps between type 1 and type 2 diabetes. The lack, however, of clear biological criteria for the diagnosis of type 2 diabetes leaves open the issue of overlapping forms of diabetes.

In addition to inflammation, which constitutes a possible link between type 1 and type 2 diabetes, both diseases are highly polygenic. Among the several problems that await solutions in type 1 and type 2 diabetes are the initial triggers that lead to failure of immune tolerance in type 1 diabetes and to failure of insulin secretion in type 2 diabetes, the relative contribution of environmental factors and of genetic variants to both diseases on a highly polygenic background, and others.