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Clinical Immunology 111 (2004) 225–233
CLINICAL IMMUNOLOGY
www.elsevier.com/locate/yclim

Short Analytical Review

Interferon alpha—a potential link in the pathogenesis of viral-induced type 1 diabetes and autoimmunity

D. Devendra and G.S. Eisenbarth*

Barbara Davis Center for Childhood Diabetes, University of Colorado Health Sciences Center, Denver, CO 80262, USA

Received 2 January 2004; accepted with revision 20 January 2004

Available online 20 March 2004

Abstract

The incidence of type 1 diabetes has been rapidly rising. Environmental factors such as viruses have been implicated as a possible agent accounting for this rise. Enteroviruses have recently been the focus in many research studies as a potential agent in the pathogenesis of type 1 diabetes. The mechanism of viral infection leading to β cell destruction not only involves multiple pathways but also the cytokine-interferon alpha (IFN-α). Our hypothesis is that activation of toll receptors by double-stranded RNA or poly-IC (viral mimic) through induction of IFN-α may activate or accelerate immune-mediated beta cell destruction. Numerous clinical case reports have implicated that IFN-α therapy is associated with autoimmune diseases and that elevated serum IFN-α levels have been associated with type 1 diabetes. In multiple animal models, given specific genetic susceptibility, poly-IC can induce insulitis or diabetes. Therapeutic agents targeting IFN-α may potentially be beneficial in the prevention of type 1 diabetes and autoimmunity.
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Keywords: Interferon alpha; Type 1 diabetes; Autoimmunity

Introduction

Type 1 diabetes results from the T cell-mediated destruction of β cells of the pancreas with evidence of islet beta cell-specific autoimmunity [1]. With the recent increase in the incidence of type 1 diabetes worldwide, many investigators have been searching for environmental triggers that could potentially play a role in the pathogenesis of the disease. For more than 100 years, viruses have been implicated in the aetiology of type 1 diabetes. The mechanism of viral infection leading to β cell destruction is becoming clearer and the potential role of viral infection inducing the cytokine-interferon alpha (IFN-α) has been implicated in diabetes pathogenesis. There have also been human clinical case reports supporting the association of IFN-α therapy and the appearance of type 1 diabetes or islet autoantibodies, strengthening the link with viruses. In this review, we highlight the evidence that virus-induced IFN-α is implicated in the pathogenesis of type 1 diabetes and that potential therapies that are able to neutralize IFN-α may be able to suppress the disease. The simplest hypothesis we will emphasize is that activation of toll receptors by double-stranded RNA or poly-IC (viral mimic) through induction of cytokines such as interferon alpha may activate or accelerate immune-mediated beta cell destruction.

Increasing incidence of type 1 diabetes

The prevalence of diabetes is rising rapidly, especially in industrialized countries, and is also presenting at a much earlier age in children [2,3]. While the majority of attention has been focused on the increase in type 2 diabetes, there has also been a parallel rise in type 1 diabetes [4]. This is illustrated in Fig. 1 by using the Yorkshire region in the United Kingdom as an example. In the northern hemisphere, it has consistently been found that more cases of type 1 diabetes are diagnosed during autumn and winter [5,6], suggesting that epidemics of viruses may be responsible for this trend. An epidemiology study of type 1 diabetes in Philadelphia indicated that an epidemic of type 1 diabetes

* Corresponding author. Barbara Davis Center for Childhood Diabetes, University of Colorado Health Sciences Center, 4200 East 9th Avenue, Box B140, Denver, CO 80262. Fax: +1-303-315-4892.
E-mail address: George.Eisenbarth@UCHSC.edu (G.S. Eisenbarth).

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doi:10.1016/j.clim.2004.01.008

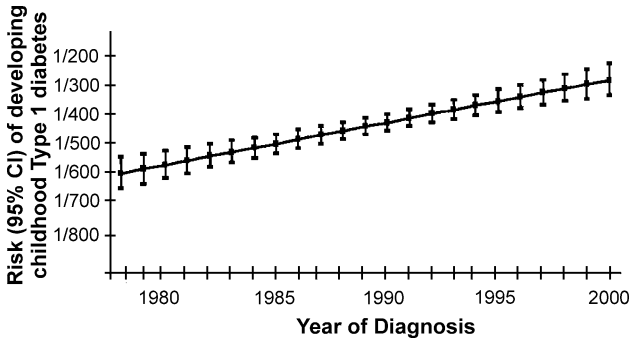

Fig. 1. Risk of developing childhood (0–14 years) type 1 diabetes in Yorkshire, UK (1978–2000) (taken from Feltbower, R.G., et al. Type 1 diabetes in Yorkshire, UK: time trends in 0–14- and 15–29-year-olds, age at onset and age-period-cohort modelling. *Diabetic Medicine* 20 (6) 437–441).

