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The Role of Innate Immune Pathways in Type 1 Diabetes Pathogenesis

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Abstract

Purpose of review—Type 1 diabetes is an autoimmune disease typically believed to result from malfunctions in adaptive immune response signaling which result in activation of self-reactive T cells. However, recent research has indicated components of the innate immune response as having a key role in the initiation of the autoimmune process of type 1 diabetes. This review will highlight recent reports which examined the role of innate immune response signaling and the connections to type 1 diabetes pathogenesis.

Recent findings—Investigations indicate that components of innate immunity, including inflammation and Toll-like receptor signaling, are involved in pancreatic islet infiltration and insulinitis. Recent studies examining the role of viral infections in T1D development also implicate innate immune response signaling in disease pathogenesis.

Summary—Current research indicates that components of innate immune response signaling are involved in the initiation of the autoimmune process which results in the eventual destruction of β cells during T1D pathogenesis. Continuing efforts by researchers to uncover the molecular pathways of innate immunity linked to T1D development could potentially lead to therapeutics capable of preventing and curing the autoimmune disease.

Keywords

type1 diabetes; innate immunity; toll-like receptors

Introduction

The innate immune response comprises one branch of the complex human immune system and is responsible for mounting an initial defense when triggered by the presence of foreign pathogens [1*]. Given the multifaceted role of innate immunity within the human body, it is not surprising several components of this normally protective mechanism have been linked to the development of autoimmune diseases [2]. Type 1 diabetes (T1D), also known as insulin dependent diabetes mellitus or juvenile diabetes, is one such autoimmune disease where dysregulation within innate immune response signaling has been linked to disease progression [3]. The development of T1D is a result of the autoimmune destruction of the pancreatic β cells within the islets of Langerhans and is generally believed to be a result of the interaction of the immune system with an intricate network of environmental and genetic factors [4]. Recently,

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evidence has linked abnormalities within innate immunity as potentially having a key role in T1D pathogenesis [5]. Interpreting and understanding this emerging research may enable the development of new therapies which modulate innate immune responses to protect against immune-mediated diseases such as T1D.

Components of innate immunity and their role in T1D pathogenesis

The innate immune response functions within the human immune system to provide initial protection against environmental pathogens that invade the body. This task is accomplished through the general recognition of conserved structures shared amongst large cohorts of microorganisms, known as pathogen-associated molecular patterns (PAMPs) [6**]. In contrast to the adaptive immune system, which is capable of generating immunological memory to fragments of foreign pathogens, innate immunity does not have the capacity to remember antigenic challenges [3;7]. Instead innate immunity is a main contributor to the majority of inflammatory responses which occur throughout the body and utilizes a wide variety of cells and cellular mechanisms to fulfill its role in the human immune response [8]. Due to the influence innate immunity has in immune system functioning, it is conceivable to believe some immune responses have the potential to initiate an autoimmune response through failing to discriminate self from non-self. In this review, we will highlight recent reports which examine components of innate immunity that have been linked to autoimmune disease pathogenesis, specifically focusing on T1D.

The inflammatory response

The innate immune response involves a group of cellular receptors known as pattern recognition receptors (PRRs) which are found in intracellular compartments, secreted throughout tissue fluids and blood, and on cellular surfaces [9]. These PRRs include Toll-like receptors (TLRs), nucleotide oligomerization domain-like receptors (NLRs), and retinoic acid-inducible gene-I-like helicases, which recognize pathogens through the interaction with PAMPs [9;10]. Upon PAMP binding to its cognate PRR, a variety of defense mechanisms are induced, including the release of cytokines and chemokines responsible for inflammatory pathways [10]. Typically, the inflammatory response serves to protect the body against further tissue injury from foreign pathogens and seeks to restore tissues to a status which allows for appropriate healing [11]. However, excessive or defective inflammatory signaling can have adverse consequences and increase the risk of developing an autoimmune disease such as T1D [11;12*].

Inflammation in the islets of the pancreas, termed insulinitis, has been shown to damage β cells leading to the progressive loss of insulin production [13]. Recently, immunopathological analyses of islet inflammation on pancreatic samples obtained post-mortem from 29 recent-onset type 1 diabetic patients suggest a defined sequence of insulinitis, with immune cells recruited at precise stages of T1D development [14]. Amongst cells recruited during insulinitis, data suggests that $CD8^+$ cytotoxic cells and macrophages may contribute to the early loss of β cells, while late recruitment of $CD20^+$ cells may have an increased role during the latter stages of insulinitis [14]. Additional reports have also indicated a role for inflammation in T1D pathogenesis, as inflammatory protein markers are increased in long term type 1 diabetics and correlate with T1D complications, including progressive nephropathy [15-18]. Taken together, these reports suggest proper regulation of the inflammatory pathways triggered by innate immunity may be a key component in preventing development of T1D.

