Immunologic endocrine disorders

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Autoimmunity affects multiple glands in the endocrine system. Animal models and human studies highlight the importance of alleles in HLA-like molecules determining tissue-specific targeting that, with the loss of tolerance, leads to organ-specific autoimmunity. Disorders such as type 1A diabetes, Graves disease, Hashimoto thyroiditis, Addison disease, and many others result from autoimmune-mediated tissue destruction. Each of these disorders can be divided into stages beginning with genetic susceptibility, environmental triggers, active autoimmunity, and finally metabolic derangements with overt symptoms of disease. With an increased understanding of the immunogenetics and immunopathogenesis of endocrine autoimmune disorders, immunotherapies are becoming prevalent, especially in patients with type 1A diabetes. Immunotherapies are being used more in multiple subspecialty fields to halt disease progression. Although therapies for autoimmune disorders stop the progress of an immune response, immunomodulatory therapies for cancer and chronic infections can also provoke an unwanted immune response. As a result, there are now iatrogenic autoimmune disorders arising from the treatment of chronic viral infections and malignancies. (J Allergy Clin Immunol 2010;125:S226-37.)

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Multiple endocrine diseases are immune mediated and now predictable. Autoimmune disorders can cluster in individuals and their relatives. A family history of autoimmunity and screening for autoantibodies can identify at-risk subjects. Knowledge of these disorders and their disease associations can lead to earlier diagnosis and management, resulting in less morbidity and, in some cases, mortality. We will review endocrine organ-specific autoimmune diseases, autoimmune polyendocrine syndromes, and iatrogenic endocrine autoimmune disorders with an emphasis on immunopathogenesis, hopefully leading to immunotherapy for standard and experimental clinical care.

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Abbreviations used

ACTH:	Adrenocorticotropic hormone
AIRE:	Autoimmune regulator gene
APS-1:	Autoimmune polyendocrine syndrome type 1
APS-2:	Autoimmune polyendocrine syndrome type 2
CGMS:	Continuous glucose monitoring system
CTLA:	Cytotoxic T lymphocyte–associated antigen
FOXP3:	Forkhead box protein 3 gene
GAD:	Glutamic acid decarboxylase
GO:	Graves ophthalmopathy
HT:	Hashimoto thyroiditis
IA-2:	Islet-associated antigen (ICA512)
IPEX:	Immune dysfunction, polyendocrinopathy, enteropathy, X-linked
NOD:	Nonobese diabetic
POEMS:	Polyneuropathy, organomegaly, endocrinopathy, serum monoclonal protein, and skin changes
POF:	Premature ovarian failure
PTPN22:	Protein tyrosine phosphatase nonreceptor 22
TGA:	Tissue transglutaminase
TPO:	Thyroid peroxidase
TSH:	Thyroid-stimulating hormone
TSHR:	Thyroid-stimulating hormone receptor
TSI:	Thyroid-stimulating immunoglobulin
ZnT8:	Zinc T8 transporter

DIABETES MELLITUS

Background

Based on the American Diabetes Association classification, type 1A diabetes is the immune-mediated form of diabetes, whereas type 1B represents non–immune-mediated forms of diabetes with β-cell destruction, leading to absolute insulin deficiency.[1] There are additional forms of insulin-dependent diabetes with defined causes. Type 2 diabetes is overall the most common form of diabetes and is characterized by insulin resistance and less β-cell loss. In the United States, with a population of approximately 300 million, there are about 1.5 million persons with type 1A diabetes, and of these, approximately 170,000 are less than 20 years of age. The incidence of type 1A diabetes, similar to that of other immune-mediated diseases, such as asthma, is doubling approximately every 20 years.[2] Diabetes almost always develops in the setting of genetic susceptibility best defined by polymorphisms of HLA alleles.[3] Currently, there is no known cure for type 1A diabetes, and treatment for the disease consists of lifelong insulin administration. Immunotherapies aimed at preventing β-cell destruction at the time of clinical onset are actively being studied.

Genetic susceptibility

There are monogenic and polygenic forms of both immune-mediated and non–immune-mediated diabetes. Monogenic non-immune diabetes includes permanent neonatal diabetes mellitus, transient neonatal diabetes, and maturity-onset diabetes of the

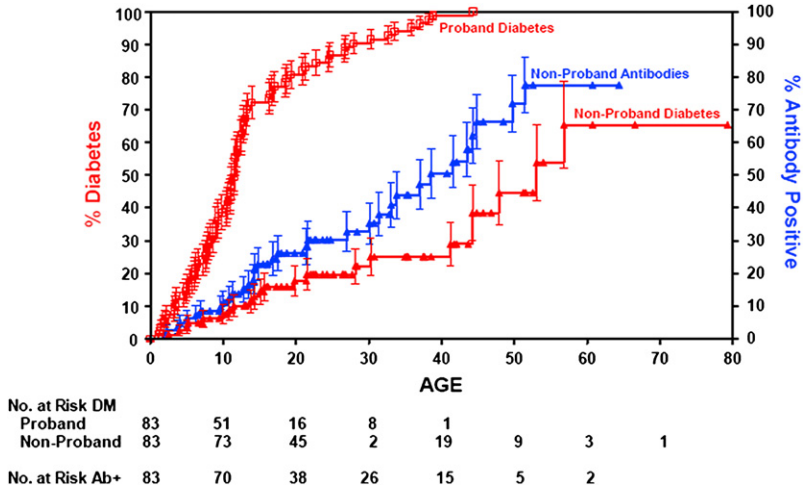

FIG 1. Progression to diabetes of initially discordant monozygotic twin siblings of patients with type 1 diabetes showing progressive conversion to diabetes. Approximately 80% become concordant for expression of anti-islet autoantibodies. *Ab*, antibody; *DM*, diabetes mellitus. Used with permission from Redondo et al.[5]

