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The Interplay of Autoimmunity and Insulin Resistance in Type 1 Diabetes

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Abstract

Type 1 diabetes (T1D) is a common chronic disease characterized by selective autoimmune destruction of the pancreatic islet beta cells and subsequent dependence on exogenous insulin. Certain alleles including the high-risk HLA genotype, HLA-DR3-DQ2/DR4-DQ8, place individuals at increased risk of developing T1D. Autoantibodies to beta cell antigens are used in the diagnosis of T1D, and studies have shown that they can be used to predict risk of developing T1D in first degree relatives of probands. The annual global incidence of T1D is increasing by 3–5% per year. Many environmental factors have been implicated in the rising incidence of T1D. Proponents of the accelerator hypothesis argue that T1D and type 2 diabetes (T2D) are the same disorder of insulin resistance, although with different genetic backgrounds. While insulin resistance is a recognized hallmark of T2D, it also appears to play a significant role in the pathogenesis of T1D and its vascular complications. In this article, we will review: 1) immunogenetics of T1D, 2) risk factors for the development of islet autoimmunity and T1D, 3) mechanisms of insulin resistance in T1D, and 4) links between insulin resistance and complications in T1D. Further studies are needed to define environmental factors causing T1D as well as the role of insulin resistance in the pathogenesis of T1D and its complications.

Introduction

Combined, type 1 and type 2 diabetes mellitus affect approximately 25.8 million people in the United States, 215,000 of whom are under age 20 (NDIC, 2011). Type 1 diabetes (T1D) is characterized by selective autoimmune destruction of the pancreatic beta cells and is associated with specific HLA subtypes and autoantibodies, with resultant dependence on

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exogenous insulin. Newly diagnosed type 2 diabetes (T2D) is characterized by hyperglycemia with insulin resistance (IR) and increased insulin levels, usually associated with obesity. In the multi-center SEARCH trial, the incidence of diabetes in youth under age 20 was 24.3 per 100,000 person years, with T1D accounting for 74% of the cases, T2D for 20%, and the remainder other forms of diabetes, such as monogenic diabetes (SEARCH for Diabetes in Youth Study Group *et al.*, 2007). Approximately 40% of patients who develop T1D will be diagnosed before age 20, resulting in a prevalence of 1 per 200 children. The annual global incidence of T1D is increasing by 3–5% per year (Diamond Project Group, 2006).

Prior to the 1980s, nearly all cases of diabetes presenting in children were T1D; however, recently the proportions have changed. Today, among children diagnosed after age 10, half of African-American and Hispanic patients and more than half of Asian/Pacific Islanders and American Indians have T2D, rather than T1D. However, the majority of non-Hispanic Caucasian adolescents diagnosed with diabetes still have T1D, and nearly all children with diabetes diagnosed under age 10 in the U.S. have T1D (SEARCH for Diabetes in Youth Study Group *et al.*, 2007).

With rising obesity rates in children, it is increasingly difficult to differentiate between T1D and T2D on clinical grounds alone. Islet autoantibodies, stimulated C-peptide levels, and genetic markers provide tools to augment a clinical diagnosis. In this article, we aim to review: 1) immunogenetics of T1D, 2) risk factors for the development of islet autoimmunity and T1D, 3) mechanisms of insulin resistance in T1D, and 4) links between IR and complications in T1D.

Type 1 Diabetes

T1D is defined as hyperglycemia from hypoinsulinemia, secondary to autoimmune destruction of the insulin-producing beta cells in pancreatic islets. The immune system fails to maintain tolerance to beta-cell autoantigens, often in the setting of the HLA-DR3, DQ2, and/or DR4, DQ8 haplotypes. Chronic inflammation in the islets leads, usually after years, and rarely in just months, to insulin-dependent diabetes.