was observed approximately 2 years after a measles epidemic [7]. The increase in the incidence of type 1 diabetes in such a short period has led to the impression that an environmental agent may play a role in the pathogenesis of type 1 diabetes [8]. Two not mutually exclusive hypotheses are decrease in environmental factors that increase diabetes risk versus increase in factors that increase risk. The concordance for type 1 diabetes is approximately 40–50% for monozygotic twins [9], suggesting that environmental factors such as viruses, diet, and β cell toxins may be involved in the initiation. Two recent reports indicate that the age in infancy of introduction of cereal influences the incidence of islet autoimmunity in genetically susceptible individuals [10,11]. Twin and other family studies indicate that genetic factors alone cannot explain the aetiology of type 1 diabetes. Seasonality, increasing incidence and potential epidemics of type 1 diabetes as well as numerous cross-sectional and retrospective studies suggest that certain viruses and some aspects of early childhood diet may contribute to type 1 diabetes. On the contrary, some may argue that children are now being exposed to a very sterile environment (e.g., introduction of vaccines, sanitation, less overcrowding at home) and that potential environmental suppressers of type 1 diabetes are missing from our current environment. This oversimplification is the basis of the "hygiene hypothesis" [12]. An interplay between genetic susceptibility and environmental triggers or suppressers is thought to provide the fundamental element for disease and provides potential targets for both disease prediction and prevention [1]. Studies measuring the expression of diabetes-related autoantibodies in young children from birth document that the appearance of these markers predicts the future development of type 1 diabetes [13–15]. The long prodromal phase preceding the onset of type 1 diabetes suggests that there is an opportunity to predict and design trials for the prevention of the disease [1]. Therefore, if a viral link is confirmed, vaccines can be introduced during this "pre-diabetes" phase and prevent the further destruction of β cells.

Viruses, vaccines, and type 1 diabetes

The first documented association between viruses and type 1 diabetes was the link with mumps virus [16]. Before the worldwide use of vaccines against mumps, this virus had been implicated in the pathogenesis of type 1 diabetes [17]. Currently, there are many other viruses associated with type 1 diabetes and Table 1 lists some of them. The only confirmed viral link to human type 1 diabetes is congenital rubella infection. Intrauterine exposure leading to congenital rubella syndrome is associated with diabetes, which may appear many years after the original exposure [18]. With the widespread use of vaccines, this virus is unlikely to be a major causative agent in the pathogenesis of type 1 diabetes today. Perhaps some may argue that the introduction of viral-specific vaccines may account for the increase in the incidence of type 1 diabetes, but to date, various epidemiological studies have not shown an association [19].

Attention has recently been focused upon the role of enteroviruses as a possible agent in the pathogenesis of type 1 diabetes. The coxsackie virus, particularly coxsackie B4, has been implicated as a possible causative agent in type 1 diabetes. Antibodies to these viruses were more prevalent in newly diagnosed type 1 diabetes patients and especially in the 10–18-year-old age group when compared with control subjects [20,21]. More than 15 studies have confirmed this association although multiple

Table 1
A summary of studies examining the association of viruses and immunizations with type 1 diabetes (adapted from Devendra D., Liu E., and Eisenbarth G.S. Type 1 diabetes: BMJ in preparation)

Agent	Study	Effect
Viruses		
Enterovirus	DIME study (Finland)	Associated with diabetes autoantibodies
	Swedish study	In utero infection associated with T1D
	DAISY study (US)	No association with T1D
Mumps, rubella, measles, chickenpox, rotavirus	Multiple studies from different countries	Associated with diabetes autoantibodies
Immunization		
BCG	Swedish study	None of these studies showed a positive association between vaccinations with autoimmunity or T1D
Common childhood vaccinations	EURODIAB study	
Hemophilus influenzae; diphtheria, tetanus, and as above	BabyDIAB (Germany)	
Hepatitis B, Hemophilus influenzae b, polio, and diphtheria tetanus pertussis	DAISY (US)	

