[Frontiers in Bioscience 13, 4241-4257, May 1, 2008]

Viral infections in the pathogenesis of autoimmune diseases: focus on type 1 diabetes

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TABLE OF CONTENTS

1. ABSTRACT

Susceptibility to autoimmune diseases is dictated by a complex interplay of genetic determinants and environmental factors. Viral infections have long been suspected to be involved in the etiology of several autoimmune disorders. In particular, the incidence of type 1 diabetes worldwide is increasing at a yearly rate that cannot be solely attributed to genetic changes in the population and environmental factors certainly play an important role in the pathology of this autoimmune disease. In this review, we will focus our discussion on the evidence supporting a role for viral infections in the pathology of viral induced autoimmunity based on the example of type 1 diabetes. We will place a particular emphasis on the major candidate viruses and on the current state of knowledge regarding the mechanisms responsible for the induction of autoimmunity following viral infections. The lessons learned from type 1 diabetes provide a great framework of knowledge that can be applied to most viral-induced autoimmune diseases.

2. INTRODUCTION

Autoimmunity results from a loss of tolerance leading to an inappropriate immune response directed against self antigens leading to organ-specific destruction or systemic disease. The predisposition of an individual to autoimmune diseases is largely, but incompletely, dictated by genetic determinants. Several lines of evidence suggest a significant contribution from environmental factors in both the induction and the progression of autoimmune disease in genetically predisposed patients. Among these environmental factors, viral infections have long been suspected as agents in the pathology of autoimmune diseases. Clinical and epidemiological evidence has linked a plethora of viruses to organ specific autoimmune disorders including Type 1 diabetes (T1D) (1), autoimmune myocarditis (2) and multiple sclerosis (3) as well as several systemic autoimmune disorders including, systemic lupus erythematosus (4) and myasthenia gravis (5) (Table 1). However, despite several years of research, it has remained

Table 1. Viruses associated with the induction of autoimmune diseases other than T1D

Autoimmune Disease	Associated Viruses	References
Autoimmune Myocarditis	Coxsackievirus	148
Autoimmune Thyroiditis	Epstein-Barr virus	149
	Hepatitis C virus	150
	Human T-Lymphotropic virus type 1	151
Multiple Sclerosis	Coronavirus	152, 153
	Epstein-Barr virus	154-156
	Human herpes virus 6	157
	JC virus	158
	Measles virus	159
	Endogenous Retroviruses	160-162
Myasthenia Gravis	Hepatitis C Virus	163
	Human foamy virus	164
	Human T-lymphotropic virus type 1	5
Rheumatoid Arthritis	Epstein-Barr virus	165
	Parvovirus B19	166
Sjögren's syndrome	Coxsackievirus	167
	Epstein-Barr	168
	Hepatitis C virus	169
	Human herpes virus-6	170
	Human T-Lymphotropic virus type 1	171
Systemic lupus erythematosus	Cytomegalovirus	172
	Epstein-Barr virus	173
	Parvovirus B19	174

difficult to directly establish a causal link between specific viruses and the induction of autoimmunity in humans. This is most likely explained by the complex interplay of genetic and environmental factors that lead to disease induction following infection. This suggests that the majority of individuals infected with a particular virus harboring the capacity to induce autoimmune diseases do not develop autoimmunity, thereby rendering the determination of a single culprit difficult. Furthermore, establishment of disease will often occur long after viral clearance making it difficult to properly identify any potential causative agents. Despite these difficulties, research in small animal models has firmly demonstrated that under certain circumstances viral infection can induce or exacerbate autoimmunity defining an important role for viruses in the etiology of autoimmune disorders. In this review, we will focus on the role of viruses in the induction of T1D as this has been the subject of intense research over the last few decades. We will discuss both the epidemiological data linking several viral candidates to disease onset and the various mechanisms of disease induction that have been proposed. Although this review focuses on T1D, the mechanisms discussed here are likely to extend to the induction of several other autoimmune disorders following viral infection.

3. THE CASE FOR VIRAL-INDUCTION OF TYPE 1 DIABETES

T1D results from the destruction of the insulin producing beta cells in the islets of Langerhans of the pancreas by autoreactive T cells. Disease onset occurs after a large majority of beta cells have been destroyed and the autoimmune response is initiated years before appearance of clinical symptoms (6). Progression of the autoimmune response can be, in part, followed by measuring levels of beta cell antigen specific autoantibodies which appear long before the onset of clinical symptoms (7). If left untreated, T1D can lead to several life threatening symptoms and the only treatments currently available involve the direct injection of insulin or islet transplantation (8). Several factors seem to combine to confer susceptibility to T1D with genetic determinants playing a prominent role. The human leukocyte antigen (HLA) region is the primary genetic determinant of susceptibility (9) and several other genetic loci, including the insulin promoter (10), PTPn22 (11) and CTLA-4 (12-14), also combine to increase susceptibility. Several genetic regions contribute to confer susceptibility to diabetes development in the non-obese diabetic (NOD) mouse, a commonly studied animal model of T1D, where spontaneous development is controlled by at least 20 genetic loci including the major histocompatibility region (15). In humans, the rate of diabetes is increasing worldwide at a rapid rate (16-19) that cannot be explained by changes in the genetic makeup of the population alone particularly as the incidence of disease has been on the rise in populations with HLA alleles generally associated with reduced susceptibility (20). T1D often presents with geographic distribution patterns that do not correlate with genetic differences. For example, there is a large discrepancy in the incidence of T1D between Finland and neighboring regions of Russia despite similar prevalence of HLA alleles associated with susceptibility to disease (21). Furthermore, although certain populations are associated with lower incidences of T1D, immigration to areas associated with higher risk correlates with an increase of T1D within these normally protected populations. For example, although Asian populations have one of the lowest T1D incidences in the world, prevalence of T1D in Asian populations living the United Kingdom is almost identical to the higher prevalence that occurs within the caucasian population (22). Most convincingly, the concordance rate of T1D incidence in monozygotic twins is approximately only 40% clearly indicating that environmental factors combine with genetic predisposition to influence the likelihood of developing disease (23). These factors are likely to include changes in diet, exposure to beta cell toxins or pathogens such as viruses (24).

Viruses were first recognized as inducing agents of T1D when it was observed that disease onset sometimes follows acute viral infections. This was further supported

with epidemiological data indicating that T1D onset follows seasonality in both hemispheres in a manner that is strongly correlated with the seasonality of a number of viral infections (25, 26). Several instances of local epidemics of T1D resembling sudden infectious epidemics have also been reported (27-30). Furthermore, seasonal onset is often observed in less genetically predisposed populations, suggesting the contribution of risk factors other than genetic determinants in those cases (31). This may also explain why broad human studies, which are usually carried out on the most genetically susceptible populations, have commonly failed to clearly identify any candidate viruses. Most convincingly, two separate groups have reported the isolation of enteroviruses directly from the pancreas of patients that succumbed to acute onset T1D. Upon adaptation of these strains to allow them to replicate in mice, infection with these isolated viral strain induced hyperglycemia and a diabetes-like disease in infected animals, clearly demonstrating that viruses can lead to T1D (32, 33). One of the strains isolated from an acute onset T1D patient was identified as coxsackievirus B4 (CB4) (32) and has become a commonly used tool to study the induction of T1D by viruses. The diabetogenic properties of CB4 have since been clearly demonstrated in genetically susceptible mouse models (34-36). Accumulating evidence points to viral infections representing at least one of the environmental stimuli responsible for the rapid increase of T1D observed worldwide in the last few decades.

4. VIRUSES ASSOCIATED WITH THE INDUCTION OF TYPE 1 DIABETES

Since the first reports of T1D onset following a viral infection were published, a large number of viruses have been suggested as potential triggers of autoimmune diabetes. In this section, we will discuss the most likely candidates for the induction of T1D and the data supporting a role for each of these viruses in the induction of disease.

4.1. Mumps virus

Mumps is a single-stranded RNA virus from the paramyxovirus family and was one of the first viruses linked with diabetes. In the late 1800's, a case of acute onset diabetes was reported in a patient shortly following a mumps infection (37). This causal link was later supported by the observation that mumps epidemics were sometimes followed by sudden sharp increases in T1D onset a few years later (38). Mumps virus infections are further correlated with the presence of islet specific antibodies (39). Since the early 1980's, vaccination campaigns aimed at controlling measles, mumps and rubella (MMR vaccine) have been in place in most western countries. One follow-up study in Scandinavia reported a plateau in the rising incidence of T1D a few years following the start of this vaccination campaign (40), strongly suggesting a direct role for one of these viruses in the etiology of T1D. However, despite the ongoing vaccination efforts, the plateau in T1D incidence was short-lived and incidence is once again rising sharply (16-19). This implies that although one of the targets of the MMR vaccine may have been a major environmental contributor to T1D, other viruses are also involved. This further suggests that vaccination approaches aimed at reducing diabetogenic infection in children may represent a fruitful strategy to reduce T1D onset.

4.2. Rubella Virus

Rubella is a single stranded RNA virus from the Togavirus family and has been strongly linked to T1D. Approximately 20% of congenital rubella syndrome (CRS) sufferers have been reported to develop T1D later in life (41-46). Interestingly, some studies have failed to demonstrate the presence of increased beta cell specific antibodies in CRS patients that develop T1D suggesting that congenital rubella-induced T1D may not be autoimmune in nature but may instead result from direct effects of the viral infection (47). However, evidence from animal models (48) and the presence of cross-reactive determinants between rubella virus and GAD65 (49), a pancreatic beta cell autoantigens, still suggest that autoimmune processes may be involved. Although CRS has clearly been linked to the induction of T1D, vaccination campaigns have dramatically reduced Rubella virus infections worldwide without affecting the increasing incidence of T1D onset. This suggests that Rubella virus infections are unlikely to be the main etiological agent responsible for the current rise of T1D.