Autoimmunity

Autoantibodies to biochemically characterized beta-cell autoantigens -- insulin (IA), the tyrosine phosphatase insulinoma antigen (IA-2), glutamic acid decarboxylase (GAD), and zinc transporter 8 (ZnT8) (Wenzlau *et al.*, 2007) -- help to define pre-T1D as well as T1D, if measured shortly after initiation of insulin therapy. Insulin autoantibodies (IAA) are masked by antibodies induced by exogenous insulin and become very difficult to measure after just 10 to 14 days of insulin therapy. Autoantibodies to ZnT8 (ZnT8A) tend to disappear quickly after the diagnosis of diabetes, while those against GAD (GADA) and IA-2 (IA-2A) tend to persist longer, but are rarely seen 10 or more years after diagnosis. Testing for at least two of these autoantibodies at diagnosis is now considered standard of care in T1D. Good commercial assays exist for IA-2A, GADA, and ZnT8A, with the former two being recently harmonized (Bonifacio *et al.*, 2010). IAAs are low-affinity antibodies and harder to measure; however, high-quality non-radioactive assays for IAAs are close to being commercially

available. The search for additional antibodies is an active area of research. In non-obese diabetic (NOD) mice, a new antigenic epitope of chromogranin A protein was shown to induce a significant immune response by $CD4^+$ T cells (Nikoopour *et al.*, 2011). Another study in NOD mice showed that $CD8^+$ T cells in the pancreas are autoreactive and are dependent on local expression of cognate peptide-major histocompatibility (pMHC) complexes and do not have to engage with pMHC expressed on the surface of the beta cell to be retained within the pancreas (Wang *et al.*, 2010).

The prevalence of antibodies in patients with T1D varies depending on the study population and methods of antibody assessment. In the multi-center SEARCH trial of newly diagnosed cases of T1D and T2D in youth, 52% were positive for GADA, 60% were positive for IA-2A, and 38% were positive for both (Dabelea *et al.*, 2011). This study did not test for IAA or ZnT8A and obtained the blood sample months to years after diagnosis. In contrast, the Childhood Diabetes in Finland Study Group found that among newly diagnosed children with T1D, 91% tested positive for at least two antibodies and 71% for three or more. Further, IA-2A was detected in 86% of the cases (Savola *et al.*, 1998).

Genetics

At the time of diagnosis, over 85% of patients with T1D lack a family history of the disease in immediate relatives. However, by age 20, 4.4% of the siblings of T1D probands develop T1D (7% if the proband was diagnosed under age 7). In parents, the overall risk by age 40 is higher in fathers (3.6%) than in mothers (1.7%) of probands, and two-fold higher in parents of probands diagnosed under age 7 than in those diagnosed later (Steck *et al.*, 2005).

Individuals with the HLA-DR3-DQ2/DR4-DQ8 genotype are at approximately 20-fold increased risk for T1D compared to the general population. This high risk genotype is present in 2.4% of newborns (Rewers *et al.*, 1996). By age 15, 5% of children with this genotype will develop islet autoimmunity and T1D, compared with only 0.3% in the general population. A number of additional HLA class II genotypes confer moderately increased risk for T1D, while others are protective. The high-risk DR3-DQ2/DR4-DQ8 genotype is an additional predictor of progression to diabetes in children expressing one or two autoantibodies, but not among patients expressing three. Once islet autoimmunity develops, there is no difference in the rate of progression to T1D between relatives of type 1 diabetics and the general population (Steck *et al.*, 2011).

Non-HLA associated loci that result in increased risk of T1D include those that influence immunity (*INS, PTPN22, IL2RA, SH2B3),* insulin production and metabolism (*ERBB3)*, and many others (Concannon *et al.*, 2009). A number of novel loci identified through genome-wide association studies (GWAS) have been confirmed in prospective population-based studies. However, jointly they confer only a small additional risk compared to the effect of HLA-DR and HLA-DQ. Among those with the high-risk HLA genotype, the *PTPN22* 1858 T allele is independently associated with the development of persistent islet autoimmunity (Steck *et al.*, 2009). The *INS* gene is weakly associated with the development of persistent autoimmunity, but not with progression to T1D when controlling for HLA genotype and other factors (Steck *et al.*, 2009). Studies to identify other genetic causes for

T1D are underway. An up-to-date review of all genes implicated in the development of T1D can be found at T1Dbase (www.t1dbase.org).