studies have not been able to confirm this finding [22]. Although there may be some methodological limitations to some of these studies, enteroviruses remain a strong candidate as a possible environmental trigger in type 1 diabetes. The presence of enterovirus RNA in peripheral blood cells of most newly diagnosed type 1 diabetes children supports the hypothesis that a viral infection acts as an important exogenous factor [23]. There have been studies showing that exposure to coxsackie B4 has led to the diagnosis of diabetes in one member of a family and followed rapidly in another member of the same family [24,25]. In another case, a set of two 14-month-old twins developed diabetes within 12 days of each other after being exposed to echovirus 6 [26]. As mentioned previously, there appears to be a seasonality effect on the onset of type 1 diabetes with a peak in autumn and winter. A recent study from Finland indicated that the appearance of diabetes-associated autoantibodies had a similar pattern [27].

Coxsackie B4 strains have been studied to detect the nucleotide sequences of a virus that may be diabetogenic. In one study, 25 nucleotide differences were noted in the diabetogenic virus compared with the prototype CB4 virus. The authors suggested that nucleotide changes in the non-coding region of the genome are of particular importance in altering the replication rates [28]. In another study, more extensive changes (111 amino acid substitutions) were observed in a diabetogenic strain of the coxsackie B4 virus (from a human source). Capsid proteins VP1 and VP2 showed the largest changes from the prototype virus [29]. Probably the most convincing evidence comes from studies that describe the isolation of viruses from the pancreas of patients that died from acute onset of type 1 diabetes [30,31]. The viruses isolated were able to transfer disease to animal models. In the examination of pancreas obtained from non-diabetic organ donors, a subject with positive islet autoantibody was found to have beta cell-specific positivity for VP-1 and IFN-α, whereas islet autoantibody negative subjects did not show this particular staining [32].

A Swedish diabetes registry indicated that IgM and IgG enterovirus antibodies were detected in more mothers who gave birth to diabetic children compared to control mothers [33]. This study and studies looking at congenital rubella syndrome stress the importance of the intrauterine environment in the pathogenesis of type 1 diabetes. Similarly, a case of neonatal diabetes (positive islet autoantibodies) was associated with a mother who was exposed to echovirus 6 during pregnancy [34]. In a large Finnish series, levels of antibodies to enterovirus were greater in the mothers of children who had diabetes before the age of 3 years [35]. Based on the cumulative evidence available, a spectrum of enteroviruses of the coxsackie and echo type may be associated with type 1 diabetes, with coxsackie B4 being the most common. Another viral strain, the Kilham rat virus (KRV), causes autoimmune diabetes in diabetes-resistant (DR)-BB rats without direct infection of the β cells of the pancreas. The infection of DR-BB rats with KRV resulted in the disruption of Th1-like $CD45RC^{+}CD4^{+}$ and Th2-like $CD45RC^{-}CD4^{+}$ T cells that lead to selective activation of β cell cytotoxic effector T cells [36].

Studies with animal models indicate that under some circumstances, viral infection can actually prevent the development of diabetes. In the NOD mouse, multiple different infections (viruses, mycoplasma, and even worms) and even a simple injection of complete Freund's adjuvant can prevent diabetes. Viruses such as encephalomyocarditis (EMC)-D and lymphocytic choriomeningitis virus (LCMV) can prevent or decrease the incidence of diabetes [37]. It is thought that infection with LCMV, for instance, may deplete a subpopulation of $CD4^{+}$ T cells though the specific mechanism by which disease is prevented, is unknown.

The mechanism of viral-induced diabetes

Many different possible mechanisms may lead to β cell damage by viruses. Viruses may directly infect and destroy β cells of the pancreas or act indirectly by triggering autoimmunity. Viruses such as EMC-D can induce type 1 diabetes by directly infecting and destroying β cells through cytolysis. Although a direct viral infection of the β cells may not be necessary to induce insulitis or diabetes, infection of the surrounding tissue may lead to β cell destruction by the release of immune mediators such as cytokines [38,39]. In contrast, retroviruses may infect beta cells and induce antigens leading to specific beta cell autoimmunity. Viruses such as coxsackie virus can infect β cells and induce the expression of IFN-α and subsequently chemokines that will stimulate lymphocytes to home to pancreatic β cells leading to β cell destruction. Fig. 2 gives an overview on the potential mechanisms involved in the viral pathogenesis of type 1 diabetes.