4.3. Enteroviruses

The enterovirus genus of the picornaviradae family includes several common human pathogens. Enteroviral infections in humans typically occur through the oral-fecal route and once infection is established, the virus can disseminate to a number of organs including the pancreas (50, 51). Members of this genus, particularly coxsackieviruses and echoviruses have long been suspected to be environmental inducers of T1D. The first evidence of a link between coxsackieviral infection and autoimmune diabetes was presented in a report by Gamble *et al.* in which a higher prevalence of viral-specific antibodies in T1D patients compared to control populations was demonstrated (52). This was later supported by the isolation of coxsackievirus directly from the pancreas of a child that had died as a result of acute onset of T1D (32). Infection with this isolated virus was subsequently observed to induce a diabetes-like disease in mice (32). The same viral strain was further demonstrated to possess the capacity to induce or dramatically accelerate disease onset in two mouse models on the NOD genetic background (34, 35). Several studies have since confirmed the presence of increased coxsackievirus specific antibody titers in recent onset patients compared to control populations (52-58). Furthermore, recent onset T1D patients present with higher prevalence of enteroviral RNA compared to control patients (59, 60). A recent report detailed an active echovirus 3 infection concurrently with the development of IA-2 and islet cell autoantibodies (61). Interestingly, it was recently demonstrated that recent-onset T1D patients have decreased T cell responses *in vitro* to CB4 antigens. This suggests that patients at risk for T1D may have difficulty clearing coxsackieviral infections potentially leading to heightened pancreatic damage and thereby increasing the likelihood of autoimmune consequences (62). Conversely, it was demonstrated that patients with ongoing diabetes have a greater frequency of CB4 specific T cells than recent

onset or non-diabetic patients inferring that coxsackieviral infections may also exacerbate pre-established autoimmunity (63). Congenital enterovirus infections have also been linked to the pathogenesis of T1D as one group reported that patients that developed T1D tested positive for neonatal enterovirus RNA more commonly than a control population that did not develop disease (64). Taken together, this evidence strongly suggests that enteroviruses are good candidates as one of the major environmental agent contributing to the increased T1D incidence observed over the last few decades.

Despite these strong indications of the role of enteroviruses in the pathogenicity of T1D, results from several large epidemiological studies have remained inconsistent. The Finnish diabetes prediction and prevention study demonstrated an important temporal relationship between enteroviral infection and development of T1D with infections detected in 57% of children that developed T1D associated autoantibodies within a 6 month period compared to only 31% in age-matched control children that did not develop autoantibodies (65). A separate study in Finland confirmed that the presence of enteroviral RNA was elevated in children that develop autoantibodies as compared to children from a control population (66). Interestingly, viral RNA was not detected in diabetic children demonstrating that, although the presence of viral RNA in children that have not yet developed the disease could be considered a risk factor for T1D, viral persistence probably does not play a role in the autoimmune pathology (67). These results were further confirmed in the Trial to Reduce IDDM in the Genetically at Risk project where a greater percentage of children that developed autoantibodies were positive for both enteroviral RNA and antibodies compared to age matched children that do not develop autoimmunity (68). These results, however, have been contradicted by several other studies. For example, It was determined that overall levels of enterovirus infections are lower are countries with high incidence of T1D as compared to countries with higher frequencies (eg.: Finland and Russia) (69). Several reports from longitudinal studies in Europe (70), the United States (71) or Australia (72) have further failed to demonstrate a link between any enteroviral infections and the development of T1D related autoantibodies. Several factors could explain these discrepancies. It is important to consider that these studies use different methodologies and the populations studied have different genetic profiles rendering direct comparison difficult. Further, there are a large number of enterovirus serotypes (73) and it is possible that not all of these will demonstrate diabetogenic properties possibly confounding the analysis of some of the data. Finally, these studies have all been interested in demonstrating a link between enteroviral infection and the onset of autoimmunity. However, as will be discussed below (section 5.3.), results from animal models indicate that coxsackieviral infection may simply precipitate ongoing autoimmune processes rather than initiating them. Taken together, the accumulated data strongly suggests a link between enteroviruses and T1D and the controversy that remains simply highlights the need for continued research in this area.

4.4. Rotavirus

Rotavirus is a double stranded RNA virus from the reovirus family that is a major cause of gastroenteritis in children worldwide (74). Rotavirus replication is usually focused in gut epithelial cells but it also has been demonstrated to cause acute systemic viremia and some cases of pancreatitis have been documented (75, 76). They were first suspected to be involved in the etiology of T1D due to shared sequences between a viral protein (VP7) and some major T cell epitopes from antigens derived from pancreatic beta cells (77). Furthermore, infections with rotavirus occur predominantly in young children (74), an age group that has seen a dramatic rise in incidence of T1D in the last decades. Longitudinal studies in Australian children at risk of T1D have demonstrated increased incidence of islet specific antibodies shortly after detection of rotavirus infection (72). This study further demonstrated that increases in islet antibodies were correlated with signs of repeated rotavirus infection indicating that yearly epidemics of this virus could contribute in an additive fashion to the induction of islet specific autoimmunity (72). These results are further supported by studies demonstrating that reoviruses can specifically infect pancreatic beta cells and induce diabetes in infant mice (78, 79). The plausibility of the role of rotavirus in human T1D was further enhanced by the recent discovery of T cells specific for the shared VP7 sequences in children presenting with signs of autoimmunity strongly suggesting the presence of cross-reactive responses between rotavirus and pancreatic beta cells (47). However, a second study of children at risk in Finland did not validate these results and failed to associate rotavirus infection with the development of islet specific antibody (80). These studies, however, only used IgG levels to define rotavirus infection and used a viral strain uncommonly found in humans for their analyses, two factors that may have led to an increased frequency of false negatives and render this study more difficult to properly analyze (47, 80). These differences in methodology leading to contradicting results highlight some of the difficulties inherently associated with conclusively determining the role of any particular pathogens in the induction of autoimmunity in human populations. Despite these contradictions, it seems likely that rotavirus may also contribute to the pathogenesis of T1D and together with enteroviruses may be responsible for the increased incidence of T1D in certain parts of the world.

4.5. Cytomegalovirus

Cytomegalovirus (CMV) is a member of the herpes virus family and has been associated with induction of T1D by a few studies. The link between CMV infection and T1D induction was first established in a report of a child developing T1D after suffering from a congenital CMV infection (81). This was later supported by a report of a patient with CMV infection developing T1D after suffering from severe pancreatitis (82). Studies of non-diabetic siblings of T1D patients have demonstrated a strong correlation between anti-CMV antibodies and the presence of islet-specific antibodies (83). Another study demonstrated that 80% of patients with islet specific antibodies tested positive for both anti-CMV antibodies and

the presence of CMV genetic material (84). The potential for cross-reactivity between CMV epitopes and islet antigen has also been hypothesized at the level of both T cell and B cell responses (85, 86). However, several epidemiological studies have failed to demonstrate a link between CMV and the development of islet specific antibodies or T1D (54, 87, 88). Despite these contradicting epidemiological studies, the potential role of CMV infection in the etiology of T1D is supported by data from animal models. The rat homolog of human CMV, rat CMV was demonstrated to accelerate T1D onset in the two separate diabetes prone rat model (Bio-breeding rat, BBDP and LEW.1WR1 rats) (89, 90). The exacerbation of disease in these models is proposed to occur through a similar mechanism (details below in section 5.3.) to what is observed following CB4 infection of NOD mice derived models (91). This indicates that CMV may predominantly accelerate already ongoing autoimmune processes rather than initiate them.

4.6. Endogenous retroviruses

Endogenous retroviruses are commonly found within mammalian genomes. They represent proviral DNA from retroviruses that have become associated with host following integration within the genome. An endogenous retrovirus named IDDMK$_{1,2}$22 was originally isolated from the pancreas of two recent onset T1D patients and was believed to be responsible for the induction of T1D (92). It was hypothesized that a virally encoded superantigen may have been responsible for inducing or expanding self-reactive T cells in a non-specific manner leading to the targeting and destruction of the pancreas in genetically susceptible individuals (see section 5.5.) (92). However, this retrovirus was later demonstrated to be ubiquitous within human populations and not specifically associated with T1D patient casting a doubt over its role in autoimmunity (93, 94). Other lines of evidence still link endogenous retroviruses to T1D. For example, 64% of sera from diabetic patients and 75% of sera from non-diabetic first-degree relatives of T1D patients presented with anti-insulin autoantibodies that cross-reacted with a retroviral antigen compared to only 3% in age-matched controls (95). Another study observed retrovirus-like particles specifically in the pancreas of patients who died shortly after T1D onset while none were observed in control patients (96). These data are further supported by research in the NOD mouse model where expression of endogenous retroviruses has been associated with the start of invasive insulitis and the onset of T1D (97-99). In that model it has been hypothesized that the presentation of retroviral antigens following a wave of beta cell apoptosis that is a potential inducer of onset of autoimmunity in the NOD mouse and could represent a key step in the induction of autoimmunity (96). Alternatively, it remains possible that the onset of autoimmunity is associated with the expression of endogenous retroviruses and that expression of these viruses is a result rather than a cause of autoimmunity. The role of endogenous retroviruses in the induction of T1D remains very intriguing and further research on the subject is needed to further clarify their potential role.

4.7. Parvoviruses

There is very little data linking parvoviral infection to the onset of T1D in humans. One report described the onset of several autoimmune phenotypes including T1D in one patient following acute parvovirus B19 infection (100). Conversely, another study of recent onset T1D patients failed to establish a link between disease onset and parvovirus B19 infection (101). This study, however, focused solely on recent onset patient which cannot rule out the role of parvovirus infections prior to onset of disease as a modifier of susceptibility to T1D. Despite the paucity of information linking parvovirus B19 to T1D in humans, one of the most described animal models of T1D induction by viruses relies on the Kilham Rat virus (KRV), a member of the parvovirus family. KRV infections are sufficient to induce T1D in diabetes resistant Bio-Breeding rats (BBDR), a BBDP derived rat strain that does not spontaneously develop diabetes (102). Interestingly, KRV does not directly infect the islets (103) but, rather, induces T1D by affecting the delicate balance that maintains peripheral tolerance (see mechanism discussion below, section 5.4.) (104, 105). Further studies, possibly taking advantage of the longitudinal studies of children at risk, are needed to clarify the role of parvovirus infection in human T1D.

4.8. Other viruses

Several other viruses including Epstein-Barr virus (106, 107), Hepatitis A virus (108) and Hepatitis C virus (109) have been associated with onset of T1D. Although in most cases, the data associated with these viruses remains sparse or inconclusive indicating that further research is required. The large number of viruses that have been associated with the induction of T1D highlights that viral-induction of T1D may represent a common final step associated with several infections or even combinations of different infections. Taking into account that most human studies have a limited pool of participants to draw from, it is easier to understand why it has remained very difficult to conclusively identify any single viral culprit in the induction of autoimmune diseases.

5. MECHANISMS OF INDUCTION OF TYPE 1 DIABETES BY VIRAL INFECTION

The mechanisms through which viruses ultimately lead to autoimmune diseases such as T1D in humans are poorly understood. Several hypotheses have been proposed but very little human data is currently available to support any of them. Research in animal models has advanced our understanding of how some of these mechanisms relate to induction of disease. One key highlight from this research is that a wide variety of mechanisms could be used by viruses to induce autoimmunity and that this is also likely to be true for humans. Understanding the exact mechanisms by which viruses can induce autoimmunity may allow a better evaluation of the epidemiological data with a view towards finding new candidate viruses. More importantly, this may lead to the design of new therapies aimed specifically at reducing the autoimmune consequences of certain infections. In this section we will discuss the data

supporting the main mechanisms through which viruses are proposed to induce T1D.

