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Type 1 Diabetes: Current Perspectives

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Abstract

Type 1 diabetes, resulting from the autoimmune destruction of insulin producing islet beta cells is caused by genetic and environmental determinants. Recent studies agree that counterintuitively, the major genetic susceptibility factors are decreasing in frequency as the incidence of the condition increases. This suggests a growing role for environmental determinants but these have been difficult to identify and our understanding of gene/environment effects are limited. Individuals "at risk" can be identified accurately through the presence of multiple islet autoantibodies and current efforts in type 1 diabetes research focus on improved biomarkers and strategies to prevent or reverse the condition through immunotherapy.

Keywords: Type 1 diabetes, Autoimmunity, Insulin, Islet autoantibodies, Genes

1 Introduction

Type 1 diabetes (T1D) represents approximately 10 % of diabetes overall and results from the autoimmune destruction of insulin producing beta cells in the islets of Langerhans [1]. The condition is usually diagnosed on clinical grounds and symptoms appear when approximately 70–80 % of pancreatic islets are destroyed [2]. Individuals with T1D cannot survive without insulin replacement and, even when treated with insulin, remain at risk of complications including nephropathy, retinopathy, and coronary heart disease.

Although commonly associated with onset in childhood and adolescence, with a peak age at diagnosis of 12 years, approximately half of all cases of T1D are diagnosed in adulthood [3]. Epidemiological studies show that the incidence of T1D is unequally distributed in the world's population, with a high incidence rate in Caucasians (40/100,000/year in Finland) and a relatively low rate among Asian and South American populations (0.1/100,000/year) [4]. The incidence of the condition has been increasing rapidly in recent decades for unknown reasons: the current rate of increase is 3 % per year worldwide [5]. If present trends continue, doubling of new cases of type 1 diabetes in European children younger than 5 years is predicted between 2005 and 2020, and prevalent cases younger than 15 years will rise by 70 % [6].

2 Genetic Susceptibility to Type 1 Diabetes

The genetic background of T1D is very complex influenced by combinations of genes and environmental determinants. Identical twins with evidence of autoimmunity studied over a long follow-up period were concordant in over 50 % indicating that the etiology of the condition is approximately half genetic and half environmental [7]. The life-long risk of developing the disease in a child born in a family with T1D is estimated as 20 %, 8 %, 5 %, or 3 %, if the child has two affected first-degree relatives, an affected sibling, father, or mother, respectively [8]. The younger the individual is at diagnosis, the greater the risk to siblings [9, 10].

The importance of the Human Leucocyte Antigen (HLA) region (8 Mb of chromosome 6p21), in susceptibility to type 1 diabetes has been known since the 1970s [3]. The HLA has multiple roles in T cell selection, antigen presentation and immune responses, all of which can influence the onset and progression of T1D. The HLA region generally can be split into three different parts, class I, class II, and class III (Figs. 1 and 2).

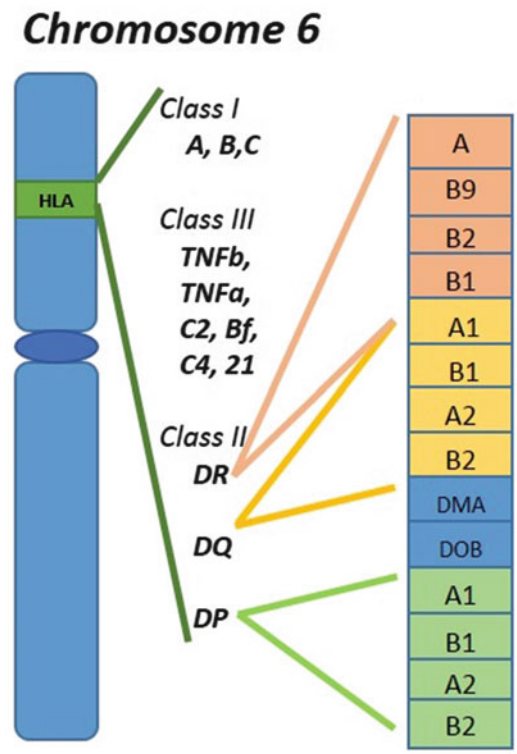

Fig. 1 MHC region of chromosome 6. MHC region is comprised of 3 loci corresponding to HLA Class I, II and III. In HLA Class II region DR, DQ and DP loci are presented. Risk alleles for T1D are located in DR and DQ regions

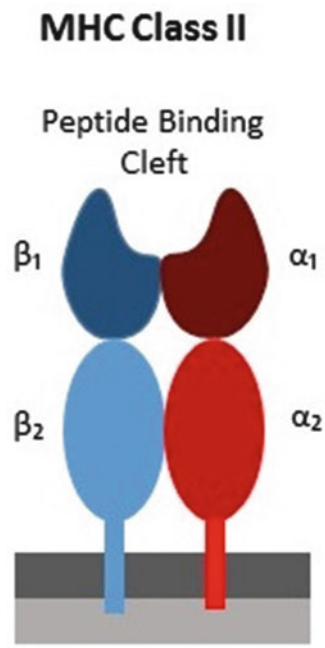

Fig. 2 MHC class II. MHC class II molecules are heterodimeric and consist of two peptides—α and β chains, which include α1, β1 domains encoding binding cleft, and α2, β2—membrane bound domain