A popular model of a viral pathogenesis invokes molecular mimicry. According to this model, an initial response to viral proteins or antigens which may share similarities to self-tissues (e.g., β cells of pancreas) will provoke an immune response that will destroy self-tissue in the body after clearance of the virus [40]. This concept has been postulated as a possible mechanism of coxsackie virus infection in type 1 diabetes due to a sequence homology between the viral non-capsid protein P2C and GAD [41]. Antibodies to P2C were detected in serum of type 1 diabetes patients, and 80% of these patients reacted with GAD 65 (residues 256–268) [42]. This finding was substantiated with T cell response to the peptide P2C and GAD 65 reactivity being seen in three individuals [43]. However, other studies have not shown that this region of GAD can cross react with native viral

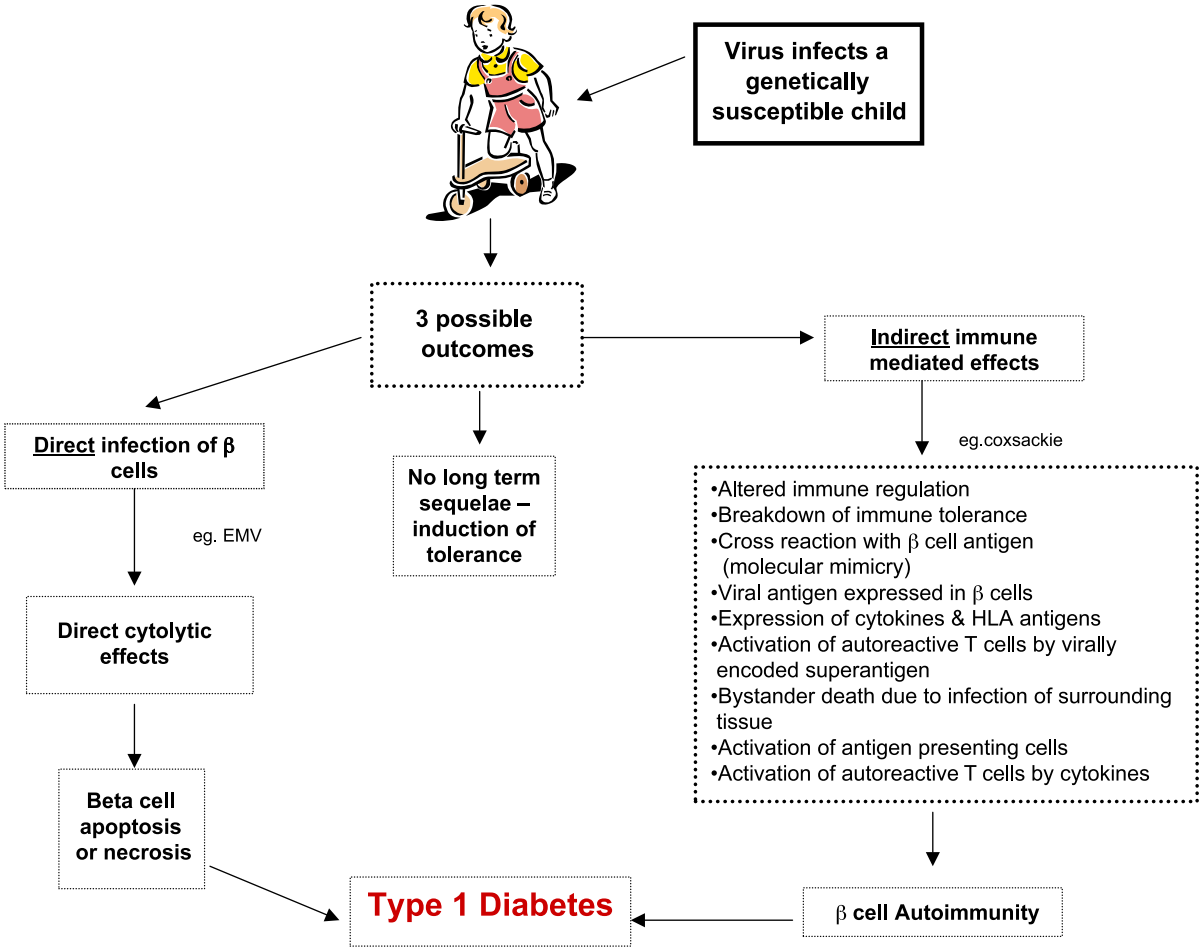

Fig. 2. Mechanisms of viral-induced type 1 diabetes.

antigens of Coxsackie B1–6, rubella, or cytomegalovirus [44]. Although molecular mimicry is an attractive model for viral pathogenesis of autoimmune diseases, there has been no convincing data that clearly demonstrate that mimicry is important in the development of type 1 diabetes [45].