5.1. Direct destruction of pancreatic beta cells

One of the simplest mechanisms through which viruses can induce T1D in patients is by direct infection and destruction of the insulin producing beta cells in a process that does not involve any autoimmune reaction. The picornavirus encephalomyocarditis virus (EMCV) has been demonstrated to induce T1D in animal models. Infection with a high dose of the D strain of EMCV results in acute onset of T1D in more than 90% of infected animals within 4 days of infection (110). Treatment of mice with antibodies that block T cell responses were not sufficient to block induction of T1D following infection indicating that destruction of the beta cells is not mediated by T cells (111). Evidence does point to a partial contribution for macrophages in the destruction induced by EMCV but the exact mechanism remains to be elucidated (112). Infections of mice with lower doses of EMCV viruses that are more likely to represent a natural infection also resulted in induction of diabetes and this induction was entirely dependent on macrophages, potentially through the release of cytokines and free oxygen radicals (112-114). Another member of the picornavirus family, the cardiotropic Mengovirus, also results in direct destruction of beta cells in mice and the induction of T1D without any evidence of an autoimmune response (115). There is very little evidence to link either of these viruses to diabetes induction in humans. The extremely rapid onset of diabetes in mice following infection is more reminiscent of the few cases of "fulminant" T1D that have been reported in humans (116). As such, this mechanism is unlikely to be responsible for the steady increase of autoimmune diabetes worldwide, where disease induction is usually preceded by a long period of asymptomatic autoimmunity.

5.2. Molecular mimicry

Molecular mimicry is an elegant theory that stipulates that regions of similarities between viral and self antigen epitopes could lead to an inappropriate cross-reactive immune response resulting in autoreactive T cell activation and tissue destruction. This theory was first formulated when it was observed that monoclonal antibodies raised against viral protein could cross-react with cellular epitopes (117). Molecular mimicry has been proposed to explain the viral etiology of several autoimmune diseases including multiple sclerosis (118) and T1D (119). As mentioned in the previous sections, several potential mimics between beta cell antigens and T1D associated viruses have been identified including CB4 (120, 121), rotavirus (77) and CMV (85). In the late 1980s, two separate models were established by the groups of Dr. Oldstone and Dr. Zinkernagel to test the potential role of molecular mimicry in the viral induction of T1D (122, 123). In both of these models, a viral protein of the lymphocytic choriomeningitis virus (LCMV) was expressed directly within pancreatic beta cells under the control of a rat insulin promoter (RIP-LCMV). Peripheral tolerance to these neo-antigens was maintained and no spontaneous diabetes was observed in these models. However, LCMV infection resulted in rapid induction of diabetes in almost all of the mice compared to no diabetes induction following LCMV infection of non-transgenic littermates (122, 123). Although these models elegantly demonstrated that molecular mimicry could, in principle, be responsible for the induction of T1D following infection, these models rely entirely on identity (the protein expressed in the pancreas is identical to the one expressed by the virus) and, therefore, do not represent a situation that would naturally be encountered. These models and others relying on the pancreatic expression of neo-antigens derived from a virus have also been extremely useful to further dissect some of the requirements of viral-induction of autoimmunity. First, they demonstrated that the mere presence of self-reactive T cells is not sufficient to induce autoimmunity. For example, it was demonstrated that several lines of LCMV-GP mice (transgenic mice expressing the glycoprotein of LCMV within the pancreas) expressed the neo-antigen exclusively in the beta cells and this was correlated with very high numbers of autoreactive T cells compared to transgenic mouse lines where the expression of the antigen was also detectable in the thymus (124). Despite these high numbers of autoreactive T cells T1D did not develop spontaneously confirming that changes induced following infection are still required for induction of disease (124). These models have further highlighted the role of cytokines and chemokines as blocking the effects of IFN-gamma, TNF-alpha or IP-10 by genetic or antibody blocking methods have all been demonstrated to either abrogate or dramatically reduce T1D onset following infection (125-127). These results indicated that in the presence of a high number of self-reactive T cells, changes in the cytokine/chemokine milieu induced by viral infection can be sufficient to precipitate the induction of autoimmunity. The RIP-LCMV model was also used to demonstrate that a true mimic can at least accelerate autoimmunity although, in that model, it was not sufficient to induce autoimmunity by itself. A cross-reactive epitope between the nucleoprotein of LCMV and Pichinde viruse (PV) has been described. This cross-reactive section occurs over a stretch of 8 amino acids, of which 6 are identical, on a sub-dominant epitope that does not play a major role in initial infections with either virus (128). Although PV infection was not sufficient to induce T1D in RIP-LCMV mice, it was observed that a PV infection 4 weeks after initial LCMV infection can dramatically enhance onset of disease (129). These results highlight that once autoimmune process has begun, infection with a virus that bears a cross-reactive mimic might result in disease enhancement. Therefore, it is possible that in patients where autoimmune attack of the pancreas is already ongoing, infection with any virus that includes cross-reactive epitopes may serve to precipitate destruction of islet cells and onset of disease. This mechanism could therefore extend to a variety of the candidate virus that have been discussed in this review but proper timing of infection would be required for these viruses to induce disease. Alternatively, molecular mimicry may be an important source of potentially autoreactive T cells. Peripheral tolerance could be maintained until subsequent events alter the regulatory T cells (Tregs)/effector T cell balance. As such, molecular mimicry between one virus and pancreatic self-antigen can serve to modify pre-

disposition to disease as well as precipitate ongoing autoimmune processes.

5.3. Bystander damage (release of sequestered antigens)

Several T cell receptor transgenic models were generated on the NOD background to study the role of T cell clones of various specificities in the progression of T1D. One of these, the BDC2.5 model, was created from a T cell clone of unknown specificity derived from a diabetic NOD mouse (130, 131). Interestingly, despite the majority of T cells in this model being specific for a pancreatic antigen, these mice never develop diabetes or progress beyond a stage of non-invasive insulitis (termed peri-insulitis) where T cells home to the pancreas without infiltrating or destroying the beta cells (34, 132). This model further demonstrates that the mere presence of autoreactive T cells is not sufficient to induce disease. Infection of these mice with coxsackievirus B4 was sufficient to rapidly induce T1D in the majority of infected mice (34). Interestingly, the gender bias normally observed for the spontaneous induction of T1D in NOD mice is not observed following infection of BDC2.5 mice strongly suggesting that the induction of disease following infection involves mechanisms that are distinct from the mechanisms of spontaneous disease induction (34). Although the exact specificity of the BDC2.5. clone remains unknown, it was determined that the clone does not directly respond to CB4 antigens. This strongly indicated that, despite regions of shared specificity between the viral P2-C protein and the pancreatic antigen GAD65, molecular mimicry is not responsible for induction of disease following CB4 infection, at least in the BDC2.5 model (34). Instead, CB4 infection induced T1D by causing bystander damage leading to the release of previously sequestered pancreatic antigens leading to the activation of the pre-existing self-reactive T cell population (34). This further suggests that ignorance of an autoreactive T cell clone's cognate antigen is an important mechanism for the maintenance of peripheral tolerance to pancreatic islet antigens. CB4 infects pancreatic beta cells without direct induction of cell death (133). Instead, infection leads to the upregulation of cell surface markers associated with cellular stress, particularly Death Receptor 4 and subsequent engulfment of infected islets by antigen presenting cells (APCs) (133). Adoptive transfer of purified APCs from CB4 infected NODscid mice were later demonstrated to be sufficient to induce BDC2.5. T cell proliferation *in vitro* and, more importantly to adoptively transfer disease to uninfected BDC2.5. mice clearly confirming the importance of APCs in the induction of T1D following infection (133). Our recent results have demonstrated that transgenic expression of TGF-beta within pancreatic beta cells, protects from CB4-induced T1D and that this correlated with a decreased activation of macrophages but not dendritic cells (Richer *et al.*, manuscript in preparation). Our results further highlight the importance of APCs, particularly macrophages, in the induction of T1D following CB4 infection. The role of APCs has been well described in spontaneous T1D (134) and it seems likely, based on the literature, that they would also play a central role in the induction of T1D following CB4 infection. Studies on the BDC2.5 model have further supported that the primary contribution of CB4 infection to the induction of disease is to cause pancreatic damage and release sequestered antigens. Treatment with the double-stranded RNA molecular mimic, poly I:C, was not sufficient to induce disease in BDC2.5 mice (135). Poly I:C is recognized by receptor Toll-like receptor 3, an innate receptor involved in viral recognition, leading to a cascade of events culminating in the production of pro-inflammatory cytokines. These results strongly suggest that non-specific activation of T cells mediated by viral-induced inflammatory cytokine is not sufficient to induce disease. Conversely, it was demonstrated that a single low dose of streptozotocin was sufficient to induce disease (135). At low dose, this pancreatic toxin results in minimal pancreatic damage and was demonstrated to partially mimic the effects of CB4 infection by causing the engulfment of beta cells by APCs and activation of the pre-existing population of autoreactive T cells (135). The presence of a pre-existing population of autoreactive T cells seems to be an absolute requirement for CB4-induction of T1D based on data gathered in two separate mouse models. BDC2.5 mice were crossed with two separate mouse strains resulting in crossed strains presenting with a varying level of autoreactive T cells. Only mice harboring a high (WT BDC2.5 mice) or intermediate (BDC2.5 X Balb/C F1 mice) level of autoreactive T cells were susceptible to viral induced T1D while mice with low levels (BDC2.5 X C57Bl/6 F1 mice) of autoreactive T cells were protected from disease induction (136). In the NOD mouse, it was observed that only mice that were at least 8 weeks old were susceptible to acceleration of disease following CB4 infection while younger mice were impervious to disease (35). The authors suggested that the accumulation of a critical threshold of autoreactive T cells was a strict requirement for induction of disease. These results were later confirmed for other diabetogenic viral strains of coxsackievirus where only older NOD mice were susceptible to viral-induced acceleration of disease (137). Taken together, this indicates that coxsackievirus infection represents that last step in disease induction and essentially serves to precipitate the already ongoing autoimmune reaction. This mechanism is likely to extend to any virus that can induce stress or cause damage to the pancreatic beta cells.

