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Review

Autoimmune facet of type 1 diabetes

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Abstract

Type 1diabetes (T1D) is an autoimmune disease commonly observed in the young population and characterized by the destruction of pancreatic β-cells. Defective self and non-self-recognition in collaborative functioning of the innate and adaptive immune system lead to the pathogenesis of T1D. The present review brings to light the components of innate immunity like macrophages, Toll-like receptors (TLR), viral components in prompting T1D. Macrophages mediate β-cell cytotoxicity and cause inflammatory response; TLRs trigger the release of various cytokines and activate adaptive immune response; viruses mimic their components as ligands to initiate TLR signaling and therefore contribute to T1D pathogenesis. Both humoral and cellular components of adaptive immune responses are involved in the development of T1D. In humoral autoimmunity, the presence of different autoantibodies that detect respective β-cells autoantigens can start to damage pancreatic β-cells. The appearance of a particular autoantibody at onset age is considered as a diagnostic marker. The cellular response attributes mainly in T1D pathogenesis, with the help of CD4+ and CD8+T cells CD4+T cells release cytokines and mediate phagocytosis, it also stimulates B cells for antibody production thus cognating humoral and cellular autoimmune response. CD8+Tcells generate direct cytotoxicity to β-cells when MHC (Major histocompatibility complex) II molecules present antigenic peptides.

Keywords

Autoimmunity; Innate immunity; Adaptive immunity; Type 1 diabetes; Humoral immunity; Cell-mediated immunity

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Introduction

The immune system is comprised of innate and adaptive immunity, which works in the vicinity. Both immune systems act as per recognition and response strategy with the help of their respective components. When the cells of innate and adaptive immune system escape from autoreactivity through clonal deletion or negative selection, it is known as immune tolerance. The malfunctioning of this precise process of immune tolerance gives birth to autoreactive B and T cells, which proceeds towards autoimmunity [1]. During the incidences of autoimmunity bodily elements like DNA, secreted proteins, cells are targeted by antibodies that are generated by B cells during immune response, thus trigger various autoimmune diseases (AIDs). AIDs are common and serious clinical issues that are prevalent in the young population [2]. AID varies in accordance with the affected organs, with their clinical manifestations either limited to a particular tissue or disseminated. Along with these variations, AIDs are believed to proceed in consecutive phases of initiation, propagation and resolution. Like many other complex disorders, it is believed to arise from a combination of genetic and environmental factors [3, 4]. Genetic control of the immune response to polypeptide antigens is well known. Various AIDs like type 1 diabetes (T1D), rheumatoid arthritis, multiple sclerosis are polygenic in their inheritance patterns. A particular allele combination of several genes is responsible for solitary susceptibility towards certain autoimmune disease [5, 6].

T1D is an organ-specific AID featured by the destruction of pancreatic β-cells. The decreased β cell mass with infiltration of mononuclear cells into Islets of Langerhans is known as Insulitis and it is the hallmark of T1D. Fifteen to 30% of T1D patients reported other autoimmune comorbidities like thyroiditis, Addison's disease, celiac disease [7, 8]. Plenty of evidence elicits the impact of autoimmunity and its types upon the pathogenesis of T1D. Therefore, brushing the knowledge of basic concepts and interpreting the emerging researches may enable the advancement of in-use therapies to restrict the incidence of immune driven diseases like T1D.

Innate Immunity Involvement in Pathogenesis of Type 1 Diabetes

The innate immune system implements the initial defense when triggered by a foreign pathogen. It is known for its non-specific defense mechanism and is incapable of maintaining the repertoire of antigenic encounters. Therefore, it does not have a memory of foreign pathogens [9- 11]. The innate immunity job is done by an array of skilled molecules referred to as pathogen associated molecular patterns (PAMPs) [9]. Studies have correlated the aberration in innate immunity with TID pathogenesis [10]. However, it is a major contributor to generate an inflammatory response by utilizing a variety of cells and induce cellular mechanisms for the fulfillment of immune response. The cells involved in innate immunity are macrophages, dendritic cells, natural killer cells, neutrophils, epithelial cells. Every cell functions in its respective way, from phagocytosis to direct lysis of the host cell [12, 13]. In autoimmune responses, the immune system fails to discriminate between self and non-self, thus links to the pathogenesis of AID [9].