IFN-α: biological effects and role in the pathogenesis of type 1 diabetes

The interferons have been grouped into two classes—type I (IFN-α, IFN-β) and type II (IFN-γ). The human genome contains more than 20 different IFN-α genes [46]. It is unclear why there is a great diversity of IFN-α, but it has been hypothesized that the different genes provide a wide range of responses to a variety of different environmental triggers [47]. Mice lacking the receptor for IFN-α are susceptible to various viruses, confirming the antiviral activity of IFN-α [48]. Many reports suggest that IFN-α acts on dendritic cells to mature and efficiently induce a T cell response [49]. Although almost all cells can produce IFN-α, human plasmacytoid dendritic cells (pre-dendritic cells) are a major source of IFN-α upon exposure to viruses [50,51]. However, some experiments suggest that plasmacytoid dendritic cells are not essential for the IFN-α response to certain viruses, therefore suggesting the existence of alternative interferon-producing cells in vivo [52]. Nevertheless, dendritic cells are important in bridging the innate and adoptive immune responses. Besides the action of IFN-α on dendritic cells, this cytokine has numerous effects on the immune system including the upregulation of MHC class I molecules, upregulation of chemokines, natural killer cell activation, and stimulating CD8 T cell proliferation [53]. A recent study indicated that expressing the suppressor of cytokine signalling 1 (SOCS-1) gene in beta cells of the pancreas suppressed IFN-α signals and accelerated coxsackie virus-induced diabetes in NOD mice [54], thus confirming the antiviral role of IFN-α. A group of endogenous negative regulatory factors of IFN-α called interferon regulator factor (IRF) may also play a role in the regulation of IFN-α response [55]. However, their exact role in type 1 diabetes and autoimmunity has not been elucidated.

While viruses are the most potent inducer of IFN-α, other agents such as bacteria, interleukin-2, hypoxia, IFN-γ, polyanions DNA or RNA, and vasoactive intestinal peptide

are capable of inducing IFN-α. The viral double-stranded RNA present during infection interacts with Toll-like receptor 3 (TLR-3) activating MyD88 adaptor molecule and the protein kinase activated dsRNA (PKR). Subsequently, other pathways are activated including the NFκB pathway, which leads to apoptosis of the cell. Fig. 3 demonstrates a schematic diagram outlining the role of virus and IFN-α in the pathogenesis of type 1 diabetes. Apoptosis is a potent inducer of IFN-α expression, but IFN-α itself can induce apoptosis [56]. Some gene products such as PKR, oligoadenylate synthase (OAS), and RNAse L appear to contribute to the anti-viral effects after IFN-α activation (see Fig. 3). IFN-α leads to RNA degradation through the OAS–RNAse L system and decrease protein synthesis throughout the activation of PKR. Although the anti-viral defense system targets double-stranded viral RNA, other normal cellular function can be affected. For instance, in tissue culture, IFN-α can decrease insulin synthesis and secretion [57,58]. Human beta cells of the pancreas show more marked induction of OAS than alpha cells that secrete glucagon [59,60]. These findings may be a possible explanation for some of the predeliction of beta cells to autoimmune destruction.

A viral mimic poly-IC (poly inosine–cytosine), an IFN-α inducer, induces diabetes in diabetes-resistant (BB) rat, other rat strains with RT1-U MHC alleles, and in streptozocin-treated mice [61,62]. Poly-IC also induces diabetes in transgenic mice in which beta cells express the co-stimulatory molecule B7.1 [63]. "Normal" Balb/c mice when immunized with an insulin B-chain peptide B:9–23 develop insulin autoantibodies but do not develop insulitis. When poly-IC is added with the B:9–23 peptide, insulitis develops, though the mice do not progress to diabetes [63]. New Zealand Black (NZB) mice also develop insulitis and insulin autoantibodies when immunized with the B:9–23 insulin peptide with poly-IC [64]. Multiple RNA viruses may act like poly-IC in a susceptible host. Of note, treatment of NOD mice with poly-IC prevents diabetes, suggesting a paradox in the biological function of IFN-α as a possible anti-inflammatory cytokine [65]. Similarly, oral IFN-α suppressed autoimmune diabetes when administered to NOD mice and has also been suggested in human studies to prolong the honeymoon period in newly diagnosed type 1 diabetes subjects [66,67]. A phase II randomized, placebo-controlled trial is currently underway to confirm this observation [68].