Toll-like receptors

Another central contributor to the innate immune response is a group of PRR proteins collectively termed TLRs. TLRs are responsible for recognizing components of foreign

pathogens thereby signaling activation of the innate immune response [19]. These receptor proteins remain a highly studied and often investigated family of proteins due to their importance in numerous cellular signaling pathways and their roles in disease prevention and development. Recent reports in animal models and humans studies indicate ligation of TLRs and their subsequent downstream signaling pathways, including induction of inflammatory cytokines and activation of adaptive immune responses, have a direct role in the pathogenesis of T1D [4;20;21].

Due to the critical role TLRs have in innate immunity, and their reported influence in the development of autoimmune diseases, their expression was examined in type 1 diabetic patients as compared to healthy control individuals [22*]. The expression of TLR2 and TLR4 were both increased in monocytes obtained from type 1 diabetic patients [22]. Moreover, the activity of TLR2 and TLR4 along with downstream targets of TLR signaling, including MyD88, nuclear factor- κ B (NF- κ B), and TIR-domain-containing adapter-inducing IFN- β (TRIF), were all significantly upregulated in the type 1 diabetic patients [22]. A follow-up study which investigated ligands of both TLR2 and TLR4 in patients with type 1 diabetes found elevated levels of the ligands in the patients [23]. The data from these studies indicate the inflammatory response initiated by TLR2 and TLR4 signaling may have significant consequences in T1D development.

Because numerous impediments exist in conducting research in human subjects, animal models have served as a better scientific tool to understand the cellular mechanisms which lead TLRs to participate in the pathogenesis of T1D [4]. By using animal models researchers are better able to understand clinical observations through in depth analysis not feasible in humans [4; 24]. Recent research with various animal models has provided numerous insights into the connection between TLRs and T1D. By generating non-obese diabetic (NOD) mice deficient in TLR3 or TLR9, researchers were able to show in the NOD model that TLR3 is not required for autoimmune diabetes onset while TLR9-deficient mice had a significantly decreased incidence of diabetes as compared to TLR9 heterozygotes [25]. TLR3 is an intracellular receptor which signals through the adaptor molecule TRIF and detects dsRNA of viruses while TLR9 signaling occurs through the MyD88 pathway and recognizes bacterial CpG DNA [26; 27]. This data may indicate TLRs have different roles in the development of T1D.

However, variability does exist when examining the importance of TLR signaling amongst animal models [28*]. TLR3 expression and functionality has been confirmed on pancreatic β cells [29] and a recent study indicated that TLR3 ligands, including polyinosinic:polycytidylic acid (poly I:C), induce β cell apoptotic pathways [30]. Recent studies have also shown that TLR2, a membrane receptor protein which recognizes lipopolysaccharides of microorganisms [31], both exacerbates and prevents initiation of T1D [32;33*]. Besides having a role in innate immune response signaling, a polymorphism in the TLR2 gene was recently shown to significantly associate with allergic asthma and T1D development in humans [34*]. Therefore, these new reports uncover several mechanisms of the innate immune response involved in TLR signaling and the connections to insulinitis development and T1D. The latter report also identifies a genetic variant which associates with a higher risk for T1D in humans.

Viral infections

Viral infections are strongly implicated in triggering T1D in humans with a genetic predisposition [4;35]. The components of viruses are also strong activators of TLR signaling with TLRs acting as sensors to identify the molecular patterns associated with numerous types of viruses [36]. Currently, the exact mechanism by which viral infections lead to T1D remains elusive, but numerous studies provide evidence for various mechanisms, including inflammation caused by innate immune response signaling [4;28]. Many types of viruses, such as mumps, rubella, enteroviruses, cytomegalovirus, and DNA rotavirus, have all been

implicated as contributors to T1D pathogenesis [4;37-40]. Because components of these viruses serve as TLR ligands, this creates a logical assumption that innate immune signaling plays a critical role in development of T1D. Indeed, there are many proposals that attempt to address why the exact role for viral infections in human T1D still remains unknown [4].

