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Potential role of type I interferon in the pathogenic process leading to type 1 diabetes

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Abstract

Purpose—Understanding the relationship between viral infections and the development of type 1 diabetes (T1D) are essential for T1D prevention. Virus-induced innate immune responses, specifically type I interferon (IFN-I) and the IFN gene signature, orchestrate early events of β- cell dysfunction preceding islet autoimmunity. We summarize recent advances in how IFN-I and the IFN gene signature can drive T1D development.

Recent findings—IFN-I, particularly interferon-alpha (IFN-α), and the IFN gene signature have been detected in islets and peripheral blood of T1D patients. T1D risk genes in the IFN-I signaling pathway regulate antiviral responses in β-cells driven by IFN-I and proinflammatory cytokines. Polymorphisms in these genes may cause chronic dysregulated IFN signaling in islets, characterized by hyperexpression of IFN-I, the IFN gene signature and major histocompatibility complex (MHC) class I during viral infection. Islet cell inflammation mediated by aberrant IFN signaling drives β-cell apoptosis by initiating autoreactivity against β-cell antigens. The profound elevation in IFN-I and the IFN gene signature observed in some forms of T1D are also seen in a novel group of human autoimmune and autoinflammatory diseases called interferonopathies.

Summary—Despite significant advances, further studies are required to functionally dissect the mechanisms by which excessive IFN-I contributes to the evolution of autoimmunity that destroys β-cells.

Keywords

Type 1 diabetes; type I interferon; IFN gene signature; innate immunity

Introduction

T1D is a chronic disorder characterized by the immune-mediated destruction of insulin-producing β-cells in pancreatic islets that ultimately leads to insulin deficiency. The immune

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Conflicts of interest

There are no conflicts of interest.

cell infiltration of islets, insulitis, precedes β-cell destruction and classically consists of autoreactive B and T cells, natural killer (NK) cells, macrophages, and dendritic cells (DCs) (1). Both innate and adaptive immune mechanisms lead to the inflammation in β-cells mediated by proinflammatory cytokines and chemokines, activation of β-cell-reactive T cells, and failure of immune tolerance (1). While T1D has a strong genetic component, the differences in the concordance rate between monozygotic twins (2), an increasing incidence of T1D, and geographical and seasonal variance suggest the contribution of nongenetic factors in the pathogenesis of this disease (3). Studies in humans and animal models support the role of enteroviruses, particularly coxsackie B virus (CVB), as a causal environmental determinant (3). In addition, enteroviruses may contribute to fulminant T1D, a subtype of T1D characterized by a rapid onset of insulin-deficiency and severe hyperglycemia without islet-related autoantibodies (3). Genes in the type I interferon (IFN-I) signaling pathway, including interferon induced with helicase C domain 1 (*IFIH1)* and tyrosine kinase 2 (*TYK2)*, are associated with T1D susceptibility (4). IFN-I and IFN-induced gene signatures induced by virus infection in pancreatic islets may provide a connection between enteroviruses and T1D pathogenesis in the early events of disease leading to initiation of the autoimmune assault against β-cells. This review discusses and summarizes recent advances towards understanding the role of virus-induced, IFN-I-initiated innate immunity in the early phase of T1D pathogenesis. In addition, Table 1 provides a glossary of key terms used in the review.