Inflammatory Response

It is an accomplishment of innate immunity, which includes various cellular receptors known as pattern recognition receptors (PRRs), found on cellular surfaces or released in tissue fluids. These PRRs and PAMP interactions trigger the release of a variety of cytokines and chemokines accountable for inflammatory pathways [14, 15]. Inflammatory response combats the serious consequences of tissue injury from antigenic attack and restores the tissues for healing. The defective inflammatory response may have the risk for developing AID like T1D. The term Insulitis has been coined to refer to inflammation in the islets of Langerhans in the pancreas. Various studies confirm that the increment of inflammatory markers in prolonged T1D, with significant correlation, actively contributes to the progression of T1D towards nephropathy [16, 17].

Wilcox and team, in immunopathological analysis of the inflamed islet of T1D patient sample, reported the recruitment of particular immune cells at a specific stage of T1D advancement [18]. An observation has been reinforced by a research in which α-1- antitrypsin, a protease inhibitor, was injected to NOD (non-obese diabetic) mice, which protect the tissue from enzymes generated by inflammation and also reverses new-onset diabetes [19]. Macrophages and other antigen-presenting cells (APC) initiate T cells sensitization and activate regulatory mechanisms [20].

Macrophages play a major role in the development of β-cell-cytotoxic T cell complex during T1D. Along with CD8+ cytotoxic cells, macrophages are also responsible for the early loss of β-cells at a later stages of insulitis, and CD20+cells additionally play a role in β-cell destruction [18,20].

Pattern Recognition Receptors

Toll-like receptors (TLR) are a type of PRR which recognizes foreign molecules and induces innate immune system by initiating the consecutive signaling pathways such as production of cytokines, activation of adaptive immune cascades, and manifests directly in the pathogenesis of T1D [21]. Previous studies reported the profound effect of TLRs in the development of AID, thus the expression of TLRs was assessed in T1D showing the increased expression of TLR2 and TLR4 along with nuclear factor (NF-κ) and interferon-β (IFN-β) on monocytes [22]. A cohort study reported elevated ligands of TLR2 and TLR4 in T1D patients with significantly noticed consequences of disease progression [23].

Various studies demonstrated the role of TLR in the pathogenesis of T1D with the help of animal models. In non-diabetic mice models, researchers revealed that TLR3 is not required for the onset of autoimmune diabetes while TLR9 deficient mice showed a significantly decreased incidence of diabetes [21, 24].

Diverse results appear in TLR signaling, as in a recent study, TLR3 induces β cell apoptotic pathway, TLR2 recognizes lipopolysaccharide receptors of microorganisms and avoids initiation of T1D and, on the other hand, it also corroborates in worsening the disease [25]. Thus, numerous studies revealed varied TLR signaling outcomes in relation to insulitis and T1D.

Virus Components

It is well known that viruses in viral infections trigger TLR signaling by identifying the molecular structures associated with the respective viruses. Although, viral infections imply the induction of T1D, the exact mechanism is still elusive. Numerous viruses like rotavirus, rubella, mumps serve their components as TLR ligands, thus it is possible to gain an obvious understanding of the functioning of the innate immune system through TLR signaling [26].

Numerous studies reported the association between virus and T1D pathogenesis. As in an autopsy sample of the pancreas of newly diagnosed patients with T1D, enterovirus was detected, whereas in another study, enteroviral capsid protein vp1 was seen in the islets of 44 newly diagnosed T1D patients [27]. As mentioned above, TLR9-deficient mice showed a reduction in the incidence of diabetes, but in a study focusing only on TLR9 over bio breeding diabetes-resistant (BBDR) rats infected with Kilham rat virus (KRV), 25-40% of rats constantly developed T1D [28, 29]. The theory behind these results enlightens that KRV infection induces a transcription factor (STAT-1) through TLR9 signaling pathways. Therefore, viral infections can efficiently develop autoreactivity. In these reports, the componential mechanism of the innate immune system sheds light on the association with insulitis progression and T1D [28, 29].

