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Review

Role of immune system in type 1 diabetes mellitus pathogenesis

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ABSTRACT

The immune system is the body's natural defense system against invading pathogens. It protects the body from infection and works to communicate an individual's well-being through a complex network of interconnected cells and cytokines. This system is an associated host defense. An uncontrolled immune system has the potential to trigger negative complications in the host.

Type 1 diabetes results from the destruction of pancreatic β-cells by a β-cell-specific autoimmune process. Examples of β-cell autoantigens are insulin, glutamic acid decarboxylase, tyrosine phosphatase, and insulinoma antigen. There are many autoimmune diseases, but type 1 diabetes mellitus is one of the well-characterized autoimmune diseases. The mechanisms involved in the β-cell destruction are still not clear; it is generally believed that β-cell autoantigens, macrophages, dendritic cells, B lymphocytes, and T lymphocytes are involved in the β-cell-specific autoimmune process. It is necessary to determine what exact factors are causing the immune system to become unregulated in such a manner as to promote an autoimmune response.

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1. Introduction

Diabetes mellitus is a metabolic disorder that leads to the development of a number of complications including ketoacidosis, kidney failure, heart disease, stroke, and blindness. Type 1 diabetes usually starts in people younger than 30 and is therefore also termed juvenile-onset diabetes, even though it can occur at any age. It was also termed insulin-dependent diabetes mellitus. Type 1 diabetes incidence has more than doubled in the past 20 years and is set to double again before 2020 [1]. It is a well-known autoimmune disease that is characterized by a specific adaptative immunity against β-cell antigens. This disease is one of the classical examples of organ-specific autoimmune disease characterized by lymphocytic infiltration or inflammation in pancreatic

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islets called "insulitis." Insulitis ultimately leads to the destruction of the insulin producing β-cells, resulting in diabetes. This is usually associated with infiltration of innate immune cells. These cells produce cytokines which promote β-cell apoptosis and increase infiltration of islet-specific T cells. Islet-specific T cells attack and destroy β-cells.

T cells play an important role in the induction of type 1 diabetes mellitus. The inflammatory infiltrate in islets consists mostly of T lymphocytes, but the data on the predominance of CD4+ (Th4 or helper) [2] or CD8+ (Th8 or cytotoxic) [3]. CD4+ T cells have been subdivided into different subset based on their cytokine secretion profiles: Th1, Th2, Th17, and Treg (regulatory T cells) [4,5]. Cytokines produced by Th1 are mediators in cellular immunity, whereas cytokines produced by Th2 are stimulators of humoral immune responses and antibody production. Th17 T cells may play a role in the induction of autoimmune tissue injury. Th1 cells are responsible for aggressive disease, while Th2 T cells infiltrate more slowly and do not induce diabetes [6]. The inflammation generated by Th1 cells might attract T cells that would not normally accumulate in the islets. Treg cells are primary controllers of immune responsiveness and peripheral immunological tolerance [7]. These cells also regulate several organ-specific autoimmune diseases such as type 1 diabetes [8]. Treg cells control natural killer (NK) cells in an insulitic lesion. They also control progression to type 1 diabetes in NOD mice by reining in NK cells, inhibiting both their proliferation and production of interferon-γ [9]. A variable number of B cells or macrophages have also been described in the inflammatory infiltrate [3]. Studies using human and murine models of diabetes have demonstrated that the autoimmune destructive process in type 1 diabetes requires both CD4 and CD8 T cells as well as macrophages [10,11]. These cells are nondestructive; however, they accumulate in an islet lesion [12]. A triggering event needs to occur, which promotes β-cell destruction. It is to note that clinical manifestations of diabetes occur after 90% of an individual's β-cell mass is destroyed [13].

2. Autoantibodies

Islet cell autoantibodies reacting with antigens located in the cytoplasm of all endocrine cells within the pancreatic islets were first described by Bottazzo et al. [14]. Islet reactive T cells exist in patients with type 1 diabetes. Studies identified autoantibodies to four islet gene groups: insulin or proinsulin (PI), glutamic acid decarboxylase (GAD65 or GAD67), insulinoma-associated atigen-2 (IA-2 or ICA512 or IA-2β or PHOGRIN), and zinc transporter 8 (ZnT 8) [15]. Autoantibodies to other islet antigens, such as heat shock protein (HSP), chromogranin A and their peptides [16], islet-specific glucose-6-phosphatase catalytic subunit-related protein (IGRP) [17], and human islet amyloid polypeptide (IAPP) precursor protein [18] have been identified. In addition to mentioned autoantigens, still others have been identified, such as autoantibodies to glucose transporter 2 (GLUT2) [19], sulphatide [20], ganglioside GM2-1 [21], carboxypeptidase H [22], and three distinct-associated autoantigens of 38 kDa molecular mass (autoantigen to nuclear transcription factor jun-B) [23], Imogen 38 [24] and glima 38 (glycosylated islet cell membrane antigen of 38 kDa) [25]. Islet autoantibodies rarely appear prior to age 6 months [26]. Risk is incremental in relation to whether antibodies are against two, three, or four of the antigen group. On the other hand, type 1 diabetes risk can vary in relation to which of the islet autoantibodies are present [27]. For example, the presence of antibodies to IA-2 is associated with highest risk [15]. Autoantibodies alone do not appear to be sufficient to induce β-cell destruction. Transplacentally transferred antibodies related to type 1 diabetes are usually eliminated from the peripheral circulation of infants before 9 months of age [28]. No differences were found in autoantibody frequencies between the offsprings from mothers vs. fathers with type 1 diabetes up to the age of 5 years [29].