Virus-activated innate immune responses and the IFN-I pathway

The innate immune system consists of pattern-recognition receptors (PRRs) which detect conserved pathogen-derived structural motifs known as pathogen-associated molecular patterns (PAMPs) (5). PRR-activated signaling following recognition of viral PAMPs establishes an effective immune response driven by IFN-I (α, β), IFN-II (γ), and IFN-III (λ1-4), and induces IFN-stimulated genes (ISGs) which encode mediators for establishing an antiviral and inflammatory state in the host (5). The multigene family of human IFN-I consists of IFN-α (13 variants), IFN-β, and several less-defined members (IFN-k, -ε, and -w) which signal through the cognate IFN-α/β receptor (IFNAR) comprised of the IFNAR1 and IFNAR2 subunits (6). Blood leukocytes and fibroblasts as well as plasmacytoid DCs secrete IFN-I (6). The differential tissue expression and PRR preference of IFN-I and unique binding affinities to IFNAR result in diverse antiviral, antiproliferative, and immunomodulatory outcomes (6). Canonical binding of IFN-I to IFNAR activates the phosphorylation of tyrosine kinases Janus kinase 1 (JAK1) and TYK2 which phosphorylate the cytoplasmic effectors signal transducer and activator of transcription 1 (STAT1) and STAT2, leading to dimerization and interaction with interferon regulatory factor 9 (IRF9) to form the interferon-stimulated gene factor 3 (ISGF3) complex (5). Upon nuclear translocation, the ISGF3 complex binds to IFN-stimulated response elements in ISG promoters to coordinate the transcriptional induction of hundreds of ISGs (5). *IFIH1*, DExD/H-box helicase 58 *(DDX58)*, and *TLR3* are also instantly upregulated as ISGs for enhanced viral detection and IFN signaling. ISG protein products, including myxovirus resistance 1 (MX1), ISG15, protein kinase R (PKR), 2′,5′-oligoadenylate synthetase (2′,5′-OAS), and many others, primarily act to restrict viral entry, replication, and release; they may also function to regulate the production of various cytokines and chemokines to

orchestrate innate and adaptive responses in various biological and pathological settings. This pattern of upregulated ISGs following IFN-I stimulation, termed the IFN gene signature, is detectable by transcriptome analysis (7).

The IFN-activated inflammatory response is further amplified by recruitment of innate immune cells including macrophages, monocytes, NK cells, and DCs that secrete inflammatory molecules and establish an effector immunological response by antigen presentation to lymphocytes (5). Innate immune responses are likely activated through viral-activated PRRs during β-cell autoimmunity. Endosomal Toll-like receptors (TLRs) are expressed in islets and their activation by viral replication intermediates results in production of IFN-I (8). The *IFIH1*- encoded melanoma differentiation-associated protein 5 (MDA5) and *DDX58*-encoded retinoic acid-inducible gene I (RIG-I) are cytosolic sensors. Both sensors contain a helicase domain that binds RNA ligands derived during viral replication (9) and a caspase activation and recruitment domain required for mitochondrial antiviral signaling protein (MAVS) downstream signaling (9). MAVS signaling leads to the phosphorylation and nuclear translocation of IRF3 or IRF7 and activation of the nuclear factor kappa B (NF-κB) pathway. This is followed by transcriptional induction of IFN-I and IFN-III and activation of ISGs, proinflammatory cytokines, and antigen presentation for antiviral immunity (9). MDA5 senses double-stranded RNA (dsRNA), polyinosinic:polycytidylic acid (poly I:C), and CVB (10, 11). Compelling data on *IFIH1* suggest its critical role for the regulation of innate immune responses in T1D, discussed below.

IFN-I pathways and T1D susceptibility

More than 50 genetic loci are implicated in T1D development. The strongest genetic determinant of T1D, human leukocyte antigen (HLA) class II genes, confer ~50% genetic predisposition for disease development. Non-HLA loci are also linked to T1D (12). Novel candidate genes, identified by genome-wide association studies, have several naturally occurring single-nucleotide polymorphisms (SNPs) associated with T1D susceptibility (12). These variants are thought to influence T1D development through modulation of innate and adaptive immunity, inflammatory responses, apoptosis, endocrine function, and responses to environmental cues (13).

Both protective and risk variants of *IFIH1* have been identified in T1D and other autoimmune diseases (14–16). A common risk variant of *IFIH1* is a non-synonymous SNP (nsSNP) at rs1990760 associated with multiple autoimmune disorders including T1D (17). This variant causes the substitution A946T within MDA5 and is present at an allelic frequency of ~57% in European populations (18). Homozygous T946/T946 increases the risk of T1D by 35% compared to the non-predisposing A946 allele (19). Peripheral blood mononuclear cells (PBMCs) from healthy donors homozygous for the risk variant allele *IFIH1* A946T and cell lines expressing it display elevated basal and poly I:C-triggered IFN-I production (18). T1D-protective variants of *IFIH1* are predicted to be complete or partial loss-of-function mutations, leading to reduced IFN-α/β response. Two such variants, E627* and I923V, are associated with reduced IFN-I levels in poly I:C-stimulated PBMCs of T1D patients (20). SNPs identified in *TYK2* are also associated with multiple autoinflammatory

and autoimmune disorders including T1D (21, 22). The nsSNP rs2304256 may confer protection against T1D by reducing TYK2 function (22). This SNP causes a missense mutation in the JAK-homology 4 region, a region critical for interactions between TYK2 and interferon alpha and beta receptor subunit 1 (IFNAR1). Knocking down *TYK2* in human β-cells resulted in diminished levels of poly I:C-induced IFN-α production and IFN-α-induced MHC class I expression (23). A *TYK2* promoter variant has been associated with an enhanced risk for T1D (24).