Adaptive Immunity in Type 1 Diabetes

The adaptive immune system is highly specific, utilizes T cells, and APC for recognition of antigens. Adaptive immunity creates immunological memory that induces T cell facsimile which further coordinates with B cells to generate antigen-specific antibodies. Both T cell types, CD4+ and CD8+, are required for the initiation of T1D. By distributing B cells antigens over APCs, T cells differentiate into effector cells; CD4+ as insulin reactive and CD8+ mainly kill β-cells. CD4+ T cells assist CD8+ T cells for antibody production by B cells and activate native macrophages [30].

Humoral Immunity

Autoantibodies are contemplated as ill-fated byproducts of the immune system and responsible for causing harm to an individual. The presence of autoantibodies is the signal of emerging β-cell immunity, for the prognosis of T1D. Detection of five autoantibodies has been proposed for the prognosis of T1D [31]. Autoimmune etiology of T1D revealed the presence of Islet specific antibodies in the serum of patients than healthy individuals. Islet specific autoantibodies were the first to be observed and because of their specificity, they are viewed as diagnostic markers for T1D [32]. Various other autoantibodies for specific antigen were identified, such as insulin autoantibody (IAA), glutamic acid decarboxylase autoantibody (GADA), islet antigen-2 autoantibody (IA-2), and zinc transporter autoantibody (ZnT8-A). According to various surveys, the frequency of detected autoantibodies is clearly associated with the risk of bringing the disease into an overt condition, and the constant presence of at least one of them by the age of 5 years confirms the risk of disease progression. Thus, the circulation of autoantibodies to the respective islet cells antigen can initiate destruction of β-cells [32, 33]. Extension of humoral autoimmune response takes place in a short span of time; if such broadening does not happen after the appearance of the initial presence of antibodies, it rarely appears after [34].

Insulin has been declared as the primary autoantigen. The A chain of insulin requires post-translational modification which allows it to be recognized by T cells. IAA is the first seen autoantibody in young children during the preclinical phase and has shown firm genetic susceptibility with T1D. IAA is a diagnostic marker for TID, resulting from autoreactive B cells and CD4+ T cell interactions [35, 36].

Glutamic acid decarboxylase (GAD) is an effective autoantigen of T1D which exists in two isoforms: GAD65 and GAD 67 [36]. It recognizes mainly middle and C terminal epitopes of an autoantigen. Knip reported that in siblings of T1D affected children, the initial response was limited to the middle region, spreading fast towards C terminal and only in few cases to N terminal [36]. Elevated GADA levels were detected in patients suffering from T1D and autoimmune thyroid disease than in patients with T1D alone. It is supposed to be explained by the fact that GADA are expressed in β-cells and in the thyroid gland as well [7, 37].

After GAD, IA-2 is another important autoantigen. It is a transmembrane protein-tyrosine phosphatase-like protein and recognizes the cytoplasmic domain of the IA-2 molecule for activity. About 65% of patients with early-onset T1D showed autoantibodies to IA-2 and 35-50% had autoantibodies to IA-2β [38-40].

Antigen ZnT8 is composed of 6 transmembrane domains [41, 42]. In 60-80% of newl-onset T1Ds, ZnT8 was attacked by autoantibodies [43]. Eiji Kawasaki reported that 90% of early childhood cases had autoantibodies to GAD and IA-2, while 5-8% of adult patients had autoantibodies for ZnT8, therefore the estimation of ZnT8 autoantibody is limited over GADA and IA-2A in case of childhood T1D diagnosis [7]. Moreover, the frequency of ZnT8 and IA-2A is inversely proportional to the onset age [44].

β-cell-antigen specific autoantibodies do not straightly cause pathogenicity or cytotoxic effect on islet cells, yet they help to present the antigens to T cells and promote the development of T1D.

Cell-mediated Immunity

It is believed that the credit of β-cell destruction in T1D goes mainly to a cellular immune response with the help of T cells. Proofs behind this theory are the presence of T cells in insulitis and drugs used to slow down disease progression directly target T cells [45]. Pancreatic section analysis of T1D individuals showed fulminant immune infiltrate in patients Islet cognating the activity of CD4+ and CD8+ T cells in β-cell killing [46]. On contrary, the pancreas section in T2D does not show T-cell infiltration like T1D, although they have remarkably high levels of inflammatory molecules [47].