Risk Factors for Islet Autoimmunity and T1D

T1D is thought to be caused by the interplay of genetic and environmental factors. Rising incidence (Diamond Project Group, 2006), outbreaks (Rewers *et al.*, 1987), and a seasonal pattern (Fleegler *et al.*, 1979) point to ubiquitous environmental factors in the pathogenesis of T1D. The incidence of T1D is doubling every 20 years (Harjutsalo *et al.*, 2008; Vehik *et al.*, 2007). It is unlikely that a new agent is responsible, since the apparent pandemic has been observed for at least the past fifty years. However, the penetrance of this still unidentified factor appears to have increased especially among younger children and those with lower-risk HLA genotypes (Hermann *et al.*, 2003; Vehik *et al.*, 2008). For instance, an Australian study showed that the proportion of those with HLA-DR3 and HLA-DR4 decreased from 79% in 1950–1969 to only 28% in 2000–2005, while the proportion of those who were heterozygous for intermediate-risk genotypes increased from 20% to 48% over that same time period (Fourlanos *et al.*, 2008). Yet, the incidence of T1D in those with the highest-risk HLA genotype has remained unchanged. A recent study in Germany of high-risk HLA subjects followed from birth suggested that, in recent years, those at increased genetic risk have progressed to T1D more rapidly than in the past (Ziegler *et al.*, 2011). Several large prospective studies have made important inroads into our understanding of the role of infectious and dietary agents in triggering islet autoimmunity leading to T1D (TEDDY Study Group, 2008; Rewers *et al.*, 1996; Steck *et al.*, 2011; Ziegler *et al.*, 2003). A review of dietary factors and risk of T1D has recently been published (Norris, 2010).

There have been multiple studies around the world investigating whether enterovirus plays a role in the development of autoimmunity or T1D. Though results are mixed, a recent meta-analysis of 26 studies shows that there is an association between enterovirus infection and progression to autoimmunity and clinical disease (Yeung *et al.*, 2011). The Diabetes Autoimmunity Study in the Young (DAISY) study found that the rate of progression from autoimmunity to T1D was significantly higher after enterovirus detection (Stene *et al.*, 2010). Certain *IFIH1* polymorphisms are associated with increased risk of T1D and this may be via interactions with viruses (Liu *et al.*, 2009b). IFIH1 is a cytoplasmic helicase that plays a role in the detection of intracellular viral dsRNA of picornaviruses, the family that includes enteroviruses (Kato *et al.*, 2006), and it is hypothesized that infection with enteroviruses results in *IFIH1* activation in the pancreatic beta cell and ultimately beta cell death (von Herrath, 2009). Furthermore, *IFIH1* variants that result in reduced function of the IFIH1 protein are protective against T1D (Nejentsev *et al.*, 2009).

A large multi-center consortium, The Environmental Determinants of Diabetes in the Young (TEDDY) is under way to identify environmental factors predisposing to, or protective against, islet autoimmunity and T1D (TEDDY Study Group, 2008). If confirmed, some of the environmental triggers could be targeted in primary prevention trials.

