

Review

The impact of maternal infection or immunization on early-onset autoimmune diabetes

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Abstract

Maternal immune responses exert short and long-term influences on the newborn immune system. The transfer of maternal antibodies helps the newborn controlling infectious agents that are prevalent in the population. Furthermore, recent studies indicate that the fetus is able to mount inflammatory and cytotoxic T lymphocyte responses in the course of maternal infections. Herein, we discuss the relevance of these observations to the possible relation between maternal infection or immunization and childhood-onset autoimmune diabetes.

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1. Introduction

Autoimmune disorders represent a growing burden for health budgets as their incidence significantly increased over the last years [1,2]. This is especially well documented for early-onset type I autoimmune diabetes [3]. Identification of the mechanisms involved in the induction of autoimmunity is therefore of paramount importance. It is generally assumed that autoimmune disorders result from complex interactions between genetic traits and environmental factors. Indeed, the relatively low concordance rate of autoimmune diseases observed among identical twin pairs [4] and the changes in the incidence of type I diabetes and multiple sclerosis when children from a given population migrate from one region to another [5,6] strongly suggest a critical role for environmental factors in addition to genetic predisposition. Although there is clinical and experimental evidence for the involvement of infectious agents in the pathogenesis of autoimmunity, in most autoimmune diseases the trigger has not been formally identified, leaving room for hypotheses and allegations, especially on the putative role of vaccines [7].

The impact of maternal infection or immunization on the newborn immune system is often attributed to antibodies crossing the placenta or transmitted through breast-feeding

[8]. However, studies on cord blood from newborns suffering from congenital infection established that the human fetal immune system is able to mount T lymphocyte responses to pathogens. Pathogen-specific T-cells can be detected in cord blood obtained from children born to mothers with parasitic, mycobacterial or viral infections [9–12]. Following congenital cytomegalovirus infection, fetal CD8⁺ T-cells acquire effector functions including Th1-type cytokine production and perforin-dependent cytolytic activity [12].

With this background, it is indeed relevant to consider the possible impact of maternal infection or vaccination on the development of early-onset autoimmune disorder with a specific attention to type 1 diabetes.

2. Infectious agents as triggers of autoimmune diseases

2.1. Clinical evidence

In the clinics, rheumatic fever caused by an anti-streptococcal immune response that cross-reacts with cardiac myosin represents the prototype of autoimmune disease of infectious origin [13]. Another well-documented example is the Guillain-Barré syndrome occurring in the course of *Campylobacter jejuni* infection and mediated by anti-bacterial lipopolysaccharide antibodies cross-reacting with human gangliosides [14]. More recently, antibodies directed against the Tax protein of the human T-lymphotropic

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virus type 1 (HTLV-1) and cross-reacting with the heterogeneous nuclear ribonucleoprotein-A1 (hnRNP-A1) self-antigen were demonstrated in HTLV-1-associated myelopathy/tropical spastic paraparesis [15]. As far as T-cell-mediated autoimmunity is concerned, cross-reactivity between microbial peptides and self-antigens was documented in several disorders including type I diabetes, multiple sclerosis and antibiotic-resistant Lyme arthritis [16–18] but from a clinical perspective a clear-cut relation between the onset of autoimmune pathology and viral infection has only been firmly established for type 1 diabetes consecutive to congenital rubella [18,19].

As far as vaccines are concerned, there are only few examples of autoimmune pathology that could be firmly attributed to vaccination despite growing attention and increasing numbers of allegations on this issue (reviewed in [7]). One example is the Guillain–Barré syndrome associated in 1976–1977 with the vaccination campaign against swine influenza. With subsequent influenza vaccines, no significant increase in the development of Guillain–Barré syndrome was noted. The other example is the autoimmune thrombocytopenia which occasionally develops after measles–mumps–rubella vaccination. The very low risk of vaccine-induced autoimmune pathology indicates that mechanisms unique to infections with virulent microorganisms might be responsible for aggressive autoimmunity.