T cells get activated by autoantigenic determinants presented by MHC II molecules, and this is done with the help of APC, which eventually develops MHC II molecules. The activated T cells attack the islets and subsequently confront the associated β- cell autoantigen thereafter causing insulitis [48, 49].

Various studies on the NOD mouse model indicated the

vulnerability of autoimmune diabetes on MHC II allele, CD4+, CD8+ T cells and B cells [50-53].

CD4+T cells act as a stimulant. They activate CD8+T cells, B cells to produce antibodies, and Islet inhabitant macrophages [54]. Recent studies recognized CD4+T cells in the NOD mouse model and human T1D patient as pro-inflammatory cells which secrete interferon-gamma (IFN-γ) and interleukins (IL) [55-58]. CD4+Tcells have subtypes Th1, Th2, Th17, and Tregs with varied immune effects [59]. Th1 cells mediate phagocytosis by releasing cytokines like IFN-γ and IL-2 which kill β-cells and exaggerate the condition [30, 59].

Th2 cells, on the other hand, suppress the activity of phagocytic cells. They produce cytokines IL-4 and IL-10, which promote antibody production and eosinophil activation [60, 61]. A study showed in a transgenic mouse model, that IL-4 secretion in islet cells safeguard the development of T1D [62]. Likewise, IL-10 also showed the protective effect, and evidence through research suggests that IL-10 establishes immune tolerance in NOD mice [20]. Immunotherapeutic strategies which promote the viability of Th2 cells and secretion of IL-4 can successfully combat the initiation of T1D. Despite the distinguished activity of Th2 cell-derived interleukins, many studies revealed the cooperated participation of Th1 and Th2 interleukins in the destruction of β-cells, and ultimately, initiate the pathogenesis of T1D [63].

Th-17 cells are IL-17 producing T cells, which contributes to various infectious diseases and autoimmune disease development [64]. It is known as inflammation-causing agent which further speeds up the process of diabetes complication, and is especially detected in children [65]. Studies have shown that IL-17 is directly targeted by therapeutic agents or that the activity of IL-17-producing cells has been stopped to control autoimmune diabetes. This therapeutic strategy suggests the involvement of IL-17 in T1D pathogenesis [66]. Another type of T cells working upon the pathogenesis of T1D is CD8+. Activation of CD8+T cells happens when antigenic peptides are presented by MHC II and through this interaction, β-cells are destroyed. The requirement for MHC I in T1D pathogenesis is ambiguous. Studies reported interactions of CD8+T cells with MHC I in the early development of the disease, while others have concluded that it occurs late in diabetes pathogenesis [67-69].

Both CD4+ and CD8+ types are responsible for β-cell destruction by producing various cytokines. But CD8+T cells perform direct cytotoxicity to pancreatic β-cells because it expresses antigen presenting MHC I molecules not MHC II [68]. In a study over the NOD mice model, it was shown that mice, which lack class I MHC do not suffer from insulitis and it initiates T1D pathogenesis representing the necessity of MHC I for T1D initiation and progression [67]. CD8+ lymphocytes secrete perforins, TNF-α, IFN-γ, IL-1β, and produce nitric oxide for the demolition of β-cells thus, take part in T1D pathogenesis [70].

Conclusion

In this review, we concisely mention the role of both innate and adaptive immunity along with their cellular lineage into the pathogenesis of T1D. T1D is an outcome of an autoimmune process associated with dysregulated signaling of the immune system. Even though the researchers have enlightened the role of individual cell type in the disease progression and have generated immunosuppressive therapies respectively, the pathway commanding the launch of the autoimmune process is still unclear. Even after this understanding, incidence of the disease continues to rise. Thus, there is a need to find answers to inhibit the initiation of an autoimmune response to avoid not only T1D, but also other autoimmune diseases. We perceive the role of immune cells with recent researches for further advancement of understanding and treatment.

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The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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