The accelerator hypothesis

Early observation that children with T1D tend to grow slightly faster than population controls prior to diagnosis (Blom *et al.*, 1992) gave some support to the accelerator hypothesis (Wilkin, 2001), which proposes that the T1D epidemic (as well as the rise in T2D) is related to increasing rates of childhood obesity and IR. A rather speculative part of the accelerator hypothesis postulates that IR may trigger autoimmunity or promote beta cell apoptosis and progression to diabetes in islet autoantibody-positive subjects (Xu *et al.*, 2007). Only 1.9% of overweight versus 4.4% of normal weight youth were found to be positive for GADA or IA-2A, with no evidence that being overweight promotes development of autoimmunity in the general population (Libman *et al.*, 2011). Those most affected by the rising incidence of T1D are young children, and studies of weight, height, and growth velocity in the initial three years of life have been inconclusive (Rewers, 2011). The Australian Baby Diab study found that weight and body mass index (BMI) *z* scores (but not length) are predictors of development of islet autoimmunity (Couper *et al.*, 2009). The DAISY study analyzed growth velocity in 1,714 young children at high genetic risk for T1D, and 143 developed islet autoimmunity and 21 progressed to T1D (Lamb *et al.*, 2009). Greater height growth velocity (but not weight or BMI growth velocity) predicted development of islet autoantibodies (hazard ratio 1.6, 95% CI 1.3–2.1) and T1D (hazard ratio 3.3, 95% CI 1.7–6.4) for a one standard deviation difference in velocity.

The Melbourne Prediabetes Family study, the Childhood Diabetes in Finland study, and the Diabetes Prevention Trial of Type 1 Diabetes studies of islet-antibody-positive first-degree relatives of individuals with T1D showed that those who progress to T1D have greater IR relative to insulin secretion (Fourlanos *et al.*, 2004; Mrena *et al.*, 2006; Xu *et al.*, 2007). However, these studies used imperfect measures of IR, rather than the gold-standard hyperinsulinemic-euglycemic clamp. There is a need for large prospective studies to determine the contribution of growth and IR to the risk of developing islet autoimmunity and progression to T1D. While the accelerator hypothesis remains to be validated, there is some evidence that IR may play a role in the progression to T1D, but evidence is still lacking as to whether IR influences development of islet autoimmunity (Rewers, 2011).

Insulin Resistance

Individuals with T2D have IR at the level of adipose, hepatic and skeletal muscle tissue (Lamb *et al.*, 2009). The mechanisms of IR in T1D remain less well defined than in T2D, but are likely due to a combination of supraphysiologic levels of exogenous insulin and, in some cases, obesity. In the past, it was thought that IR in T1D was primarily related to hyperglycemia (Vuorinen-Markkola *et al.*, 1992; Yki-Järvinen *et al.*, 1987), but this assumption has been challenged in recent years. In the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study, adults with T1D have both impaired glucose utilization and impaired insulin-induced non-esterified fatty acid suppression, independent of glycemic control (Schauer *et al.*, 2011). Further, these adults have IR in hepatic and skeletal muscle tissue despite good glycemic control (Bergman, personal communication). Lastly, in adolescents with T1D, IR is not related to hemoglobin A1c (Nadeau *et al.,* 2010).

Skeletal muscle plays a pivotal role in determining systemic IR, as it is responsible for up to 80% of insulin-stimulated glucose uptake (DeFronzo *et al.*, 1992). Skeletal muscle IR is a known feature of T1D (DeFronzo *et al.*, 1982) and is due to decreased glucose transport into myocytes (Cline *et al.*, 1997; Vuorinen-Markkola *et al.*, 1992) from impaired insulin-stimulated upregulation of GLUT4 mRNA (Yki-Järvinen *et al.*, 1992). The insulin receptor is a transmembrane tyrosine kinase receptor and, when activated by insulin binding, causes a cascade of reactions including, but not limited to, tyrosine phosphorylation of the insulin receptor substrate 1 (IRS-1) and association with phosphatidylinositol 3-kinase. In muscle and adipose tissue, this results in translocation of existing GLUT4 from the endoplasmic reticulum to the cell surface, as well as production of *de novo* GLUT4 protein (Shulman, 2000). As there are many sites of activation, there are many potential sites for dysregulation. Obese individuals with T1D have lower levels of GLUT4 protein in skeletal muscle, much like their obese T2D counterparts, yet studies have shown no correlation between the level of GLUT4 protein and HbA1c, fasting plasma glucose, insulin, or duration of diabetes (Kahn *et al.*, 1992). Further, GLUT4 translocation is decreased with higher doses of insulin in rats with T1D (Okamoto *et al.*, 2011). In T1D mice, insulin treatment induced serine rather than tyrosine phosphorylation of IRS-1 and decreased transport of glucose, similar to that seen in T2D (Liu *et al.*, 2009a).

