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Coxsackievirus infection as an environmental factor in the etiology of type 1 diabetes

Martin J. Richer, Marc S. Horwitz *

Department of Microbiology and Immunology, The University of British Columbia, Vancouver, British Columbia, Canada

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ABSTRACT

Susceptibility to type 1 diabetes (T1D) is dictated by a complex interplay between genetic determinants and environmental influences. Accumulating evidence strongly supports viral infection as an important factor in the etiology of T1D. To this effect, several viruses have been associated with the capacity to induce or exacerbate T1D in both humans and mice. The most convincing evidence linking viral infection and autoimmunity comes from studies on enteroviruses, particularly coxsackievirus. In this review we will discuss the evidence associating coxsackievirus infection to T1D and present the current state of knowledge on the potential mechanism of coxsackievirus-mediated T1D.

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1. Introduction

Over the last several decades, incidence of type 1 diabetes (T1D) has been rapidly increasing worldwide. Despite the importance of genetic determinants in the development of T1D, the reported annual increases in incidence of 3 to 5% are far too rapid to be explained by genetics alone and are a strong indicator that environmental factors are involved in the etiology of T1D [1]. Several potential environmental factors have been the subject of investigation including diet, toxins and infectious agents. In this review, we will discuss the evidence linking one of these infectious agents, coxsackievirus, with T1D and discuss potential mechanisms of coxsackieviral-induced T1D.

2. Coxsackievirus as a causative agent of type 1 diabetes

T1D results from the autoimmune destruction of the insulin producing β cells of the pancreas. This autoimmune reaction is initiated long before onset of clinical symptoms, which do not appear until a vast majority of β cells have been destroyed. Autoantibodies directed at pancreatic islet antigens can usually be detected prior to clinical symptoms and

* Corresponding author. 3551-2350 Health Sciences Mall, Vancouver, BC, Canada V6T 0A5. Tel.: +604 822 6298; fax: +604 822 6041.
E-mail address: mhorwitz@interchange.ubc.ca (M.S. Horwitz).

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represent a useful tool for identifying at-risk patients [2]. Genetic determinants influence the susceptibility to T1D and this is dictated primarily by the human leukocyte antigen (HLA) although several other loci including CTLA-4, the insulin promoter and a region including the innate viral sensor, mda-5, are also susceptibility factors [3,4]. Several lines of evidence have demonstrated that despite this influence, genetic factors only account for approximately 50% of the overall susceptibility. For example, migration of populations that are associated with low disease susceptibility to higher risk areas leads to heightened susceptibility within these normally protected populations [5]. Similarly, despite a shared genetic profile there is a large discrepancy in the incidence of T1D between the neighboring populations of Finland and Russian Karelia [6]. Perhaps most convincingly, the rate of disease concordance between genetically identical twins is only approximately 40% [7,8]. Taken together with the rapid increase of disease worldwide, this evidence supports an important contribution of environmental factors in the induction of T1D.

The first suggestion of the role of viruses in the etiology of T1D was obtained following the observation that acute viral infections can be associated with sudden disease onset. Data demonstrating a seasonal correlation between periods of viral infections and the onset of T1D has further supported this hypothesis [7,8]. Interestingly, seasonal onset of T1D often occurs in populations considered less genetically predisposed to disease suggesting that viral infections can play a significant role in disease susceptibility [9]. Due to the complex interplay between genetic predisposition and environmental factors, it has remained challenging to firmly establish the role of particular viruses in the induction of T1D. Despite these difficulties, studies in both humans and animal models clearly suggest that viral infections can induce disease in susceptible hosts. Some of the most compelling evidence linking viruses to T1D has been generated from studies on coxsackievirus and this will be the focus of this review.

Coxsackieviruses are small, single stranded, positive-sense RNA viruses that belong to the enterovirus genus of the *Picornaviridae* family [10]. Enteroviruses are common human pathogens that are propagated in an oral-fecal manner leading to viral dissemination to several organs, including the pancreas [11]. Enteroviral infections usually present with mild symptoms but are also associated with acute conditions such as meningitis, encephalitis and pericarditis as well as chronic conditions such as chronic myocarditis, dilated cardiomyopathy and T1D [10]. Gamble and colleagues presented the first report of a link between coxsackievirus infection and T1D in 1969. They determined that viral-specific antibodies were more prevalent in T1D patients than in a control group [12]. Even more convincingly, a coxsackievirus strain isolated from the pancreas of a child who died following acute onset of T1D had the capacity to induce a diabetes- like disease in mice [13]. This isolated viral strain, coxsackievirus B4 (CB4), was further demonstrated to accelerate diabetes in genetically susceptible mouse models [14,15]. Several subsequent studies have demonstrated that recent-onset T1D patients present with increased viral-specific antibodies as well as increased viral RNA compared to non-diabetic patients [7,8,12]. Interestingly, these results were confirmed by a study undertaken in Cuba where the population has a low rate of T1D and a very high rate of enteroviral infections [16]. Taken together, these observations strongly support a link between coxsackievirus infections and the establishment of pancreatic autoimmunity.

Although the results of large-scale epidemiological studies on the role of enteroviruses in the induction of T1D have been inconsistent, several groups have demonstrated a relationship between infection and the induction of disease. The Finnish Diabetes Prediction and Prevention (DIPP) study has reported a greater rate of enteroviral infections in children that developed autoantibodies within a 6 month period than in the age-matched control group that did not develop autoantibodies [17] thus establishing a temporal link between enteroviral infection and development of pancreatic autoimmunity. The results of this study were confirmed by a separate study in Finland and by the Trial to Reduce IDDM in the Genetically at Risk (TRIGR) study where the presence of both enteroviral RNA and enteroviral specific antibodies were detected with greater frequency in children with signs of islet autoimmunity compared to a control population [18,19]. Conversely, several large-scale studies around the world have failed to establish a link between enteroviral infection and T1D [7,8]. Additionally, some studies have reported that levels of enteroviral infections are lower in some countries with high incidence of T1D compared to neighboring countries with lower incidences [20]. As coxsackieviral infection represents only one of many risk factors for T1D, it is not surprising that some of these studies failed to establish a link based simply on geographical differences in the prevalence of coxsackievirus. Additional factors including methodological differences, the genetic profiles of the population studied and time course of the study may also explain these discrepancies. Large-scale studies aimed at understanding the causes of T1D starting from a young age such as The Environmental Determinants of Diabetes in the Young (TEDDY) study should provide invaluable information on the role of environmental factors in the progression of T1D [21].

3. Mechanism of coxsackieviral induced type 1 diabetes

Several mechanisms have been proposed to explain viral-induction of T1D including direct destruction of islets, molecular mimicry, bystander damage and viral persistence. To date however, there is little data stemming from human studies to clearly support any of these options. In this section, we will review the mechanistic evidence gathered from both human studies and animal models.

The capacity of enteroviruses to infect human pancreatic islet cells has been confirmed by *in vitro* and *in vivo* studies. In one particular study, coxsackieviral infection was detected in islets of 50% ($n=6$) of the pancreatic tissue recovered from recent-onset T1D patients [22]. Virus isolation was accomplished from one of the tissues and sequencing revealed that the viral strain was CB4 [22]. Other studies have also reported the isolation of enteroviral strains from the pancreatic tissue of recent-onset T1D patients [13,23]. In one study, the isolated enteroviruses were used to determine the effect of infection on human β cell survival and function [23]. Enteroviral infection of human islets resulted in viral replication and direct cytolysis. [23], thus confirming that enteroviruses can infect and replicate within pancreatic islets and further

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