The molecular mechanisms by which loss-of-function or gain-of-function loci specific to innate immune responses influence T1D development continue to be defined. Given that ~80% of T1D susceptibility genes (13), including innate immune genes, are expressed in pancreatic islet β-cells, β-cells may play a direct role in mediating the early events related to T1D pathogenesis. Therefore, it is crucial to understand how β-cells are influenced by the innate immune response leading to their destruction.

Viral triggers initiating T1D

Enteroviruses are a prime candidate environmental trigger of T1D. CVB is a suspected causal factor for T1D based on seroepidemiological, histological, and experimental data (25). Epidemiological studies support a role for viral infections in T1D development; specifically, geographic variation in incidence, seasonality of disease presentation, and an increased incidence of T1D follow enterovirus epidemics (26). Both enterovirus IgM antibodies and viral RNA are frequently detected in blood of individuals with recent-onset T1D compared with healthy controls (27–30). In the Diabetes and Autoimmunity Study in the Young (DAISY), children positive for islet autoantibodies and enteroviral RNA in blood reportedly progress to diabetes faster compared to children with islet autoantibodies alone (31). Staining of postmortem pancreatic specimens from T1D patients reveals viral proteins (32, 33). Enteroviral RNA detection precedes islet autoimmunity by several months in genetically susceptible T1D children from a prospective longitudinal study (Diabetes Prediction and Prevention Project, DIPP) (34). In prospective studies, such as the Environmental Triggers of T1D Study, enteroviruses are frequently detected in the blood of T1D patients at the islet autoantibody seroconversion stage compared to healthy controls (35). Pancreatic β-cells from T1D donors contain CVB4 particles, viral capsid protein, and reduced levels of insulin (36). The presence of sustained, low-grade CVB in biopsies from islets of freshly isolated pancreatic tissue from living recent-onset T1D patients is reported by the Diabetes Virus Detection (DiViD) study (37). Increased frequency of coxsackie and adenovirus receptor (CAR) expression is observed in the pancreatic islets of both T1D and autoantibody-positive non-diabetic donors compared to non- diabetic controls, suggesting that enhanced CAR expression promotes virus spread to islets during T1D pathogenesis (38). Children with incompetent antibody responses against CVB capsid proteins develop early insulin-targeting autoimmunity with impaired ability to clear CVB infections in early childhood (39). Moreover, in the Environmental Determinants of Diabetes in the Young (TEDDY) study, recent respiratory infections in young children are associated with increased risk of islet autoimmunity (40). Similarly, early childhood infections are linked to islet autoimmunity and progression to T1D in children having HLA-conferred T1D risk (41).

Despite abundant data suggesting associations between enteroviral infection and T1D, proof of causality is lacking. Specific mechanisms by which viruses trigger T1D are unknown, but viral infections may modulate immune responses in susceptible individuals to promote T1D.

The role of IFN-I and the IFN gene signature in T1D

IFN signaling is implicated in the initiation of islet autoimmunity and development of T1D (42, 43). Enhanced IFN-α was first reported by Foulis *et al.* in pancreata removed at necropsy from recent-onset T1D diabetes (44). Subsequent reports show that treatment of hepatitis C virus (45) or hairy cell leukemia with IFN-α therapy (46) is associated with T1D development. Pancreatic islets isolated postmortem or from biopsies from T1D patients reveal the presence of IFN-I (36, 47), cytokines (48, 49), or ISGs (50). Elevated levels of IFN-α have been detected in sera of T1D patients (51, 52). Lundberg *et al.* report increased expression of ISGs in insulitic islets from pancreatic biopsies of patients with recent-onset T1D participating in the DiViD study (50). Independent work identifies a strong IFN gene signature in peripheral blood samples from genetically predisposed children prior to development of autoantibodies from two longitudinal birth cohorts, the BABYDIET cohort (53) and DIPP (54). In the BABYDIET cohort, Ferreira *et al.* temporally associate an IFN-signature with recent episodes of upper respiratory tract infections and note that the signature is strongest prior to seroconversion and begins to decline after detection of autoantibodies (53). Most recently, Meyer *et al.* report the presence of self-reacting neutralizing antibodies against IFN-α in autoimmune regulator (AIRE)-deficient patients that conferred protection against T1D development while those patients lacking anti-IFN-α antibodies progressed to T1D (55).