Signaling abnormalities are thought to be, in part, caused by increased lipids, either through ectopic fat distribution or increased serum free fatty acids (FFAs). It is postulated that intramyocellular lipids (IMCLs) and high levels of plasma FFAs activate serine kinases, such as IκB kinase-β, that preferentially phosphorylate serine rather than tyrosine sites on IRS-1 with subsequent decreased glucose transport through GLUT4 from the plasma into myocytes with resultant hyperglycemia (Cree and Wolfe, 2008; Shulman, 2004). Patients with T2D are known to have increased IMCLs in skeletal muscle, which are associated with IR, obesity, and defective signaling in skeletal muscle (Pan *et al.*, 1997). As in T2D, adults with T1D have increased IMCLs (Perseghin *et al.*, 2003). The delivery of increased FFAs to tissues, due to a failure of insulin to suppress adipocyte FFA release, could partially explain the increased IMCLs (Schauer *et al.*, 2011). Yet, in a small study of adolescents with T1D, subjects had evidence of IR, despite normal IMCLs, waist-to-hip ratio, and serum lipids (Nadeau *et al.*, 2010).

Hepatic IR has long been recognized in T1D as well as T2D (DeFronzo *et al.*, 1982). The liver plays a decisive role in regulation of glucose homeostasis: balance is achieved by regulation of gluconeogenesis and glycogenolysis in the fasting state and glycogen storage in the fed state. Insulin suppresses gluconeogenesis via inhibition of phosphoenolpyruvate carboxykinase and promotes glycogen synthesis through stimulation of glycogen synthase kinase-3 and inhibition of glucose 6-phosphatase (O'Brien *et al.*, 2001). In T1D rats, all three of these actions are impaired by higher doses of insulin (6 or 9 units of NPH versus 3 units) (Okamoto *et al.*, 2011). Furthermore, higher doses of insulin result in impaired insulin-induced tyrosine phosphorylation of the hepatic insulin receptor (Okamoto *et al.*, 2011). In the CACTI cohort, there is evidence of hepatic IR in T1D that seems to be unrelated to hepatic steatosis like in T2D (Bergman, personal communication, 2011).

However, another recent study showed that markers of nonalcoholic fatty liver disease were correlated with glucose disposal rate in adults with T1D (Bulum *et al.*, 2011).

IR and T1D Complications

IR is a coronary artery disease risk factor in persons without diabetes (Després *et al.*, 1996; Howard *et al.*, 1996), and has also been suggested to increase coronary artery disease risk in patients with T1D (Orchard *et al.*, 2003; Pambianco *et al.*, 2007). Cardiovascular disease (CVD) is the most frequent cause of death in those with T1D (Laing *et al.*, 2003). The Diabetes Control and Complications Trial (DCCT) was the landmark study demonstrating that tighter glucose control delays the onset and slows the progression of diabetic retinopathy, nephropathy, and neuropathy (DCCT Research Group, 1993). In the DCCT cohort, intensive treatment was also associated with weight gain, elevated blood pressure, worse lipid profiles, and higher waist-to-hip ratio, similar to the phenotype of metabolic syndrome, which would be expected to increase CVD risk (Purnell *et al.*, 1998). However, in a later DCCT study, intensive glycemic control was associated with a reduction in CVD outcomes (Nathan *et al.*, 2005).