2.2. Induction mechanisms

It is generally assumed that activation and clonal expansion of autoreactive T lymphocytes represent critical steps in the pathogenesis of autoimmune diseases. Infections might be responsible for these key events through several non-mutually exclusive mechanisms including molecular mimicry, enhanced presentation of self-antigens, bystander activation, and impaired T-cell regulation [20].

2.2.1. Molecular mimicry

The molecular mimicry hypothesis is based on sequence homologies between microbial peptides and self-antigen epitopes. This concept was initially established in an experimental model where immunization with a hepatitis B virus polymerase peptide containing a six amino acid sequence of rabbit myelin basic protein elicited an autoimmune T-cell response leading to autoimmune encephalomyelitis [21]. The demonstration that a viral infection in itself can lead to autoimmune pathology caused by molecular mimicry was established in a murine model of herpes simplex keratitis where pathogenic autoreactive T clones were shown to cross-react with a peptide from the UL6 protein of the herpes simplex virus [22]. Evidence that a viral infection can induce pathogenic autoreactive T-cells was also provided in a model of Theiler's murine encephalomyelitis virus encoding a mimic peptide [23]. Autoimmunity dependent on CD8⁺ T lymphocytes might also involve molecular mimicry as shown in the model of inflammatory bowel disease induced

in immunodeficient mice by CD8⁺ T-cell clones directed against mycobacterial heat shock protein (hsp), hsp60 and cross-reacting with the hsp60 self-antigen [24]. However, suggestive these experimental data are, there is still uncertainty as to whether molecular mimicry is a key mechanism in the pathogenesis of autoimmunity [25]. As a matter of fact, molecular mimicry in itself is probably not sufficient to trigger autoimmune pathology.

2.2.2. Enhanced presentation of self-antigens

Infection can promote processing and presentation of self-antigens by several mechanisms. First, cellular damages induced by microbes can result in the release of sequestered self-antigens that stimulate autoreactive T-cells, as clearly demonstrated in autoimmune diabetes induced by coxsackievirus B4 infection in mice [26]. Second, the local inflammatory reaction elicited in tissues by microbes promotes dendritic cell maturation which represents a key step in the induction phase of immune responses. Indeed, microbial products engage Toll-like receptors on dendritic cells, resulting in upregulation of the membrane expression of major histocompatibility complex and costimulatory molecules and secretion of cytokines promoting T-cell activation including interleukin-12 (IL-12) [27]. Third, a T-cell response directed a single self-peptide can diversify during an inflammatory reaction, by a process of “epitope spreading” which has been well documented in murine models of encephalomyelitis [20].

2.2.3. Bystander activation

The release of cytokines such as interleukin-12 can promote bystander activation of memory T-cells and thereby trigger autoimmune reactions. Indeed, Shevach and coworkers established in murine models of encephalomyelitis that quiescent autoreactive T-cells can differentiate into pathogenic Th1 effectors in presence of microbial products inducing IL-12 synthesis [28,29]. Likewise, the group of Fujinami demonstrated that viral infection can elicit relapses of autoimmune encephalomyelitis in primed animals in a non-antigen specific manner [30].

2.2.4. Regulatory T-cells

There is growing evidence that regulatory T-cells are instrumental in controlling autoreactive T-cells both in neonates and adults [31,32]. Indeed, depletion of regulatory CD25⁺ T-cells promotes autoimmunity although in adult animals this maneuver is not sufficient by itself and requires administration of self-antigen [32]. It is clear that infectious agents can have profound influences, either positive or negative, on regulatory T-cells and this will certainly represent an area of intense investigation in the near future.

2.2.5. Antibodies

Beside their pathogenic role as direct effectors of autoimmune pathology, antibodies promote or enhance autoreactive T-cell responses in several ways. Indeed, antibodies

can facilitate capture of self-antigen by antigen-presenting cells and as a consequence the activation of autoreactive T-cells [33,34]. Furthermore, they might induce inflammation in the targeted tissue and thereby promote local release of self-antigens, epitope spreading and recruitment of activated T-cells [33]. These and other mechanisms probably explain the critical involvement of maternal antibodies in the development of autoimmune diabetes in the NOD mouse strain [35]. However, there is no evidence so far for such a scenario in human type 1 diabetes [34].