The class I region, encoding HLA A, B, and C molecules, is expressed on the cell surface of nucleated cells that are involved in the presentation of endogenous antigens to CD8+ cytotoxic T cells (Tc) and contribute to risk of T1D [11] and the HLA A*24 allele is associated with rapid progression to T1D [12].

The HLA class II region encodes membrane bound proteins expressed on the cell surface of antigen-presenting cells (APCs): B-lymphocytes, macrophages, and dendritic cells that are involved in the processing and presentation of exogenous antigens to CD4+ T helper cells (Th) (Fig. 3) leading to T cell activation. The numerous subsets of T cells are derived from a single T cell precursor and some subsets have the capacity to regulate one another (Fig. 4).

Studies of the pathogenesis of type 1 diabetes proving roles for the HLA as well as effector and regulator T cell population mechanistically have utilized the predominant animal model of type 1 diabetes, the nonobese diabetic (NOD) mouse transgenic for HLA Class II [13].

HLA class II genes contribute to both susceptibility and resistance to T1D; risk is associated with the HLA class II haplotypes *DRB1*04-DQB1*0302* and *DRB1*03-DQB1*02* while the haplotype *DRB1*15-DQB1*0602* is dominantly protective. The risk of

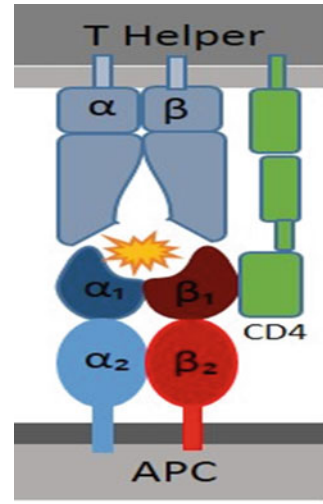

Fig. 3 Antigen presentation. During antigen presentation CD4 receptors of T helper lymphocytes bind to β domain of the HLA Class II molecule that activates the T cell

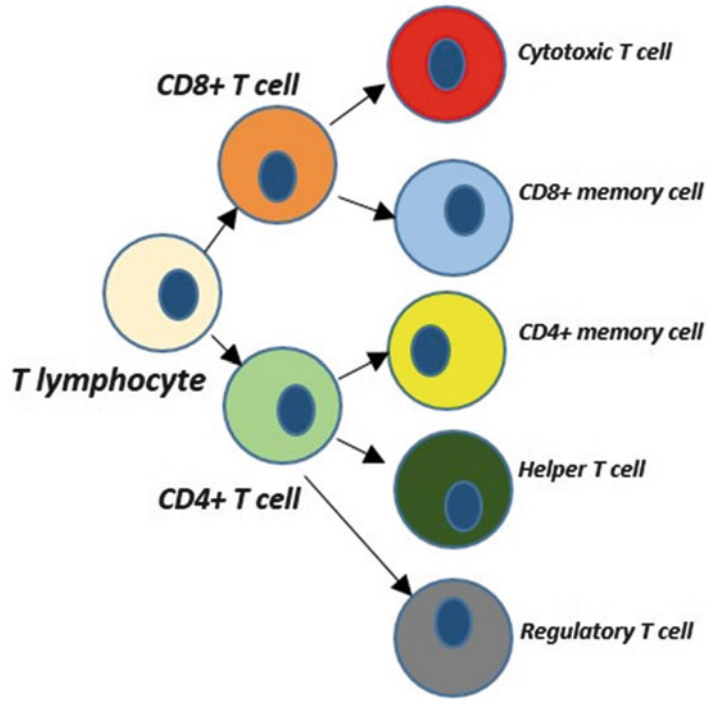

Fig. 4 T cell subsets. CD8+ T cells mature into cytotoxic T cells, CD8+ memory cells; CD4+ T cells mature into helper T cells, regulatory T cells, CD4+ memory cells