Translational studies indicate that IR and obesity may be related to CVD in patients with T1D. In the CACTI cohort of adults with T1D, obesity is a predictor of coronary artery calcification independent of any metabolic abnormalities (Rodrigues *et al.*, 2011). Furthermore, subjects with excess weight and metabolic abnormalities had higher insulin doses, suggestive of increased IR, as compared to those with excess weight but no metabolic abnormalities (Rodrigues *et al.*, 2011). Compared to non-diabetic controls, T1D patients were more insulin-resistant despite similar adiposity, body fat composition, and HDL cholesterol levels (Schauer *et al.*, 2011). In youth with T2D, cardiopulmonary fitness as measured by peak oxygen consumption (VO_2 peak) correlates strongly with IR (Nadeau *et al.*, 2009). Similarly, non-obese adolescents with T1D have evidence of impaired cardiopulmonary fitness and cardiac function, and insulin sensitivity is a predictor of VO_2 peak (Nadeau *et al.*, 2010). Furthermore, these youth had evidence of significant IR despite normal BMI and hemoglobin A1c 8.7% ± 1.6 (Nadeau *et al.*, 2010). Larger studies are needed to better understand the factors involved in risk of CVD in patients with T1D.

Studies are examining the role of oral agents in T1D that are typically used in the treatment of T2D. A meta-analysis of the use of adjuvant metformin in T1D showed a small reduction in hemoglobin A1c and a moderate reduction in insulin dose (Pang and Narendran, 2008). Use of thiazolidinediones in overweight adults with T1D resulted in reduced insulin dose and slight improvement in hemoglobin A1c, particularly for those with a BMI of 30 or greater (Strowig and Raskin, 2005). Behavioral modifications, including increased physical activity and maintenance of body weight within normal range, show promise in lowering IR associated with T1D (Schenk and Horowitz, 2007). Furthermore, continuous glucose monitoring may guide more precise insulin dosing and lead to better glycemic control while avoiding hyperinsulinemia.

There are very few studies investigating the role of carbohydrates, insulin dose, and IR. A small pilot study in Germany compared children with T1D on a low-glycemic index diet to

an optimized mixed diet and found no difference in short-term hemoglobin A1c (Marquard *et al.*, 2011), although they did not measure IR. Another study randomized obese, IR adults to either a low glycemic-index diet plus exercise or a high glycemic-index diet plus exercise. Those in the low glycemic-index group had improved insulin sensitivity after only one week (Haus *et al.*, 2011). It remains to be seen how much the pathophysiology of IR in T1D differs between those who are lean versus those who have the metabolic syndrome phenotype and more traditional T2D risk factors. Such questions demonstrate that fruitful research may emanate from areas of study that blend the expertise of T1D and T2D researchers.

Conclusions

With rates of obesity on the rise, it is becoming increasingly difficult to distinguish between T1D and T2D in overweight youth. In absence of islet autoantibodies, it may take weeks or months of observation to accurately diagnose an older child or adolescent with features of both T1D and T2D. It should be noted that for pediatric patients presenting with sustained hyperglycemia or diabetic ketoacidosis (DKA), insulin therapy must precede definitive laboratory results, even in ambiguous cases.

The high-risk HLA genotype and islet autoantibodies can be used to predict risk of developing T1D in relatives of type 1 diabetics. The incidence of T1D is rising and environmental factors likely play a role in the pathogenesis of T1D. Larger studies will hopefully clarify which environmental factors are the most important in determining risk. It is known that individuals with T1D have IR, and the mechanism of IR in skeletal muscle tissue is likely similar to that in T2D, but may be quite different in the liver. IR appears to accelerate progression to T1D in high-risk individuals with islet autoimmunity. IR is also a powerful cardiovascular risk factor, and lowering IR in patients with T1D is likely to be as important as glycemic control in prevention of long-term complications. Further studies are needed to understand the mechanisms of IR in T1D and how to mitigate long-term cardiovascular risk.

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