5.4. Disruption of regulatory T cell and effector T cell balance

Tregs are a specialized subset of T cells involved in maintaining peripheral tolerance and have been ascribed an important role in the prevention of several autoimmune diseases (138). Tregs from diabetic patients have significantly reduced suppressive function as compared to non-diabetic control subjects (139) while in NOD mice, Tregs gradually lose their suppressive capacity and this gradual loss correlates with onset of disease (140). Other T1D models derived from the NOD mouse such as BDC2.5. and NOR mice, do not spontaneously develop disease unless Tregs are depleted (141, 142). These results clearly highlight the important role of Tregs in the progression of T1D. Any disturbances affecting the finely tuned balance between autoreactive T cells and Tregs could potentially lead to or dramatically exacerbate autoimmunity. Interplay between Tregs and virus has been

shown to play a role during infections (143). Increased Treg presence can be associated with viral persistence and this, in turn, could lead to increased tissue damage thereby increasing the likelihood of autoimmunity (143). Conversely, viral infections could either directly or indirectly reduce Treg function or numbers thereby releasing autoreactive T cells from suppression leading to increased autoimmunity. To this effect, it has been demonstrated that one of the cytokines commonly produced during an acute response to viral infection, interleukin-6, is an important factor to release effector T cells from Treg suppression thereby allowing for the development of an immune response (144). Clearly, any infections leading to prolonged release of interleukin-6 could result in the inappropriate release of autoreactive T cells and promote autoimmunity. KRV infections of BBDR rats induce diabetes in this normally resistant rat model without direct infection of islet cells (103). This has been hypothesized to be a result of changes in the effector T cell/Treg balance following viral infection. Infection of BBDR rats with KRV led to an upregulation of Th1-like $CD45RC^{+}$ $CD4^{+}$ cells and cytotoxic $CD8^{+}$ T cells and a downregulation of Th2-like $CD45RC^{-}CD4^{+}$ cells (104). This indicated that alteration in the balance of T cell polarity following infection was sufficient to induce disease. It was later demonstrated that KRV infection of BBDR mice also affects the Treg balance. Following infection the levels of $CD4^{+}CD25^{+}$ T cells were decreased in the spleen of BBDR rats compared to mice infected with a closely related virus that does not induce T1D. Surprisingly, the presence of $CD4^{+}CD25^{+}$ T cells in the pancreatic lymph node was increased (105). The authors concluded that these changes in Treg populations were responsible for induction of disease although it may be important to revisit these experiments now that reagents that allow a more specific characterization of Tregs are available. In the same rat model, it has been demonstrated that activation of innate cells with TLR ligands synergizes with viral infection to induce a higher incidence of disease (145). These results further highlight that the fine balance of activation of T cells versus the maintenance of tolerance is crucial to the decision for progression towards autoimmunity. The modulation of Treg responses following infection are likely to be involved in the autoimmune pathology observed following several viral infections and should be the focus of more investigation.

5.5. Superantigens

Superantigens are gene products encoded by some bacteria and viruses that lead to the non-specific expansion of T cells bearing a particular Vbeta region on their T cell receptor. Superantigens were first linked to T1D when it was observed that T cells infiltrating the pancreas of two diabetic patients were dramatically enriched for the Vbeta 7 variable region (146). This possibility was further supported by the isolation of an endogenous retrovirus, from diabetic patients, that was found to encode a superantigen (92). Although the link between this particular endogenous retrovirus and T1D has since been questioned (93), the role of superantigens in T1D remains intriguing. Infection with any virus encoding for a superantigen could lead to the non-specific expansion of diabetogenic T cell clones thereby leading to disease onset. Alternatively, increased presence of diabetogenic T cells may not directly lead to disease but may simply predispose the host to induction of disease following a viral infection that leads to bystander damage thereby precipitating disease onset.

5.6. Multiple infections

Research by the groups of Dr. Selin and Dr. Welsh has established that sequential infections have dramatic effects in shaping T cell repertoires (147). Furthermore, different combinations or sequences of infection can lead to the generation of memory T cells with varying capacity to cross-react with other sequences depending on the order of infection (147). As such, a person's history of infection can influence immunity following every new infection and may have a strong effect on the development of immune pathology. Therefore, multiple infections are likely to represent a risk factor for T1D. For example, a primary infection could generate autoreactive T cells either through molecular mimicry or by influencing the cross-reactivity of memory T cells. Further infections can then induce disease either by expanding these autoreactive T cells above a certain threshold or by inducing bystander damage leading to the release of previously sequestered antigens recognized by these autoreactive T cells. It is therefore possible to envision that T1D induced by viral infection is in fact the result of a combination a various infections using a variety of mechanisms ultimately leading to the destruction of the pancreatic beta cells. This may, in part, explain why it has remained so difficult to identify any single culprit virus as a clear inducer of T1D.

6. CONCLUDING REMARKS

A strong causal link in humans supported by research in animal models has demonstrated that viruses can induce or accelerate the onset of autoimmune diseases including T1D. Despite this strong link, it has remained difficult to conclusively identify any single virus due to a variety of factors that have been described throughout this review. It is becoming clear that the mechanisms through which can viruses can induce T1D and likely other autoimmune disease are complex and varied. It seems increasingly likely that T1D induction by environmental agents does not occur by a single mode of disease induction but rather a complex interaction which may include several viruses, alone or in combination, leading to disease through several mechanisms. The early results that demonstrated that MMR vaccination led to a plateau in T1D incidence in certain countries gives hope that managing infections in young children may prove an efficient way to control the rising incidence of autoimmune diseases (40). To reach this goal however it will be imperative to maintain research aimed at identifying potential viral culprits, understanding the mechanisms of induction of disease following infection but also research aimed at better understanding the biology of some of these viral infections in order to be able to design vaccines or more efficient therapies aimed at controlling infections that can potentially lead to autoimmune consequences.

7. ACKNOWLEDGEMENTS

The authors would like to thank S.A. Condotta for useful discussion and critical reading of the manuscript. MSH is supported by grants from the Canadian Institutes for Health Research (CIHR). MSH is a scholar for the Michael Smith Foundation for Health Research (MSFHR) and holds a new investigator award from the CIHR. MJR is a recipient of a Senior Graduate Studentship from the MSFHR and a Doctoral Research Award from the Natural Sciences and Engineering Research Council of Canada (NSERC).

8. REFERENCES

1. van der Werf, N., F. G. Kroese, J. Rozing & J. L. Hillebrands: Viral infections as potential triggers of type 1 diabetes. *Diabetes Metab Res Rev*, 23, 169-83 (2007)

2. Fairweather, D., S. Frisancho-Kiss & N. R. Rose: Viruses as adjuvants for autoimmunity: evidence from Coxsackievirus-induced myocarditis. *Rev Med Virol*, 15, 17-27 (2005)

3. Ascherio, A. & K. L. Munger: Environmental risk factors for multiple sclerosis. Part I: the role of infection. *Ann Neurol*, 61, 288-99 (2007)

4. Zandman-Goddard, G. & Y. Shoenfeld: Infections and SLE. *Autoimmunity*, 38, 473-85 (2005)

5. Lalive, P. H., G. Allali & A. Truffert: Myasthenia gravis associated with HTLV-I infection and atypical brain lesions. *Muscle Nerve*, 35, 525-8 (2007)

6. Achenbach, P., E. Bonifacio, K. Koczwara & A. G. Ziegler: Natural history of type 1 diabetes. *Diabetes*, 54 Suppl 2, S25-31 (2005)

7. Ziegler, A. G., M. Hummel, M. Schenker & E. Bonifacio: Autoantibody appearance and risk for development of childhood diabetes in offspring of parents with type 1 diabetes: the 2-year analysis of the German BABYDIAB Study. *Diabetes*, 48, 460-8 (1999)

8. Shapiro, A. M., J. R. Lakey, E. A. Ryan, G. S. Korbutt, E. Toth, G. L. Warnock, N. M. Kneteman & R. V. Rajotte: Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N Engl J Med*, 343, 230-8 (2000)

9. Redondo, M. J. & G. S. Eisenbarth: Genetic control of autoimmunity in Type I diabetes and associated disorders. *Diabetologia*, 45, 605-22 (2002)

10. Vafiadis, P., S. T. Bennett, J. A. Todd, J. Nadeau, R. Grabs, C. G. Goodyer, S. Wickramasinghe, E. Colle & C. Polychronakos: Insulin expression in human thymus is modulated by INS VNTR alleles at the IDDM2 locus. *Nat Genet*, 15, 289-92 (1997)

11. Bottini, N., L. Musumeci, A. Alonso, S. Rahmouni, K. Nika, M. Rostamkhani, J. MacMurray, G. F. Meloni, P. Lucarelli, M. Pellecchia, G. S. Eisenbarth, D. Comings & T. Mustelin: A functional variant of lymphoid tyrosine phosphatase is associated with type I diabetes. *Nat Genet*, 36, 337-8 (2004)

12. Marron, M. P., L. J. Raffel, H. J. Garchon, C. O. Jacob, M. Serrano-Rios, M. T. Martinez Larrad, W. P. Teng, Y. Park, Z. X. Zhang, D. R. Goldstein, Y. W. Tao, G. Beaurain, J. F. Bach, H. S. Huang, D. F. Luo, A. Zeidler, J. I. Rotter, M. C. Yang, T. Modilevsky, N. K. Maclaren & J. X. She: Insulin-dependent diabetes mellitus (IDDM) is associated with CTLA4 polymorphisms in multiple ethnic groups. *Hum Mol Genet*, 6, 1275-82 (1997)

13. Nistico, L., R. Buzzetti, L. E. Pritchard, B. Van der Auwera, C. Giovannini, E. Bosi, M. T. Larrad, M. S. Rios, C. C. Chow, C. S. Cockram, K. Jacobs, C. Mijovic, S. C. Bain, A. H. Barnett, C. L. Vandewalle, F. Schuit, F. K. Gorus, R. Tosi, P. Pozzilli & J. A. Todd: The CTLA-4 gene region of chromosome 2q33 is linked to, and associated with, type 1 diabetes. Belgian Diabetes Registry. *Hum Mol Genet*, 5, 1075-80 (1996)

14. Van der Auwera, B. J., C. L. Vandewalle, F. C. Schuit, F. Winnock, I. H. De Leeuw, S. Van Imschoot, G. Lamberigts & F. K. Gorus: CTLA-4 gene polymorphism confers susceptibility to insulin-dependent diabetes mellitus (IDDM) independently from age and from other genetic or immune disease markers. The Belgian Diabetes Registry. *Clin Exp Immunol*, 110, 98-103 (1997)

15. Anderson, M. S. & J. A. Bluestone: The NOD mouse: a model of immune dysregulation. *Annu Rev Immunol*, 23, 447-85 (2005)

16. Onkamo, P., S. Vaananen, M. Karvonen & J. Tuomilehto: Worldwide increase in incidence of Type I diabetes--the analysis of the data on published incidence trends. *Diabetologia*, 42, 1395-403 (1999)

17. Gale, E. A.: The rise of childhood type 1 diabetes in the 20th century. *Diabetes*, 51, 3353-61 (2002)

18. Soltesz, G.: Diabetes in the young: a paediatric and epidemiological perspective. *Diabetologia*, 46, 447-54 (2003)

19. Haynes, A., C. Bower, M. K. Bulsara, T. W. Jones & E. A. Davis: Continued increase in the incidence of childhood Type 1 diabetes in a population-based Australian sample (1985-2002). *Diabetologia*, 47, 866-70 (2004)