3. Viral infection during fetal life as a risk factor for early-onset diabetes

Several viruses have been considered as potential causes of type 1 autoimmune diabetes in children [18,36]. So far, the congenital rubella syndrome represents the most convincing evidence for such an association [18,19].

3.1. Congenital rubella

As many as 20% of children infected in utero with rubella virus subsequently develop diabetes within 5–20 years [19,36]. The autoimmune nature of the process leading to destruction of pancreatic islets is strongly suggested by a number of findings:

- (1) The genetic predisposition to diabetes associated with congenital rubella and classical idiopathic autoimmune diabetes is similar. In both cases, the presence of HLA-DR3 and the absence of HLA-DR2 identify individuals at risk [37].
- (2) Diabetic children with congenital rubella display autoantibodies to pancreatic islets [38] as well as antibodies to thyroid microsomes or thyroglobulin and often suffer from autoimmune thyroiditis [39].
- (3) Cytotoxic T-cell clones recognizing epitopes of glutamic acid decarboxylase 65, a self-antigen involved in classical autoimmune diabetes, were isolated from individuals with congenital rubella-associated diabetes [40]. It would obviously be important to determine whether such cytotoxic T-cells already differentiated during fetal life. This possibility is suggested by the recent observation that functional virus-specific cytotoxic T-cells develop in utero following congenital cytomegalovirus infection [12].
- (4) Neonatal infection of hamsters with rubella virus results in diabetes associated with the production of autoantibodies recognizing pancreatic islet cells [41].

Interestingly, genetic predisposition, molecular mimicry and virus-induced inflammation seem to concur to the development of diabetes in individuals with congenital rubella. Molecular mimicry was documented at both antibody and T-cell levels. Indeed, a monoclonal antibody to rubella virus capsid protein was found to recognize an antigenic epitope

of beta cells [42] and more significantly T-cell clones recognizing the islet autoantigen glutamic acid decarboxylase were shown to cross-react with rubella virus epitopes [43]. Furthermore, rubella virus was shown to infect a beta cell line and to stimulate the release of interleukin-6 [44]. The importance of the direct effects of rubella virus on pancreatic islets is supported by the observation that inadvertent immunization with rubella vaccine during pregnancy did not result in congenital rubella and apparently did not predispose to diabetes [45].

3.2. Other viruses

Autoimmune diabetes associated with congenital rubella syndrome led to investigate the possible relationship between other viral infections during fetal life and early-onset diabetes in children. In a prospective study of more than 16,000 children in Sweden, no correlation was found between congenital cytomegalovirus infection and subsequent occurrence of diabetes [46]. However, the predisposing genetic factors for autoimmune diabetes were not taken into consideration so that the possibility that congenital cytomegalovirus infection might represent a triggering event in genetically susceptible individuals still exists. The same remark applies to the possible involvement of maternal infection with Coxsackie B virus which was suggested in a single study [47].

4. Conclusion

Autoimmune diabetes associated with congenital rubella demonstrates that a maternal infectious disease might indeed trigger an autoimmune process in the offspring. The key pathogenic factors involved appear similar to those responsible for infection-induced autoimmunity in adults. They include genetic predisposition, damage of the target tissue by the microbe, and stimulation of autoreactive lymphocytes by cross-reactive microbial epitopes and/or native self-antigens. The recent evidence that the fetus is able to mount inflammatory and cytotoxic T-cell responses suggests that the pathological process leading to autoimmunity in early childhood might occasionally be initiated during fetal life. It is reassuring that immunization through vaccination does not carry a similar risk of inducing autoimmune pathology, probably because vaccines do not elicit direct damage of target tissues. As a consequence, maternal immunization should be considered more as a potential strategy to control infectious agents that could cause autoimmune diseases in early life rather than a risk factor for the development of these disorders.

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