A significant number of studies have been published throughout the past year which investigated the role for viruses in innate immune response signaling and their connection to T1D pathogenesis. The class of viruses known as enteroviruses have been shown to exhibit islet cell tropism through detection of viral RNA and viral proteins in pancreatic sections of post-mortem T1D patients [41-43]. A recent study investigated the presence of enteroviruses in autopsy pancreases of patients newly diagnosed with T1D as well as control pancreases [42;44**]. The enteroviral capsid protein vp1 was detected in multiple islet cells in 44 out of 72 newly diagnosed T1D patients by using immunohistochemistry [44]. The study further revealed vp1 staining was restricted to beta cells and correlated strongly with protein kinase R (PKR). Interestingly, analysis of vp1 in islets of type 2 diabetics (T2D) revealed positive staining in 10 out of 25 patients [44]. This study confirmed previous reports of enteroviral infection in beta cells of post-mortem type 1 diabetics through more convincing techniques and adds evidence to the hypothesis stating enteroviral infection of β cells may participate in the autoimmune response which leads to T1D in genetically inclined individuals.

Further support for the notion that enteroviruses participate in T1D pathogenesis was presented in a recent case study [45]. A 39-year-old woman diagnosed with fulminant T1D, a form of diabetes in which hyperglycemia, ketoacidosis, and β cell destruction occurs rapidly [46], had an 8-fold increase in enteroviral Cocksackie B4 neutralizing antibody in her plasma [45]. Because it is not feasible to study the mechanism by which Cocksackie B4 virus leads to autoimmunity within human subjects, a recent study investigated these pathways in NOD mice [47]. The authors of this study reveal that the immune response to Cocksackie B4 virus is dependent upon TLR3 signaling as TLR3-deficient mice did not survive infection [47]. In the absence of TLR3 following Cocksackie B4 viral infection there was a decrease in production of pro-inflammatory cytokines which led to uncontrolled viral replication. Macrophages were also shown to play an important role in host protection [47]. This report provides evidence for the cellular mechanisms involved in Cocksackie B4 viral infection and demonstrates a complex interaction between viruses and innate immunity.

Other animal models have also been used to investigate the role of viruses in activation of innate immune responses and T1D development. The BioBreeding diabetes-resistant (BBDR) rat has remained a useful tool for examining T1D pathogenesis since the 1980's [48]. Recently, a study examined the role of innate immune response signaling, specifically looking at TLR9, following Kilham rat virus (KRV) infection in BBDR rats. KRV infection of BBDR rats consistently leads to T1D development in ~25-40% of the rats [4,35,49]. The investigators revealed that KRV infection induces signal transducer and activator of transcription factor (STAT)-1 through TLR9 signaling pathways [35]. The authors further discuss a potential connection with this signaling pathway to T1D through induction of a proinflammatory response in the pancreatic lymph nodes caused by antigen presenting cell (APC) maturation [35]. This innate immune inflammatory response may have the potential to activate APCs and cause presentation of islet antigens to autoreactive T cells, thus leading to β cell destruction and T1D [35].

As discussed above and indicated in current research [35], inflammation driven by the innate immune response following virus infection has the capability to lead to autoreactivity. To examine the components of the inflammatory response following KRV infection in BBDR rats, investigators used DNA microarray analysis and identified 569 upregulated genes in the pancreatic lymph nodes [50]. Analysis of the upregulated genes revealed a preponderance of

proinflammatory genes responsible for the production of cytokines and chemokines [50]. Importantly, this proinflammatory response was not induced by H-1 parvovirus infection, a non-diabetogenic KRV homologue [50]. Although the exact mechanisms linking proinflammatory signaling pathways to β cell destruction remain largely unknown, these results suggest T1D pathogenesis following viral infection may be linked to a proinflammatory microenvironment in the islets of the pancreas [28;50].

Conclusion

The innate immune response is comprised of numerous cellular components designed to protect the human body from foreign pathogens. Because of the essential role innate immunity has in the overall immune system, malfunctions in components of this immune response are detrimental to the host and have the potential to result in development of diseases. T1D is a result of an autoimmune process within the body and pathogenesis of this disease is now being linked to dysregulated signaling by the innate immune response. Although recent research has explored and answered many questions as to the role of the innate immune response in T1D development, the exact signaling pathways which initiate the autoimmune process remain elusive. Continuing efforts by researchers to investigate the cellular components of innate immunity may uncover the mechanisms responsible for initiation of the autoimmune process in T1D. Through manipulation of these molecular mechanisms, novel therapies may be discovered capable of modulating the innate immune response to prevent T1D development.

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