The development of the pathology involved several cell types of both the innate and adaptative systems. This disease is under the control of several genetic loci, but also is influenced by environmental factors.

3. Role of HLA genes in type 1 diabetes risk

In humans, the major histocompatibility complex (MHC) is known as the human leukocyte antigen (HLA) and contains over 200 genes [30]. It is located on chromosome p21.3 [31], encoding HLA class I and class II molecules [32]. Genes of HLA class I and II are highly polymorphic and consist of many different alleles [32]. These genes encode cell surface proteins that are required for interaction with cells of immune system, and are involved in immune recognition and killing. Distinct loci within HLA region determine risk [33], though the HLA class II region appears to be most influential [34]. The HLA is considered to contribute about half of the familial basis of type 1 diabetes [35]. Disease susceptibility is highly associated with inheritance of the HLA alleles DR3 and DR4 as well as the associated alleles DQ2 and DQ8. Several genes of HLA class II were found to determine a susceptibility hierarchy ranging from protection to strongly at-risk.

More than 90% of patients with type 1 diabetes express either DR3DQ2 or DR4DQ8. The DRB1*1501-DQA1*0102-DQB1*0602 haplotype, found in ~20% of the population but only 1% of patients, confers dominant protection against type 1 diabetes [36]. Heterozygous genotypes DR3/DR4 are the most in children diagnosed with type 1 diabetes prior to the age of 5 (50%) [37]. Individuals with the haplotype DRB1*Q302-DQA1*0301, especially when combined with DRB*0602-DQA1*0501, are highly susceptible to type 1 diabetes. The risk of type 1 diabetes in these individuals increases 10–20-fold. The HLA DRB1*03, *04; DQB1*0302 genotype, which confers with the highest risk of type 1 diabetes, is present in 39% of patients who develop type 1 diabetes before age 20 [38]. On the other hand, HLA class II haplotypes such as DR2DQ6 confer dominant protection [39]. Individuals with the haplotype DRB1*0602-DQA1*0102 rarely develop type 1 diabetes. The precise mechanisms through which HLA-DQ determines disease susceptibility is still not clear [40].

An association has been also found for class I alleles [41]. Most notably the presence of the HLA-B*39 allele was found to be a significant risk factor. HLA-A*02 increases the risk in individuals possessing the high-risk class II DR3/4-DQ8 haplotype [42]. HLA-A*0201 is one of the most prevalent class I alleles in patients with type 1 diabetes. The presence and functionality of HLA-A*02-restricted CD8 T cells reacting against β-cell antigens such as insulin, glutamate decarboxylase and islet amyloid polypeptide (IAPP) were found in patients with type 1 diabetes and islet transplant recipients [18,43]. Alleles at HLA DP class II loci and class I loci, such as HLA*24, B*38, and B*39, also contribute to type 1 diabetes risk, but they have not been incorporated into risk prediction models [15].

How to explain the influence of HLA genes on the development of type 1 diabetes? Several hypotheses have been introduced. A peptide competition model suggested by Nepom [44] proposed that a diabetogenic peptide is permissive for disease when it binds to a disease associated class II molecule. The competition of diabetogenic peptides between resistant and susceptibility HLA alleles might be a mechanism of disease protection. The competition effect is more profound when the source antigen is rare so that the abundance of peptide-DQ8 complex is reduced. The reduced abundance of this complex can lead to a diminished activity of DQ8-resistricted autoreactive T cells. Another model focused on the failure of the immune system to maintain tolerance to β-cells in type 1 diabetes [45]. It was suggested that HLA DQ genes associated with type 1 diabetes bias the immunologic repertoire toward autoimmune specificities, creating an immune prone individual, followed by amplification and triggering events that promote subsequent immune activation [46]. MHC class II alleles conferring susceptibility and resistance to diabetes select completely different sets of immunogenic epitopes from the β-cell autoantigen GAD65. Results obtained by Chao et al. [47] showed that substitutions of two amino acids within the I-Aβ chain, that distinguish a diabetes-susceptibility from a diabetes-resistance allele are sufficient to alter peptide binding and MHC restriction. These substitutions may also influence antigen