Studies conducted more than three decades ago have shown the overexpression of HLA-class I (MHC-I) and IFN-α in human pancreatic tissues (44, 56, 57). More recent data from the Network for Pancreatic Organ Donors with Diabetes, DiViD, and archival collection of postmortem samples demonstrate hyperexpression of HLA class I RNA and protein in insulin- containing β-cells from T1D patients (57). Hyperexpressed HLA class I is strongly associated with increased expression of STAT1 in all these cohorts (57). Prior to the symptomatic phase of T1D, β-cells undergo critical pathological changes (58). Two recent studies independently analyzed effects of IFN-α on endoplasmic reticulum (ER) stress in β-cells. One report shows that IFN-α treatment of either human islets or the human β-cell line EndoC-βH1 upregulates ER stress markers and slows the conversion of proinsulin to insulin (59). Another demonstrates the crucial contribution of IFN-α in the early phases of diabetes as a common mediator of HLA class I hyperexpression, excessive inflammation, and elevated expression of ER stress markers (60).

The growing evidence from recent studies supports IFN-α-mediated immune effects, including hyperexpressed HLA class I, in the early pathogenic events in T1D. The presence of IFN-I signature in the early events leading to T1D and its absence in protected individuals strongly implicates viruses in T1D.

IFN-III: an additional companion to IFN-I in T1D pathogenesis

The host antiviral innate immune defense also includes IFN-III (IFNλ1-4). IFN-I and IFN-III induce similar sets of genes following infection, but while IFN-I acts globally by targeting almost all nucleated cells, IFN-III utilizes a distinct receptor complex and acts primarily on mucosal epithelial cells (61). Human primary islets produce IFN-III following infection with CVB3 and treatment of islets with IFN-III results in upregulation of ISGs (62). Domsgen *et al.* report a role for the common T1D-associated rs1990760 SNP in *IFIH1* in regulating IFN-III-related responses in islets following CVB3 infection (63). Human islets carrying the protective *IFIH1* genotype T946A have significantly elevated IFN-III and ISG responses to CVB infection compared to islets carrying the risk-conferring genotype A946T. Novel findings from this study emphasize the need to focus on the immunomodulatory role of IFN-III with respect to host immune response to virus infections in T1D pathogenesis.

Dysregulated IFN: making a case for T1D interferonopathy

Type I interferonopathies are a group of rare Mendelian disorders of abnormal upregulated IFN-I that lead to autoinflammation and/or autoimmunity (64). While the inappropriate overproduction of IFN-I is a central common phenotypic feature, they originate from molecular defects in genes of functionally diverse biological pathways affecting IFN-I regulation (64). The upregulated IFN-I and IFN gene signature are associated with sporadic autoinflammatory and autoimmune diseases including systemic lupus erythematosus (SLE) (7, 65). Multiple autoimmune disorders including T1D and SLE exhibit significant genetic overlap (66). Indeed, SLE has been described as an interferonopathy with an “overlapping IFN gene signature with T1D” (67). Although definitive proof for an IFN-related clinical phenotype in T1D pathogenesis is lacking, a conceptual model in which IFN signaling acts as a common central player in the early stages of T1D is highly conceivable. Viruses such as CVB could establish a persistent infection in β-cells in genetically predisposed individuals, creating a diabetogenic environment, characterized by continuous production of IFN-I to sustain local inflammation of the pancreatic islets, eventually leading to islet autoimmunity.

Therapeutic implications: targeting IFN-I in T1D

Given that excessive IFN-I could contribute to T1D development, blocking or downregulating IFN-I signaling could be effective in halting its pathogenesis. A human monoclonal antibody (mAb) targeting multiple IFN-α subtypes was effective in a recent phase IIb clinical trial in SLE patients (68). In addition, IFN-α kinoid, a therapeutic vaccine that induces anti-IFN-α antibodies, is currently in preclinical development for SLE (69). Broad targeting of all IFN-I family and downstream ISGs is achievable with anti-IFNAR mAbs. A human mAb against the IFNAR1 subunit showed reduced disease activity in patients with SLE in a recent phase IIb clinical trial (70). Inhibition of JAK with specific inhibitors provides another feasible potential therapeutic target in T1D (71). One caveat of IFN-I blockade is an increase in viral infections, as was observed during clinical trials of IFN-I inhibition in SLE patients (68). To circumvent this issue, vaccines against viruses that potentially contribute to T1D development could be administered early in life (72).