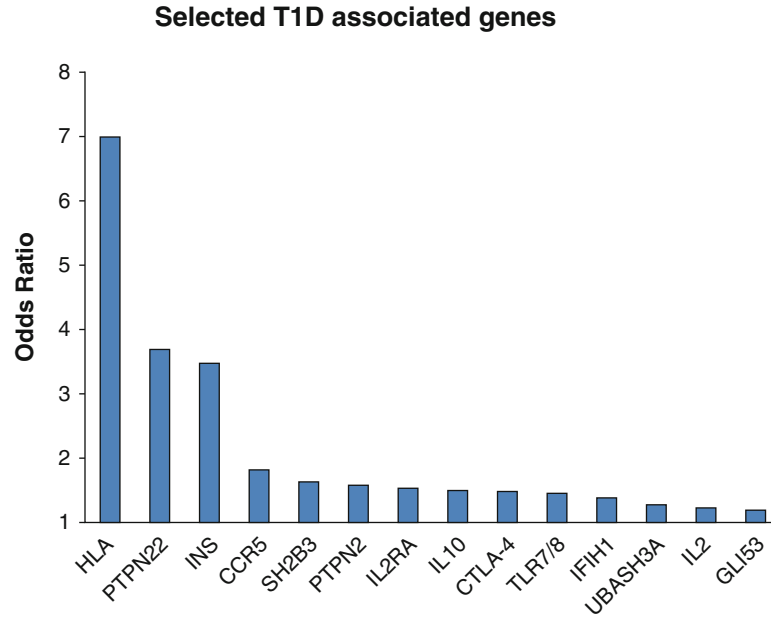

Fig. 5 The relative effects of selected T1D associated genes on susceptibility to T1D (adapted from Todd, 2010) [15]

developing T1D in siblings of affected children varies from 0.3 to 30 % depending on their HLA class II genotype [14].

Additional genetic risk markers were identified in the 1980s and 1990s but the advent of genome-wide association studies (GWAS), conducted since 2007, has allowed identification of approximately 40 additional genes that contribute to susceptibility to T1D (Fig. 5) [15]. Ongoing research now focuses on the biological pathways in immune and beta cells where these T1D associated genes function [16]. Despite these huge advances, all the genes identified to date do not account for the sum of genetic susceptibility. The concept of "missing heritability" has led to a focus on rare variants.

The increasing role of a "diabetogenic" environment was suggested following reports of the rising incidence and decreasing age at diagnosis of T1D while the frequency of the high risk HLA DR3/DR4 genotype is decreasing [17, 18]. A variety of environmental factors such as infections in early life, diet, and early development of the gut microbiome have been implicated in promoting the rising incidence of T1D [19] but none yet unequivocally proven. It is likely that one mechanism by which the environment influences risk of autoimmune diabetes is through epigenetic changes.

3 The Natural History of Type 1 Diabetes

Over the last 20 years, a series of birth cohort studies [20–23] have contributed hugely to our understanding of the natural history of the condition. Islet antibodies are markers of ongoing autoimmune destruction [24] and the best characterized are specific to the islet proteins insulin [25], glutamic acid decarboxylase (GAD) [26], IA-2 [27], and the zinc transporter ZnT8 [28, 29]. The autoimmune process begins very early in life: studies of neonatal diabetes suggest that most cases of diabetes diagnosed before 6 months are unlikely to be autoimmune, but those diagnosed after the age of 6 months have the genetic characteristics of T1D [30]. Antibodies to insulin (generally the first to appear) have been detected as early as 6–12 months of age [31]. Longer term follow-up of birth cohorts in Finland and Germany suggests that there is an explosion of islet autoimmunity in at risk children between the ages of 6 months and 3 years [21, 32]. The techniques to detect islet autoantibodies with high sensitivity and specificity have resulted from decades of collaborative workshops where blinded reference samples are tested in participating laboratories [33] resulting in high quality radioimmunoassays [34] and more recently ELISAs and chemiluminescence assays [35].

Islet autoantibody studies have demonstrated differing rates of progression in individuals positive for multiple islet autoantibodies; many progress rapidly [27] but there is also accumulating evidence for "slow burning" autoimmunity. For instance, within the Bart's Oxford study of type 1 diabetes (http://www.bristol.ac.uk/clinical-sciences/research/diabetes/research/box/), ongoing since 1985, some "at risk" individuals with two or more islet autoantibodies remain diabetes free after 20 years. A relapsing/remitting process of beta cell destruction has been postulated that could help explain differences in rates of progression but as yet there is no widely available marker of beta cell death although an assay to detect demethylated insulin for this purpose has been described [36, 37].

Although the pancreas in type 1 diabetes has been described previously [38, 39], recent histological analysis revealed new insights into the immune cell subsets comprising insulitis with the observation that B cells are present in greater frequency than expected [40]. Further analysis of T1D pancreas has been made possible by the Network for pancreatic organ donors with diabetes (nPOD) initiative (www.jdrfnpod.org). Improving techniques raise the possibility of analysis of single laser captured islet beta cells.

Once diagnosed, the insulin-free "honeymoon period" is variable and there is increasing evidence that some individuals with long-standing diabetes can continue to make low levels of insulin [41]. Large scale testing has been made possible through a straightforward test to detect c-peptide in urine [42].

Future perspectives in type 1 diabetes include improved biomarker identification to support a number of ongoing clinical trials orchestrated internationally by the TrialNet consortium (www.diabetestrialnet.org).

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