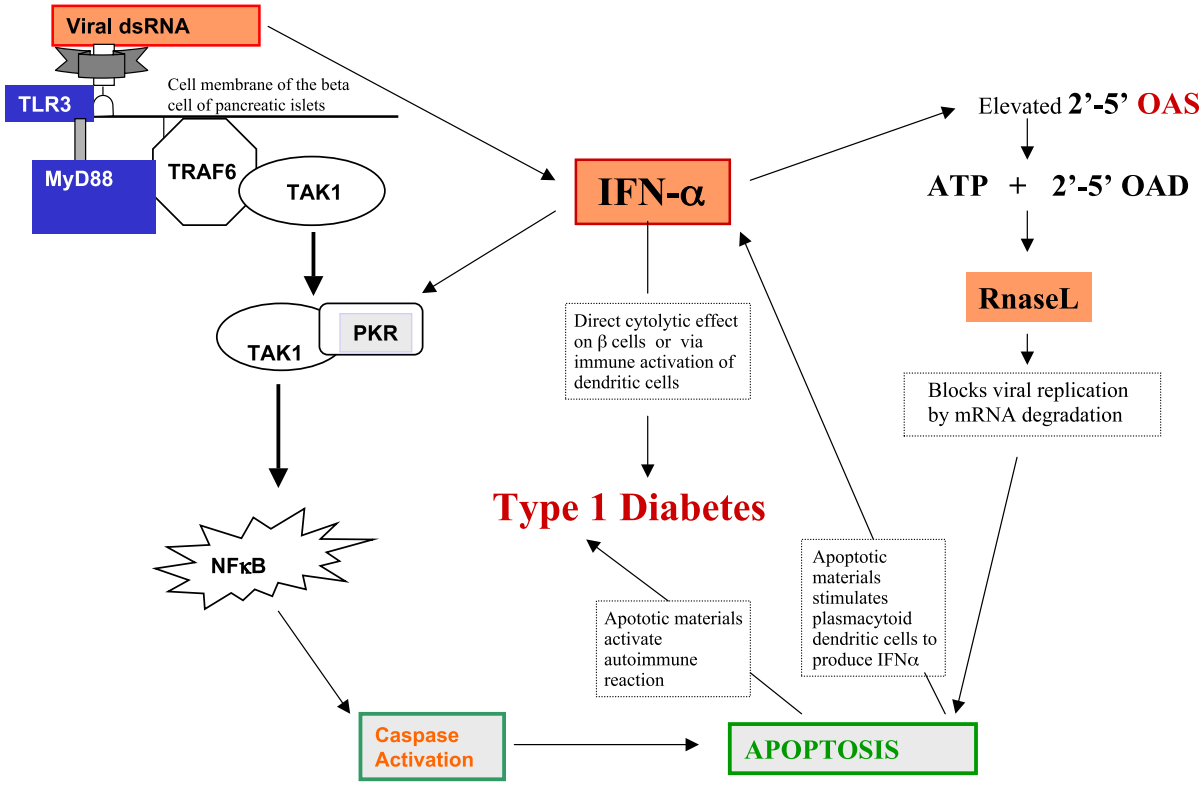

Fig. 3. The cellular and molecular pathways of viral dsRNA and interferon alpha inducing type 1 diabetes. Viral dsRNA activates the toll-like receptor-3 (TLR3) and via various differentiating factors activates the nuclear factor NFκB to induce apoptosis. Viral dsRNA also activates the production of IFN-α in various cells, which is directly cytotoxic to beta cells of the pancreas. IFN-α also induces apoptosis by activating the oligoadenylate synthase (OAS)–RnaseL pathway and the protein kinase R (PKR) pathway. Apoptotic materials induce more IFN-α and activate the immune system. Abbreviations: TAK-1, transforming growth factor β activated protein kinase 1; TLR-3, toll-like receptor 3; MyD88, myeloid differentiation factor; PKR, protein kinase R; OAS, oligoadenylate synthase; TRAF-6, tumor necrosis factor receptor associated factor 6; NFκB, nuclear factor κB.