20. Gillespie, K. M., S. C. Bain, A. H. Barnett, P. J. Bingley, M. R. Christie, G. V. Gill & E. A. Gale: The rising incidence of childhood type 1 diabetes and reduced contribution of high-risk HLA haplotypes. *Lancet*, 364, 1699-700 (2004)

21. Kondrashova, A., A. Reunanen, A. Romanov, A. Karvonen, H. Viskari, T. Vesikari, J. Ilonen, M. Knip & H. Hyoty: A six-fold gradient in the incidence of type 1 diabetes at the eastern border of Finland. *Ann Med*, 37, 67-72 (2005)

22. Raymond, N. T., J. R. Jones, P. G. Swift, M. J. Davies, G. Lawrence, P. G. McNally, M. L. Burden, R. Gregory, A. C. Burden & J. L. Botha: Comparative incidence of Type I diabetes in children aged under 15 years from South Asian and White or Other ethnic backgrounds in Leicestershire, UK, 1989 to 1998. Diabetologia, 44 Suppl 3, B32-6 (2001)

23. Hyttinen, V., J. Kaprio, L. Kinnunen, M. Koskenvuo & J. Tuomilehto: Genetic liability of type 1 diabetes and the onset age among 22,650 young Finnish twin pairs: a nationwide follow-up study. Diabetes, 52, 1052-5 (2003)

24. Akerblom, H. K., O. Vaarala, H. Hyoty, J. Ilonen & M. Knip: Environmental factors in the etiology of type 1 diabetes. Am J Med Genet, 115, 18-29 (2002)

25. Laron, Z.: Incidence and seasonality of type 1 diabetes mellitus--what now? J Pediatr Endocrinol Metab, 15, 573-5 (2002)

26. Willis, J. A., R. S. Scott, B. A. Darlow, H. Lewy, I. Ashkenazi & Z. Laron: Seasonality of birth and onset of clinical disease in children and adolescents (0-19 years) with type 1 diabetes mellitus in Canterbury, New Zealand. J Pediatr Endocrinol Metab, 15, 645-7 (2002)

27. Rewers, M., R. E. LaPorte, M. Walczak, K. Dmochowski & E. Bogaczynska: Apparent epidemic of insulin-dependent diabetes mellitus in Midwestern Poland. Diabetes, 36, 106-13 (1987)

28. Yang, Z., X. Long, J. Shen, D. Liu, J. S. Dorman, R. E. Laporte & Y. F. Chang: Epidemics of type 1 diabetes in China. Pediatr Diabetes, 6, 122-8 (2005)

29. Lipman, T. H., Y. Chang & K. M. Murphy: The epidemiology of type 1 diabetes in children in Philadelphia 1990-1994: evidence of an epidemic. Diabetes Care, 25, 1969-75 (2002)

30. Libman, I. M., R. E. LaPorte, D. Becker, J. S. Dorman, A. L. Drash & L. Kuller: Was there an epidemic of diabetes in nonwhite adolescents in Allegheny County, Pennsylvania? *Diabetes Care*, 21, 1278-81 (1998)

31. Weets, I., L. Kaufman, B. Van der Auwera, L. Crenier, R. P. Rooman, C. De Block, K. Casteels, E. Weber, M. Coeckelberghs, Z. Laron, D. G. Pipeleers & F. K. Gorus: Seasonality in clinical onset of type 1 diabetes in belgian patients above the age of 10 is restricted to HLA-DQ2/DQ8-negative males, which explains the male to female excess in incidence. *Diabetologia*, 47, 614-21 (2004)

32. Yoon, J. W., M. Austin, T. Onodera & A. L. Notkins: Isolation of a virus from the pancreas of a child with diabetic ketoacidosis. *N Engl J Med*, 300, 1173-9 (1979)

33. Champsaur, H. F., G. F. Bottazzo, J. Bertrams, R. Assan & C. Bach: Virologic, immunologic, and genetic factors in insulin-dependent diabetes mellitus. *J Pediatr*, 100, 15-20 (1982)

34. Horwitz, M. S., L. M. Bradley, J. Harbertson, T. Krahl, J. Lee & N. Sarvetnick: Diabetes induced by Coxsackie virus: initiation by bystander damage and not molecular mimicry. *Nat Med*, 4, 781-5 (1998)

35. Serreze, D. V., E. W. Ottendorfer, T. M. Ellis, C. J. Gauntt & M. A. Atkinson: Acceleration of type 1 diabetes by a coxsackievirus infection requires a preexisting critical mass of autoreactive T-cells in pancreatic islets. *Diabetes*, 49, 708-11 (2000)

36. Serreze, D. V., C. Wasserfall, E. W. Ottendorfer, M. Stalvey, M. A. Pierce, C. Gauntt, B. O'Donnell, J. B. Flanagan, M. Campbell-Thompson, T. M. Ellis & M. A. Atkinson: Diabetes acceleration or prevention by a coxsackievirus B4 infection: critical requirements for both interleukin-4 and gamma interferon. *J Virol*, 79, 1045-52 (2005)

37. Harris, H. f.: A case of diabetes mellitus quickly following mumps. *Boston Medical and Surgical Journal*, 140, 465-469 (1898)

38. Hyoty, H., P. Leinikki, A. Reunanen, J. Ilonen, H. M. Surcel, A. Rilva, M. L. Kaar, T. Huupponen, A. Hakulinen, A. L. Makela & et al.: Mumps infections in the etiology of type 1 (insulin-dependent) diabetes. Diabetes Res, 9, 111-6 (1988)

39. Helmke, K., A. Otten & W. Willems: Islet cell antibodies in children with mumps infection. Lancet, 2, 211-2 (1980)

40. Hyoty, H., M. Hiltunen, A. Reunanen, P. Leinikki, T. Vesikari, R. Lounamaa, J. Tuomilehto & H. K. Akerblom: Decline of mumps antibodies in type 1 (insulin-dependent) diabetic children and a plateau in the rising incidence of type 1 diabetes after introduction of the mumps-measles-rubella vaccine in Finland. Childhood Diabetes in Finland Study Group. Diabetologia, 36, 1303-8 (1993)

41. Patterson, K., R. S. Chandra & A. B. Jenson: Congenital rubella, insulitis, and diabetes mellitus in an infant. Lancet, 1, 1048-9 (1981)

42. Schopfer, K., L. Matter, U. Flueler & E. Werder: Diabetes mellitus, endocrine autoantibodies, and prenatal rubella infection. Lancet, 2, 159 (1982)

43. Menser, M. A., J. M. Forrest & R. D. Bransby: Rubella infection and diabetes mellitus. Lancet, 1, 57-60 (1978)

44. Forrest, J. M., M. A. Menser & J. A. Burgess: High frequency of diabetes mellitus in young adults with congenital rubella. Lancet, 2, 332-4 (1971)

45. Ginsberg-Fellner, F., M. E. Witt, B. Fedun, F. Taub, M. J. Dobersen, R. C. McEvoy, L. Z. Cooper, A. L. Notkins & P. Rubinstein: Diabetes mellitus and autoimmunity in patients with the congenital rubella syndrome. *Rev Infect Dis*, 7 Suppl 1, S170-6 (1985)

46. McIntosh, E. D. & M. A. Menser: A fifty-year follow-up of congenital rubella. *Lancet*, 340, 414-5 (1992)

47. Honeyman, M.: How robust is the evidence for viruses in the induction of type 1 diabetes? *Curr Opin Immunol*, 17, 616-23 (2005)

48. Rayfield, E. J., K. J. Kelly & J. W. Yoon: Rubella virus-induced diabetes in the hamster. *Diabetes*, 35, 1278-81 (1986)

49. Ou, D., L. A. Mitchell, D. L. Metzger, S. Gillam & A. J. Tingle: Cross-reactive rubella virus and glutamic acid decarboxylase (65 and 67) protein determinants recognised by T cells of patients with type I diabetes mellitus. *Diabetologia*, 43, 750-62 (2000)

50. Huber, S. & A. I. Ramsingh: Coxsackievirus-induced pancreatitis. *Viral Immunol*, 17, 358-69 (2004)

51. Whitton, J. L.: Immunopathology during coxsackievirus infection. *Springer Semin Immunopathol*, 24, 201-13 (2002)

52. Gamble, D. R., M. L. Kinsley, M. G. FitzGerald, R. Bolton & K. W. Taylor: Viral antibodies in diabetes mellitus. *Br Med J*, 3, 627-30 (1969)

53. Helfand, R. F., H. E. Gary, Jr., C. Y. Freeman, L. J. Anderson & M. A. Pallansch: Serologic evidence of an association between enteroviruses and the onset of type 1 diabetes mellitus. Pittsburgh Diabetes Research Group. *J Infect Dis*, 172, 1206-11 (1995)

54. Banatvala, J. E., J. Bryant, G. Schernthaner, M. Borkenstein, E. Schober, D. Brown, L. M. De Silva, M. A. Menser & M. Silink: Coxsackie B, mumps, rubella, and cytomegalovirus specific IgM responses in patients with juvenile-onset insulin-dependent diabetes mellitus in Britain, Austria, and Australia. *Lancet*, 1, 1409-12 (1985)

55. Sadeharju, K., M. Lonnrot, T. Kimpimaki, K. Savola, S. Erkkila, T. Kalliokoski, P. Savolainen, P. Koskela, J. Ilonen, O. Simell, M. Knip & H. Hyoty: Enterovirus antibody levels during the first two years of life in prediabetic autoantibody-positive children. *Diabetologia*, 44, 818-23 (2001)

56. King, M. L., A. Shaikh, D. Bidwell, A. Voller & J. E. Banatvala: Coxsackie-B-virus-specific IgM responses in children with insulin-dependent (juvenile-onset; type I) diabetes mellitus. *Lancet*, 1, 1397-9 (1983)

57. Mertens, T., D. Gruneklee & H. J. Eggers: Neutralizing antibodies against Coxsackie B viruses in patients with recent onset of type I diabetes. *Eur J Pediatr*, 140, 293-4 (1983)

58. Frisk, G., G. Friman, T. Tuvemo, J. Fohlman & H. Diderholm: Coxsackie B virus IgM in children at onset of type 1 (insulin-dependent) diabetes mellitus: evidence for IgM induction by a recent or current infection. *Diabetologia*, 35, 249-53 (1992)

59. Clements, G. B., D. N. Galbraith & K. W. Taylor: Coxsackie B virus infection and onset of childhood diabetes. *Lancet*, 346, 221-3 (1995)

60. Andreoletti, L., D. Hober, C. Hober-Vandenberghe, S. Belaich, M. C. Vantyghem, J. Lefebvre & P. Wattre: Detection of coxsackie B virus RNA sequences in whole blood samples from adult patients at the onset of type I diabetes mellitus. *J Med Virol*, 52, 121-7 (1997)