Conclusion

Through studies on human T1D patients and experimental models, significant progress has been made towards understanding underlying mechanisms of IFN-I signaling in T1D pathogenesis. Further insights are required regarding the regulation and function of IFN-I signaling and related PRRs and mediators during T1D development. In particular, which IFN-I subtype(s), viral sensor(s), and cell type(s) play critical roles in T1D development and what underlying molecular mechanisms contribute to the complex interplay of virus, IFN-I signaling networks, and genetic susceptibility remain incompletely defined. Additional work is needed to maximize the potential of targeting IFN-I to prevent T1D.

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KEY POINTS

- T1D-predisposing alleles of genes in the IFN-I signaling pathway initiate and sustain an immunologically abnormal level of IFN-I in β-cells in response to specific viral infections.
- IFN-α, the IFN gene signature, and MHC class I expression are involved in the modulation of hyperinflammatory responses in T1D patients and in experimental models.
- Upregulated IFN and the IFN gene signature are features of β-cells in the early phase of diabetes and are followed by islet inflammation and autoimmunity.
- Blocking IFN in the early phase in prediabetic individuals can be an effective T1D preventive strategy.

Table 1

Glossary of terms

Term	Description
Coxsackie B virus (CVB)	Coxsackieviruses are ubiquitously circulating, single-stranded RNA, linear, positive-sense, nonenveloped viruses belonging to the human enteroviruses (HEV) genus of the family *Picornaviridae*. Group B Coxsackieviruses (CVB; species HEV-B) include six serotypes, B1-6. CVB can infect cells of heart, pancreas and gut due to the presence of the coxsackievirus and adenovirus receptor (CAR) and can cause severe encephalitis, myocarditis, and pancreatitis and may contribute to the initiation of islet autoimmunity in case of T1D.
IFN-stimulated gene factor 3 (ISGF3) complex	An interferon (IFN) signaling pathway-induced heterotrimeric signal transduction and transcription activation complex present in the cytoplasm comprised of three proteins: the heterodimeric STAT1 and STAT2 and IRF9. Upon nuclear translocation, ISGF3 binds to an IFN-stimulated response element (ISRE) present in the promoters of IFN-stimulated genes (ISGs) to induce their transcription.
Mitochondrial antiviral signaling protein (MAVS)	A downstream transmembrane adaptor protein that is found primarily on mitochondria. Following sensing of pathogens by RIG-I-like receptors, MAVS is activated to mediate interaction with downstream signaling molecules, leading to the activation and nuclear translocation of the transcription factors such as IFN regulatory factor 3/7 (IRF3/7) and NF-κB and the subsequent expression of type I IFNs, inflammatory cytokines and IFN-stimulated genes.
Pathogen-associated molecular patterns (PAMPs)	Different types of conserved molecular, usually structural, motifs associated with specific pathogens that are sensed by specific PRR(s).
Pattern recognition receptor (PRR)	A host receptor localized on the cell surface, endosome or cytosol, that recognizes the presence of non-self, pathogen-associated molecular patterns (PAMPs) and initiate multiple signaling cascades to induce immune responses such as the production of type I IFNs and proinflammatory cytokines. Examples include the Toll-like receptors (TLRs; located on the cell membrane or endosomes) and RIG-I like receptors (RLRs; located in the cytosol).
RIG-I-like receptors (RLRs)	Conserved RNA helicases located in the cytosol that function as viral RNA receptors and includes the melanoma differentiation-associated gene 5 (MDA5; encoded by *IFIH1*) and the retinoic acid-inducible gene I protein (RIG-I). MDA5 and RIG-I contain a central DExD/H box helicase domain and C-terminal domain (CTD) for RNA binding and N-terminal caspase activation and recruitment domain (CARD) required for downstream innate immune signal transduction through mitochondrial antiviral-signaling protein (MAVS).