IFN-α may contribute to the initiation or acceleration of autoimmunity [69]. In one study, the investigators evaluated expression of messenger RNA for a series of cytokines in the pancreas and islets from patients with and without type 1 diabetes. They found that among a panel of cytokines evaluated, only IFN-α was significantly overexpressed in diabetic patients [70]. Increased expression of IFN-α (a marker of viral infection) correlates with several autoimmune diseases. The most convincing data are associated with type 1 diabetes and systemic lupus erythematous (SLE) [70–73]. A correlation between elevated levels of circulating IFN-α and type 1 diabetes associated with enterovirus infections has been documented [74]. Coxsackie B4 virus appears to stimulate beta cells in vitro to produce IFN-α [75]. In almost all cases of new onset type 1 diabetes, pancreatic beta cells contained IFN-α, which correlated with the overexpression of the INF-α gene [71]. Elevated IFN-α is also observed in the serum of adult diabetic patients [76]. Transgenic mice with beta cell-specific expression of IFN-α-induced autoimmune diabetes and the neutralization of IFN-α by using a monoclonal antibody protected mice from diabetes [77,78].

Studies have shown that T cells play an important role in the pathogenesis of type 1 diabetes during viral infections. Juhela et al. have demonstrated a proliferative response to coxsackie virus-infected cell lysate, which also included non-structural proteins of the virus. The response appears to be higher in autoantibody positive than in autoantibody negative subjects. This difference was most marked in children carrying the HLA-DQB1*02 allele [79]. IFN-α may favor the development of Th1 immune reaction and thereby contribute to the development of autoimmune disease by the activation of CD4 lymphocytes secreting IL-2, IFN-γ, and TNF-β [80]. In addition, IFN-α expression has been associated with hyperexpression of MHC class I antigens in human islets [81,72].

IFN-α therapy associated with autoimmunity in humans

IFN-α is used in the treatment of persistent hepatitis B and C infections, hairy cell leukemia, multiple myeloma, lymphoma, carcinoid tumors, and breast cancer [82]. The first case of type 1 diabetes developing during IFN-α therapy was documented in 1992 [83]. This particular patient (DR4/11 haplotype) with hepatitis C was GAD and IAA positive before treatment and the autoantibody titer increased with treatment. Two large retrospective studies from Japan and Italy involving almost 12,000 subjects investigating side effects of IFN-α in patients with chronic hepatitis C demonstrated diabetes incidence (0.7% and 0.08%, respectively) that was higher than the annual incidence rate in the general population of their respective countries [84,85]. Autoantibodies to islet autoantigens were not measured in these two studies; therefore, the diagnosis of autoimmune type 1 diabetes could not be confirmed. Hence, prospective studies should be designed using autoantibodies as a marker of autoimmunity, especially when IFN-α can induce insulin resistance and hyperglycemia [86–88].

The majority of studies evaluating the effect of IFN-α on pancreatic autoimmunity are performed in patients with chronic hepatitis C infection. Subjects with chronic hepatitis C (before interferon therapy) do not have a significantly higher prevalence of islet-specific autoantibodies compared with the normal (control) population [89]. Unfortunately, these studies are difficult to compare as different types of interferon and different dosages and duration were used. Taking into account the various case reports and studies, the cumulative number of patients with Hepatitis C who were autoantibody positive before treatment was 3% (12/440). This increased to 7% (34/440) after IFN-α treatment [90]. These cases suggest that IFN-α can play a role in the expression of pancreatic autoantibodies and perhaps also in a small subset of patients leading to the subsequent development of type 1 diabetes. In a review by Fabris et al., 30 cases of type 1 diabetes during IFN-α therapy are analyzed. One-half (9/18) of the patients (who were tested) who developed diabetes had anti-islet autoantibodies before therapy and 77% (22/30) at onset. Of note, transient insulin dependency was noted in eight of the patients, suggesting that early interruption of IFN-α therapy may be useful if hyperglycemia is detected. Fabris et al. [90] recommend that patients with hepatitis C be tested for anti-islet autoantibodies and if present, they are informed of the risk of developing type 1 diabetes. Seroconversion to islet autoantibody positivity has been observed in some Hepatitis C patients who were subjected to IFN-α therapy. Thus, confirming the possible ability of IFN-α therapy to induce islet autoantibody in humans, which substantiates similarities