young. In general, children with these disorders lack all anti-islet autoantibodies, and therefore autoantibody assays can aid in identifying children to consider for genetic analysis. It is important to identify those who do not have type 1A diabetes, with estimates showing that approximately 1.5% of children presenting with diabetes have monogenic forms of diabetes. Several monogenic forms of diabetes are reported to be better treated with sulfonylurea therapy than with insulin (eg, mutations of the ATP-sensitive β cell–selective potassium channels and hepatocyte nuclear factor 1 alpha mutations),[4] and diabetes caused by glucokinase mutations requires no therapy at all. Approximately one half of permanent neonatal diabetes is due to mutations of the proinsulin gene that leads to β-cell loss. Two monogenic syndromes with immune-mediated diabetes are autoimmune polyendocrine syndrome type 1 (APS-1) and the immune dysfunction, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, which will be discussed subsequently. The rest of this section will focus on the more common polygenic form of diabetes, type 1A diabetes.

Approximately 1 in 300 persons from the general population will have type 1A diabetes compared with 1 of 20 siblings of patients with type 1A diabetes. The concordance rate for monozygotic twins with type 1A diabetes is greater than 60% (Fig 1),[5] and a recent analysis of long-term twin data indicates that there is no age that an initially discordant monozygotic twin is no longer at risk.[5] Compared with monozygotic twins, initially discordant dizygotic twins are less often positive for anti-islet autoantibodies than nontwin siblings.[6] Offspring of a father with type 1A diabetes have a greater risk compared with offspring of a mother.[7]

The major determinant of genetic susceptibility to type 1A diabetes is conferred by genes in the HLA complex, which is divided into 3 regions: classes I, II, and III. Alleles of the class II genes, DQ and DR (and to a lesser extent DP), are the most important determinants of type 1A diabetes. These class II molecules are expressed on antigen-presenting cells (macrophages, dendritic cells, and B cells) and present antigens to $CD4^+$ T lymphocytes. DR3 and DR4 haplotypes are strongly associated with type 1A diabetes, with more than 90% of patients with type 1A diabetes possessing 1 or both of these haplotypes versus 40% of the US population.[8] Each unique amino acid sequence of DR and DQ is given a number. Because DRA does not vary, haplotypes can be defined by specific DRB, DQA, and DQB alleles. The highest-risk DR4 haplotypes vary at both DR (DRB1*0401, DRB1*0402, or DRB1*0405) and DQ (DQA1*0301 or DQA1*0302). DR3 haplotypes are almost always conserved with DRB1*03 combined with DQA1*0501 or DQB1*0201. The highest-risk genotype has both DR3 DQB1*0201/DR4 DQB1*0302. This genotype occurs in 30% to 50% of children with type 1A diabetes; approximately 50% of children with type 1A diabetes before the age of 5 years are DR3/4 heterozygotes versus 30% of young adults presenting with type 1A diabetes and 2.4% of the general population in Denver, Colorado. The excess risk for heterozygous haplotypes might be related to the transencoded DQ molecule (DQA and DQB encoded by different chromosomes) that can form in DR3/4 heterozygous individuals, namely DQA1*0501/DQB1*0302.[3]

In addition to HLA genes, many genetic loci contributing to diabetes risk have been implicated through genome-wide association studies (Fig 2),[9] which involves analyzing thousands of single nucleotide polymorphisms from large populations to find alleles associated with a particular disease. These alleles can increase risk (ie, high-risk alleles) or protect against a certain disease. Although HLA alleles confer the highest risk, multiple non-HLA genetic polymorphisms modify disease risk. The group of longer variable number of tandem nucleotide repeats 5′ of the insulin gene protects against diabetes. The decreased diabetes risk is associated with greater insulin message and resultant deletion of autoreactive T cells in the thymus.[10] Alleles of other identified genes primarily influence immune function, such as the protein tyrosine phosphatase nonreceptor 22, which regulates T-cell receptor signaling. The R620 W single amino acid change of protein tyrosine phosphatase nonreceptor 22 decreases T-cell receptor signaling (gain of function) and increases the risk of many autoimmune disorders, including type 1A diabetes, Addison disease, Graves disease, rheumatoid arthritis, and others.[11] Recently, a further genome-wide association study analysis identified 2 additional loci, *UBASH3A* and *BACH2*, associated with type 1A diabetes, loci having odds ratios of 1.16 and 1.13, respectively. Both of these loci were