61. Williams, C. H., S. Oikarinen, S. Tauriainen, K. Salminen, H. Hyoty & G. Stanway: Molecular analysis of an echovirus 3 strain isolated from an individual concurrently with appearance of islet cell and IA-2 autoantibodies. *J Clin Microbiol*, 44, 441-8 (2006)

62. Skarsvik, S., J. Puranen, J. Honkanen, M. Roivainen, J. Ilonen, H. Holmberg, J. Ludvigsson & O. Vaarala: Decreased *in vitro* type 1 immune response against coxsackie virus B4 in children with type 1 diabetes. *Diabetes*, 55, 996-1003 (2006)

63. Juhela, S., H. Hyoty, M. Roivainen, T. Harkonen, A. Putto-Laurila, O. Simell & J. Ilonen: T-cell responses to enterovirus antigens in children with type 1 diabetes. *Diabetes*, 49, 1308-13 (2000)

64. Dahlquist, G. G., J. Forsberg, L. Hagenfeldt, J. Boman & P. Juto: Increased prevalence of enteroviral RNA in blood spots from newborn children who later developed type 1 diabetes: a population-based case-control study. *Diabetes Care*, 27, 285-6 (2004)

65. Lonnrot, M., K. Korpela, M. Knip, J. Ilonen, O. Simell, S. Korhonen, K. Savola, P. Muona, T. Simell, P. Koskela & H. Hyoty: Enterovirus infection as a risk factor for beta-cell autoimmunity in a prospectively observed birth cohort: the Finnish Diabetes Prediction and Prevention Study. *Diabetes*, 49, 1314-8 (2000)

66. Salminen, K. K., T. Vuorinen, S. Oikarinen, M. Helminen, S. Simell, M. Knip, J. Ilonen, O. Simell & H. Hyoty: Isolation of enterovirus strains from children with preclinical Type 1 diabetes. *Diabet Med*, 21, 156-64 (2004)

67. Lonnrot, M., K. Salminen, M. Knip, K. Savola, P. Kulmala, P. Leinikki, T. Hyypia, H. K. Akerblom & H.

Hyoty: Enterovirus RNA in serum is a risk factor for beta-cell autoimmunity and clinical type 1 diabetes: a prospective study. Childhood Diabetes in Finland (DiMe) Study Group. *J Med Virol*, 61, 214-20 (2000)

68. Sadeharju, K., A. M. Hamalainen, M. Knip, M. Lonnrot, P. Koskela, S. M. Virtanen, J. Ilonen, H. K. Akerblom & H. Hyoty: Enterovirus infections as a risk factor for type I diabetes: virus analyses in a dietary intervention trial. *Clin Exp Immunol*, 132, 271-7 (2003)

69. Viskari, H., J. Ludvigsson, R. Uibo, L. Salur, D. Marciulionyte, R. Hermann, G. Soltesz, M. Fuchtenbusch, A. G. Ziegler, A. Kondrashova, A. Romanov, B. Kaplan, Z. Laron, P. Koskela, T. Vesikari, H. Huhtala, M. Knip & H. Hyoty: Relationship between the incidence of type 1 diabetes and maternal enterovirus antibodies: time trends and geographical variation. *Diabetologia*, 48, 1280-7 (2005)

70. Fuchtenbusch, M., A. Irnstetter, G. Jager & A. G. Ziegler: No evidence for an association of coxsackie virus infections during pregnancy and early childhood with development of islet autoantibodies in offspring of mothers or fathers with type 1 diabetes. *J Autoimmun*, 17, 333-40 (2001)

71. Graves, P. M., H. A. Rotbart, W. A. Nix, M. A. Pallansch, H. A. Erlich, J. M. Norris, M. Hoffman, G. S. Eisenbarth & M. Rewers: Prospective study of enteroviral infections and development of beta-cell autoimmunity. Diabetes autoimmunity study in the young (DAISY). *Diabetes Res Clin Pract*, 59, 51-61 (2003)

72. Honeyman, M. C., B. S. Coulson, N. L. Stone, S. A. Gellert, P. N. Goldwater, C. E. Steele, J. J. Couper, B. D. Tait, P. G. Colman & L. C. Harrison: Association between rotavirus infection and pancreatic islet autoimmunity in children at risk of developing type 1 diabetes. *Diabetes,* 49, 1319-24 (2000)

73. Smura, T., S. Blomqvist, A. Paananen, T. Vuorinen, Z. Sobotova, V. Bubovica, O. Ivanova, T. Hovi & M. Roivainen: Enterovirus surveillance reveals proposed new serotypes and provides new insight into enterovirus 5'-untranslated region evolution. *J Gen Virol,* 88, 2520-6 (2007)

74. Parashar, U. D., E. G. Hummelman, J. S. Bresee, M. A. Miller & R. I. Glass: Global illness and deaths caused by rotavirus disease in children. *Emerg Infect Dis*, 9, 565-72 (2003)

75. De La Rubia, L., M. I. Herrera, M. Cebrero & J. C. De Jong: Acute pancreatitis associated with rotavirus infection. *Pancreas,* 12, 98-9 (1996)

76. Nigro, G.: Pancreatitis with hypoglycemia-associated convulsions following rotavirus gastroenteritis. *J Pediatr Gastroenterol Nutr,* 12, 280-2 (1991)

77. Honeyman, M. C., N. L. Stone & L. C. Harrison: T-cell epitopes in type 1 diabetes autoantigen tyrosine phosphatase IA-2: potential for mimicry with rotavirus and other environmental agents. *Mol Med,* 4, 231-9 (1998)

78. Onodera, T., A. B. Jenson, J. W. Yoon & A. L. Notkins: Virus-induced diabetes mellitus: reovirus infection of pancreatic beta cells in mice. *Science*, 201, 529-31 (1978)

79. Campbell, I. L. & L. C. Harrison: Viruses and cytokines: evidence for multiple roles in pancreatic beta cell destruction in type 1 insulin-dependent diabetes mellitus. *J Cell Biochem*, 40, 57-66 (1989)

80. Blomqvist, M., S. Juhela, S. Erkkila, S. Korhonen, T. Simell, A. Kupila, O. Vaarala, O. Simell, M. Knip & J. Ilonen: Rotavirus infections and development of diabetes-associated autoantibodies during the first 2 years of life. *Clin Exp Immunol*, 128, 511-5 (2002)

81. Ward, K. P., W. H. Galloway & I. A. Auchterlonie: Congenital cytomegalovirus infection and diabetes. *Lancet,* 1, 497 (1979)

82. Yasumoto, N., M. Hara, Y. Kitamoto, M. Nakayama & T. Sato: Cytomegalovirus infection associated with acute pancreatitis, rhabdomyolysis and renal failure. *Intern Med*, 31, 426-30 (1992)

83. Nicoletti, F., G. Scalia, M. Lunetta, F. Condorelli, M. Di Mauro, W. Barcellini, S. Stracuzzi, M. Pagano & P. L. Meroni: Correlation between islet cell antibodies and anti-cytomegalovirus IgM and IgG antibodies in healthy first-degree relatives of type 1 (insulin-dependent) diabetic patients. *Clin Immunol Immunopathol,* 55, 139-47 (1990)

84. Pak, C. Y., H. M. Eun, R. G. McArthur & J. W. Yoon: Association of cytomegalovirus infection with autoimmune type 1 diabetes. *Lancet*, 2, 1-4 (1988)

85. Pak, C. Y., C. Y. Cha, R. V. Rajotte, R. G. McArthur & J. W. Yoon: Human pancreatic islet cell specific 38 kilodalton autoantigen identified by cytomegalovirus-induced monoclonal islet cell autoantibody. *Diabetologia*, 33, 569-72 (1990)

86. Hiemstra, H. S., N. C. Schloot, P. A. van Veelen, S. J. Willemen, K. L. Franken, J. J. van Rood, R. R. de Vries, A. Chaudhuri, P. O. Behan, J. W. Drijfhout & B. O. Roep: Cytomegalovirus in autoimmunity: T cell crossreactivity to viral antigen and autoantigen glutamic acid decarboxylase. *Proc Natl Acad Sci U S A*, 98, 3988-91 (2001)

87. Ivarsson, S. A., B. Lindberg, K. O. Nilsson, K. Ahlfors & L. Svanberg: The prevalence of type 1 diabetes mellitus at follow-up of Swedish infants congenitally infected with cytomegalovirus. *Diabet Med*, 10, 521-3 (1993)

88. Hiltunen, M., H. Hyoty, J. Karjalainen, P. Leinikki, M. Knip, R. Lounamaa & H. K. Akerblom: Serological evaluation of the role of cytomegalovirus in the pathogenesis of IDDM: a prospective study. The Childhood Diabetes in Finland Study Group. *Diabetologia,* 38, 705-10 (1995)

89. van der Werf, N., J. L. Hillebrands, F. A. Klatter, I. Bos, C. A. Bruggeman & J. Rozing: Cytomegalovirus infection modulates cellular immunity in an experimental model for autoimmune diabetes. *Clin Dev Immunol, 10*, 153-60 (2003)

90. Mordes, J. P., R. Bortell, E. P. Blankenhorn, A. A. Rossini & D. L. Greiner: Rat models of type 1 diabetes: genetics, environment, and autoimmunity. *Ilar J*, 45, 278-91 (2004)

91. Hillebrands, J. L., N. van der Werf, F. A. Klatter, C. A. Bruggeman & J. Rozing: Role of peritoneal macrophages in cytomegalovirus-induced acceleration of autoimmune diabetes in BB-rats. *Clin Dev Immunol*, 10, 133-9 (2003)

92. Conrad, B., R. N. Weissmahr, J. Boni, R. Arcari, J. Schupbach & B. Mach: A human endogenous retroviral superantigen as candidate autoimmune gene in type I diabetes. *Cell*, 90, 303-13 (1997)

93. Kim, A., H. S. Jun, L. Wong, D. Stephure, D. Pacaud, R. A. Trussell & J. W. Yoon: Human endogenous retrovirus with a high genomic sequence homology with IDDMK (1,2)22 is not specific for Type I (insulin-dependent) diabetic patients but ubiquitous. *Diabetologia*, 42, 413-8 (1999)

94. Lower, R., R. R. Tonjes, K. Boller, J. Denner, B. Kaiser, R. C. Phelps, J. Lower, R. Kurth, K. Badenhoop, H. Donner, K. H. Usadel, T. Miethke, M. Lapatschek & H. Wagner: Development of insulin-dependent diabetes mellitus does not depend on specific expression of the human endogenous retrovirus HERV-K. *Cell*, 95, 11-4; discussion 16 (1998)

95. Hao, W., D. V. Serreze, D. K. McCulloch, J. L. Neifing & J. P. Palmer: Insulin (auto)antibodies from human IDDM cross-react with retroviral antigen p73. *J Autoimmun*, 6, 787-98 (1993)