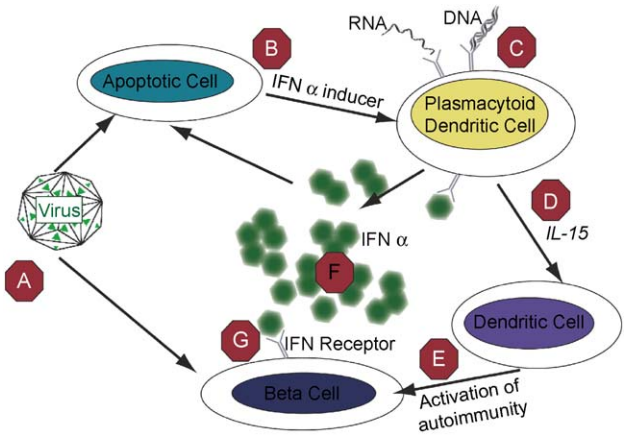

Fig. 4. Potential sites (A–G) that may inhibit viral-induced interferon alpha pathways to prevent type 1 diabetes. (A) Vaccines that prevent viral infection; (B) neutralizing IFN-α inducers; (C) blocking the stimulus that activates plasmacytoid dendritic cells; (D) blocking specific cytokines that activate dendritic cells; (E) prevention of autoimmunity by blocking specific T cell responses (e.g., CD3 monoclonal antibody); (F) neutralizing circulating IFN-α's that are predominantly produced by plasmacytoid dendritic cells; (G) blocking the IFN-α receptor at the beta cell of the pancreas.

seen in animal models as discussed in the previous section. The therapeutic use of IFN-α has also been associated with the development of psoriasis, thyroiditis, autoimmune gastritis, interstitial pneumonitis, myasthenia gravis, autoimmune hemolytic anemia, Raynaud's syndrome, Vogt–Koyanagi–Harada disease, and rheumatoid arthritis [47,91–93]. IFN-α, independent of the cumulative dose administered, was associated with the emergence or increased titers of anti-thyroid autoantibodies in patients with chronic active hepatitis B and C disease [94]. In another study evaluating the incidence of autoimmunity in chronic myeloid leukemia patients treated with IFN-α, autoimmune abnormalities were detected in 28% of the subjects [95]. Diabetes-related autoantibodies were not measured in this study.

Blocking interferon-α pathways to prevent type 1 diabetes

Therapeutic agents targeting the various pathways of IFN-α may potentially be beneficial in the prevention of type 1 diabetes. Fig. 4 illustrates the potential sites in which the neutralization of IFN-α, blocking IFN receptor sites, preventing apoptotic signals, or preventing virus infection in the first place, may potentially prevent the destruction of islet beta cell. Monoclonal antibody therapy has already been shown to be effective in preventing diabetes in animal models [47]. More recently, the neutralization of IFN-α in SLE subjects was shown to prevent the maturation of dendritic cells and subsequently prevented the expansion of autoreactive T cells [96]. However, as mentioned previously, these cells may not be the only cells responsible for IFN-α production. A therapy directed at dendritic cells might be as effective as anti-IFN-α therapy. However, a therapy targeting autoimmunity is unlikely to have any effect on how IFN-α affects apoptosis, mitochondrial function, and protein translation. Therefore, a combination therapy of blocking dendritic cell maturation and local circulating IFN-α may be more beneficial than therapy directed at dendritic cells alone. One possible area where IFN-α neutralizing or blocking antibody may be useful is in treating autoantibody positive or high-risk genotype pre-diabetic subjects when they first develop anti-islet autoantibodies during the long prodromal phase of "pre-diabetes".

Conclusion

The rise in childhood type 1 diabetes may be linked to viruses and other environmental factors. Perhaps more interestingly and crucial is the association between viral-induced IFN-α with type 1 diabetes, which has given us insight into the pathogenesis of this disease and furthermore has created potential ideas for therapeutic agents that may prevent type 1 diabetes.

Acknowledgments

This work is supported by grants from the National Institutes of Health (DK 62718, DK 32083, AI 39213, DK 55969, AI 39213, AI 46374), Diabetes Endocrine Research Center (P30 DK57516), Clinical Research Centers (MO1 RR00069, MO1 RR00051), Autoimmunity Prevention Center (AI 50864), the American Diabetes Association, the Juvenile Diabetes Foundation, and the Children's Diabetes Foundation. D.D. is also supported by an Eli Lilly fellowship.

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