96. Jun, H. S. & J. W. Yoon: A new look at viruses in type 1 diabetes. *Diabetes Metab Res Rev*, 19, 8-31 (2003)

97. Suenaga, K. & J. W. Yoon: Association of beta-cell-specific expression of endogenous retrovirus with development of insulitis and diabetes in NOD mouse. *Diabetes*, 37, 1722-6 (1988)

98. Gaskins, H. R., M. Prochazka, K. Hamaguchi, D. V. Serreze & E. H. Leiter: Beta cell expression of endogenous xenotropic retrovirus distinguishes diabetes-susceptible NOD/Lt from resistant NON/Lt mice. *J Clin Invest*, 90, 2220-7 (1992)

99. Nakagawa, C., T. Hanafusa, J. Miyagawa, M. Yutsudo, H. Nakajima, K. Yamamoto, K. Tomita, N. Kono, A. Hakura & S. Tarui: Retrovirus gag protein p30 in the islets of non-obese diabetic mice: relevance for pathogenesis of diabetes mellitus. *Diabetologia*, 35, 614-8 (1992)

100. Munakata, Y., T. Kodera, T. Saito & T. Sasaki: Rheumatoid arthritis, type 1 diabetes, and Graves' disease after acute parvovirus B19 infection. *Lancet*, 366, 780 (2005)

101. O'Brayan, T. A., M. J. Beck, L. M. Demers & S. J. Naides: Human parvovirus B19 infection in children with new onset Type 1 diabetes mellitus. *Diabet Med*, 22, 1778-9 (2005)

102. Guberski, D. L., V. A. Thomas, W. R. Shek, A. A. Like, E. S. Handler, A. A. Rossini, J. E. Wallace & R. M. Welsh: Induction of type I diabetes by Kilham's rat virus in diabetes-resistant BB/Wor rats. *Science*, 254, 1010-3 (1991)

103. Brown, D. W., R. M. Welsh & A. A. Like: Infection of peripancreatic lymph nodes but not islets precedes Kilham rat virus-induced diabetes in BB/Wor rats. *J Virol*, 67, 5873-8 (1993)

104. Chung, Y. H., H. S. Jun, M. Son, M. Bao, H. Y. Bae, Y. Kang & J. W. Yoon: Cellular and molecular mechanism for Kilham rat virus-induced autoimmune diabetes in DR-BB rats. *J Immunol*, 165, 2866-76 (2000)

105. Zipris, D., J. L. Hillebrands, R. M. Welsh, J. Rozing, J. X. Xie, J. P. Mordes, D. L. Greiner & A. A. Rossini: Infections that induce autoimmune diabetes in BBDR rats modulate CD4+CD25+ T cell populations. *J Immunol*, 170, 3592-602 (2003)

106. Hyoty, H., L. Rasanen, M. Hiltunen, M. Lehtinen, T. Huupponen & P. Leinikki: Decreased antibody reactivity to Epstein-Barr virus capsid antigen in type 1 (insulin-dependent) diabetes mellitus. *Apmis,* 99, 359-63 (1991)

107. Surcel, H. M., J. Ilonen, M. L. Kaar, H. Hyoty & P. Leinikki: Infection by multiple viruses and lymphocyte abnormalities at the diagnosis of diabetes. Acta Paediatr Scand, 77, 471-4 (1988)

108. Makeen, A. M.: The association of infective hepatitis type A (HAV) and diabetes mellitus. *Trop Geogr Med*, 44, 362-4 (1992)

109. Masuda, H., T. Atsumi, A. Fujisaku, C. Shimizu, N. Yoshioka & T. Koike: Acute onset of type 1 diabetes accompanied by acute hepatitis C: the potential role of proinflammatory cytokine in the pathogenesis of

autoimmune diabetes. *Diabetes Res Clin Pract*, 75, 357-61 (2007)

110. Yoon, J. W., P. R. McClintock, T. Onodera & A. L. Notkins: Virus-induced diabetes mellitus. XVIII. Inhibition by a nondiabetogenic variant of encephalomyocarditis virus. *J Exp Med,* 152, 878-92 (1980)

111. Yoon, J. W., P. R. McClintock, C. J. Bachurski, J. D. Longstreth & A. L. Notkins: Virus-induced diabetes mellitus. No evidence for immune mechanisms in the destruction of beta-cells by the D-variant of encephalomyocarditis virus. Diabetes, 34, 922-5 (1985)

112. Baek, H. S. & J. W. Yoon: Role of macrophages in the pathogenesis of encephalomyocarditis virus-induced diabetes in mice. *J Virol,* 64, 5708-15 (1990)

113. Baek, H. S. & J. W. Yoon: Direct involvement of macrophages in destruction of beta-cells leading to development of diabetes in virus-infected mice. *Diabetes*, 40, 1586-97 (1991)

114. Hirasawa, K., H. S. Jun, H. S. Han, M. L. Zhang, M. D. Hollenberg & J. W. Yoon: Prevention of encephalomyocarditis virus-induced diabetes in mice by inhibition of the tyrosine kinase signalling pathway and subsequent suppression of nitric oxide production in macrophages. *J Virol*, 73, 8541-8 (1999)

115. Yoon, J. W., T. Morishima, P. R. McClintock, M. Austin & A. L. Notkins: Virus-induced diabetes mellitus: mengovirus infects pancreatic beta cells in strains of mice resistant to the diabetogenic effect of encephalomyocarditis virus. *J Virol*, 50, 684-90 (1984)

116. Shimada, A. & T. Maruyama: Encephalomyocarditis-virus-induced diabetes model resembles "fulminant" type 1 diabetes in humans. *Diabetologia*, 47, 1854-5 (2004)

117. Fujinami, R. S., M. B. Oldstone, Z. Wroblewska, M. E. Frankel & H. Koprowski: Molecular mimicry in virus infection: crossreaction of measles virus phosphoprotein or of herpes simplex virus protein with human intermediate filaments. *Proc Natl Acad Sci U S A*, 80, 2346-50 (1983)

118. Libbey, J. E., L. L. McCoy & R. S. Fujinami: Molecular mimicry in multiple sclerosis. *Int Rev Neurobiol*, 79, 127-47 (2007)

119. Christen, U. & M. G. von Herrath: Induction, acceleration or prevention of autoimmunity by molecular mimicry. *Mol Immunol*, 40, 1113-20 (2004)

120. Vreugdenhil, G. R., A. Geluk, T. H. Ottenhoff, W. J. Melchers, B. O. Roep & J. M. Galama: Molecular mimicry in diabetes mellitus: the homologous domain in coxsackie B virus protein 2C and islet autoantigen GAD65 is highly conserved in the coxsackie B-like enteroviruses and binds to the diabetes associated HLA-DR3 molecule. *Diabetologia*, 41, 40-6 (1998)

121. Atkinson, M. A., M. A. Bowman, L. Campbell, B. L. Darrow, D. L. Kaufman & N. K. Maclaren: Cellular immunity to a determinant common to glutamate decarboxylase and coxsackie virus in insulin-dependent diabetes. *J Clin Invest*, 94, 2125-9 (1994)

122. Oldstone, M. B., M. Nerenberg, P. Southern, J. Price & H. Lewicki: Virus infection triggers insulin-dependent diabetes mellitus in a transgenic model: role of anti-self (virus) immune response. *Cell*, 65, 319-31 (1991)

123. Ohashi, P. S., S. Oehen, K. Buerki, H. Pircher, C. T. Ohashi, B. Odermatt, B. Malissen, R. M. Zinkernagel & H. Hengartner: Ablation of "tolerance" and induction of diabetes by virus infection in viral antigen transgenic mice. *Cell*, 65, 305-17 (1991)

124. von Herrath, M. G., J. Dockter & M. B. Oldstone: How virus induces a rapid or slow onset insulin-dependent diabetes mellitus in a transgenic model. *Immunity*, 1, 231-42 (1994)

125. Seewaldt, S., H. E. Thomas, M. Ejrnaes, U. Christen, T. Wolfe, E. Rodrigo, B. Coon, B. Michelsen, T. W. Kay & M. G. von Herrath: Virus-induced autoimmune diabetes: most beta-cells die through inflammatory cytokines and not perforin from autoreactive (anti-viral) cytotoxic T-lymphocytes. *Diabetes*, 49, 1801-9 (2000)

126. Christen, U., T. Wolfe, U. Mohrle, A. C. Hughes, E. Rodrigo, E. A. Green, R. A. Flavell & M. G. von Herrath: A dual role for TNF-alpha in type 1 diabetes: islet-specific expression abrogates the ongoing autoimmune process when induced late but not early during pathogenesis. *J Immunol*, 166, 7023-32 (2001)

127. Christen, U., D. B. McGavern, A. D. Luster, M. G. von Herrath & M. B. Oldstone: Among CXCR3 chemokines, IFN-gamma-inducible protein of 10 kDa (CXC chemokine ligand (CXCL) 10) but not monokine induced by IFN-gamma (CXCL9) imprints a pattern for the subsequent development of autoimmune disease. *J Immunol*, 171, 6838-45 (2003)

128. Brehm, M. A., A. K. Pinto, K. A. Daniels, J. P. Schneck, R. M. Welsh & L. K. Selin: T cell immunodominance and maintenance of memory regulated by unexpectedly cross-reactive pathogens. *Nat Immunol*, 3, 627-34 (2002)

129. Christen, U., K. H. Edelmann, D. B. McGavern, T. Wolfe, B. Coon, M. K. Teague, S. D. Miller, M. B. Oldstone & M. G. von Herrath: A viral epitope that mimics a self antigen can accelerate but not initiate autoimmune diabetes. J Clin Invest, 114, 1290-8 (2004)

130. Haskins, K., M. Portas, B. Bradley, D. Wegmann & K. Lafferty: T-lymphocyte clone specific for pancreatic islet antigen. *Diabetes,* 37, 1444-8 (1988)

131. Katz, J. D., B. Wang, K. Haskins, C. Benoist & D. Mathis: Following a diabetogenic T cell from genesis through pathogenesis. *Cell,* 74, 1089-100 (1993)

132. Mueller, R., L. M. Bradley, T. Krahl & N. Sarvetnick: Mechanism underlying counterregulation of autoimmune diabetes by IL-4. *Immunity,* 7, 411-8 (1997)

133. Horwitz, M. S., A. Ilic, C. Fine, B. Balasa & N. Sarvetnick: Coxsackieviral-mediated diabetes: induction requires antigen-presenting cells and is accompanied by phagocytosis of beta cells. *Clin Immunol*, 110, 134-44 (2004)

134. Jun, H. S., C. S. Yoon, L. Zbytnuik, N. van Rooijen & J. W. Yoon: The role of macrophages in T cell-mediated autoimmune diabetes in nonobese diabetic mice. *J Exp Med*, 189, 347-58 (1999)

135. Horwitz, M. S., A. Ilic, C. Fine, E. Rodriguez & N. Sarvetnick: Presented antigen from damaged pancreatic beta cells activates autoreactive T cells in virus-mediated autoimmune diabetes. *J Clin Invest*, 109, 79-87 (2002)

136. Horwitz, M. S., C. Fine, A. Ilic & N. Sarvetnick: Requirements for viral-mediated autoimmune diabetes: beta-cell damage and immune infiltration. *J Autoimmun*, 16, 211-7 (2001)

137. Drescher, K. M., K. Kono, S. Bopegamage, S. D. Carso n & S. Tracy: Coxsackievirus B3 infection and type 1 diabetes development in NOD mice: insulitis determines susceptibility of pancreatic islets to virus infection. *Virology*, 329, 381-94 (2004)

138. Rouse, B. T.: Regulatory T cells in health and disease. *J Intern Med*, 262, 78-95 (2007)

139. Lindley, S., C. M. Dayan, A. Bishop, B. O. Roep, M. Peakman & T. I. Tree: Defective suppressor function in CD4 (+)CD25 (+) T-cells from patients with type 1 diabetes. *Diabetes*, 54, 92-9 (2005)

140. You, S., M. Belghith, S. Cobbold, M. A. Alyanakian, C. Gouarin, S. Barriot, C. Garcia, H. Waldmann, J. F. Bach & L. Chatenoud: Autoimmune diabetes onset results from qualitative rather than quantitative age-dependent changes in pathogenic T-cells. *Diabetes,* 54, 1415-22 (2005)

141. Ott, P. A., M. R. Anderson, M. Tary-Lehmann & P. V. Lehmann: CD4+CD25+ regulatory T cells control the progression from periinsulitis to destructive insulitis in murine autoimmune diabetes. *Cell Immunol,* 235, 1-11 (2005)

142. Chen, Z., A. E. Herman, M. Matos, D. Mathis & C. Benoist: Where CD4+CD25+ T reg cells impinge on autoimmune diabetes. *J Exp Med,* 202, 1387-97 (2005)

143. Rouse, B. T. & S. Suvas: Regulatory T cells and immunity to pathogens. *Expert Opin Biol Ther*, 7, 1301-9 (2007)

144. Pasare, C. & R. Medzhitov: Toll pathway-dependent blockade of CD4+CD25+ T cell-mediated suppression by dendritic cells. *Science,* 299, 1033-6 (2003)

145. Zipris, D., E. Lien, J. X. Xie, D. L. Greiner, J. P. Mordes & A. A. Rossini: TLR activation synergizes with Kilham rat virus infection to induce diabetes in BBDR rats. *J Immunol,* 174, 131-42 (2005)

146. Conrad, B., E. Weidmann, G. Trucco, W. A. Rudert, R. Behboo, C. Ricordi, H. Rodriquez-Rilo, D. Finegold & M. Trucco: Evidence for superantigen involvement in insulin-dependent diabetes mellitus aetiology. *Nature,* 371, 351-5 (1994)

147. Welsh, R. M., S. K. Kim, M. Cornberg, S. C. Clute, L. K. Selin & Y. N. Naumov: The privacy of T cell memory to viruses. *Curr Top Microbiol Immunol*, 311, 117-53 (2006)

148. Tam, P. E.: Coxsackievirus myocarditis: interplay between virus and host in the pathogenesis of heart disease. Viral *Immunol,* 19, 133-46 (2006)

149. Vrbikova, J., I. Janatkova, V. Zamrazil, F. Tomiska & T. Fucikova: Epstein-Barr virus serology in patients with autoimmune thyroiditis. *Exp Clin Endocrinol Diabetes,* 104, 89-92 (1996)

150. Testa, A., P. Castaldi, V. Fant, G. F. Fiore, V. Grieco, A. De Rosa, M. G. Pazardjiklian & G. De Rosa: Prevalence of HCV antibodies in autoimmune thyroid disease. *Eur Rev Med Pharmacol Sci,* 10, 183-6 (2006)

151. Matsuda, T., M. Tomita, J. N. Uchihara, T. Okudaira, K. Ohshiro, T. Tomoyose, T. Ikema, M. Masuda, M. Saito, M. Osame, N. Takasu, T. Ohta & N. Mori: Human T cell leukemia virus type I-infected patients with Hashimoto's thyroiditis and Graves' disease. *J Clin Endocrinol Metab,* 90, 5704-10 (2005)

152. Murray, R. S., B. Brown, D. Brian & G. F. Cabirac: Detection of coronavirus RNA and antigen in multiple sclerosis brain. *Ann Neurol,* 31, 525-33 (1992)

153. Stewart, J. N., S. Mounir & P. J. Talbot: Human coronavirus gene expression in the brains of multiple sclerosis patients. *Virology*, 191, 502-5 (1992)

154. Wandinger, K., W. Jabs, A. Siekhaus, S. Bubel, P. Trillenberg, H. Wagner, K. Wessel, H. Kirchner & H. Hennig: Association between clinical disease activity and Epstein-Barr virus reactivation in MS. *Neurology*, 55, 178-84 (2000)

155. Ascherio, A. & M. Munch: Epstein-Barr virus and multiple sclerosis. *Epidemiology*, 11, 220-4 (2000)

156. Alotaibi, S., J. Kennedy, R. Tellier, D. Stephens & B. Banwell: Epstein-Barr virus in pediatric multiple sclerosis. *JAMA,* 291, 1875-9 (2004)

157. Liedtke, W., R. Malessa, P. M. Faustmann & A. M. Eis-Hubinger: Human herpesvirus 6 polymerase chain reaction findings in human immunodeficiency virus associated neurological disease and multiple sclerosis. *J Neurovirol*, 1, 253-8 (1995)

158. Ferrante, P., E. Omodeo-Zorini, R. Caldarelli-Stefano, M. Mediati, E. Fainardi, E. Granieri & D. Caputo: Detection of JC virus DNA in cerebrospinal fluid from multiple sclerosis patients. *Mult Scler*, 4, 49-54 (1998)

159. Sips, G. J., D. Chesik, L. Glazenburg, J. Wilschut, J. De Keyser & N. Wilczak: Involvement of morbilliviruses in the pathogenesis of demyelinating disease. *Rev Med Virol*, 17, 223-44 (2007)

160. Perron, H., C. Geny, O. Genoulaz, J. Pellat, J. Perret & J. M. Seigneurin: Antibody to reverse transcriptase of human retroviruses in multiple sclerosis. *Acta Neurol Scand*, 84, 507-13 (1991)

161. Perron, H., B. Lalande, B. Gratacap, A. Laurent, O. Genoulaz, C. Geny, M. Mallaret, E. Schuller, P. Stoebner & J. M. Seigneurin: Isolation of retrovirus from patients with multiple sclerosis. *Lancet*, 337, 862-3 (1991)

162. Antony, J. M., Y. Zhu, M. Izad, K. G. Warren, M. Vodjgani, F. Mallet & C. Power: Comparative expression of human endogenous retrovirus-W genes in multiple sclerosis. *AIDS Res Hum Retroviruses*, 23, 1251-6 (2007)

163. Eddy, S., R. Wim, V. E. Peter, R. Tanja, T. Jan & V. S. Werner: Myasthenia gravis: another autoimmune disease associated with hepatitis C virus infection. *Dig Dis Sci*, 44, 186-9 (1999)

164. Saib, A., M. Canivet, M. L. Giron, F. Bolgert, J. Valla, S. Lagaye, J. Peries & H. de The: Human foamy virus infection in myasthenia gravis. *Lancet*, 343, 666 (1994)

165. Toussirot, E. & J. Roudier: Pathophysiological links between rheumatoid arthritis and the Epstein-Barr virus: an update. *Joint Bone Spine*, 74, 418-26 (2007)

166. Chen, Y. S., P. H. Chou, S. N. Li, W. C. Tsai, K. H. Lin, K. B. Tsai, J. H. Yen & H. W. Liu: Parvovirus B19 infection in patients with rheumatoid arthritis in Taiwan. *J Rheumatol*, 33, 887-91 (2006)

167. Triantafyllopoulou, A. & H. M. Moutsopoulos: Autoimmunity and coxsackievirus infection in primary Sjogren's syndrome. *Ann N Y Acad Sci*, 1050, 389-96 (2005)

168. Horiuchi, M., S. Yamano, H. Inoue, J. Ishii, Y. Nagata, H. Adachi, M. Ono, J. N. Renard, F. Mizuno, Y. Hayashi & I. Saito: Possible involvement of IL-12 expression by Epstein-Barr virus in Sjogren syndrome. *J Clin Pathol*, 52, 833-7 (1999)

169. Ramos-Casals, M., M. Garcia-Carrasco, M. P. Brito Zeron, R. Cervera & J. Font: Viral etiopathogenesis of Sjogren's syndrome: role of the hepatitis C virus. *Autoimmun Rev*, 1, 238-43 (2002)

170. Fillet, A. M., G. Raguin, H. Agut, S. Boisnic, S. Agbo-Godeau & C. Robert: Evidence of human herpesvirus 6 in Sjogren syndrome and sarcoidosis. *Eur J Clin Microbiol Infect Dis*, 11, 564-6 (1992)

171. Terada, K., S. Katamine, K. Eguchi, R. Moriuchi, M. Kita, H. Shimada, I. Yamashita, K. Iwata, Y. Tsuji, S. Nagataki & *et al.*: Prevalence of serum and salivary antibodies to HTLV-1 in Sjogren's syndrome. *Lancet*, 344, 1116-9 (1994)

172. Hrycek, A., D. Kusmierz, U. Mazurek & T. Wilczok: Human cytomegalovirus in patients with systemic lupus erythematosus. *Autoimmunity*, 38, 487-91 (2005)

173. Harley, J. B. & J. A. James: Epstein-Barr virus infection induces lupus autoimmunity. *Bull NYU Hosp Jt Dis*, 64, 45-50 (2006)

174. Seve, P., T. Ferry, M. Koenig, P. Cathebras, H. Rousset & C. Broussolle: Lupus-like presentation of parvovirus B19 infection. *Semin Arthritis Rheum*, 34, 642-8 (2005)

Abbreviations: APC: Antigen presenting cells, BBDP: Bio-Breeding Diabetes Prone, BBDR: Bio-Breeding Diabetes Resistant, CB4: Coxsackievirus B4, CRS: Congenital Rubella Sybdrome, CMV: Cytomegalovirus, EMCV: Encephalomyocarditis Virus, HLA: Human Leukocyte Antigen, KRV: Kilham Rat Virus, LCMV: Lymphocytic Choriomeningitis Virus, MHC: Major Histocompatibility, NOD: Non-Obese Diabetic, PV: Pichinde Viruse, T1D: Type 1 Diabetes, Treg: regulatory T cell

Key Words: Type 1 Diabetes, Virus, Autoimmunity, Molecular Mimicry, Bystander Damage, Review

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