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Current cases in which epitope mimicry is considered as a component cause of autoimmune disease: immune-mediated (type 1) diabetes

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Abstract. Autoimmune diseases result from a combination of genetic, immunologic, hormonal, and environmental factors. Infectious agents may induce the breakdown of immunological tolerance and the appearance of autoreactivity. However, the specific relationship between infection and autoimmunity is still unclear. One of the mechanisms responsible could be molecular mimicry between the infectious agent and self. The concept of molecular mimicry is a viable hypothesis in the investigation of the etiology, pathogenesis, treatment, and prevention of autoimmune disorders. Immune-mediated (type 1) diabetes in humans and in non-obese diabetic (NOD) mice is polygenic and characterized by autoimmune destruction of insulin-producing pancreatic β cells in islets of Langerhans. In NOD mice, a T-helper 1 (Th1)-based autoimmune response arises spontaneously against glutamate decarboxylase (GAD) concurrently with the onset of insulitis. Subsequently, this Th1-type autoreactivity spreads intra- and intermolecularly to other β cell autoantigens, suggesting that a Th1–type response is responsible for the progression of the disease, whereas Th2 responses when experimentally induced are protective. In humans, a homology between GAD and the P2-C protein of Coxsackie B make a cause-and-effect molecular mimicry an attractive hypothesis. Evidence to support the concept of molecular mimicry in diabetes is reviewed.

Key words. Autoimmune diseases; cytokines; molecular mimicry; autoantigens; immune-mediated diabetes mellitus; non-obese diabetic mice.

Autoimmune diseases are characterized by tissue destruction and/or functional impairment caused by autoreactive cells and/or autoantibodies. The etiologies of classical non-organ-specific autoimmune diseases such as systemic lupus erythematosis (SLE), Sjögren's syndrome, rheumatoid arthritis (RA), organ-specific immune-mediated (type 1) diabetes (IMD), and multiple sclerosis (MS) remain unknown. There are HLA-associated autoimmune diseases that have known microbial etiologies, e.g., chronic active hepatitis subsequent to viral hepatitis. However, environmental factors are presumed to be important participants in the development of autoimmune diseases, while few viruses or bacteria have been identified as etiologic agents. In specific instances where the inducing infectious agent is known, the underlying mechanism for the development of the specific autoimmune response is still unclear.

Epidemiological evidence shows that rheumatic fever may follow a streptococcal pharyngitis, while *Trypanosoma cruzi* infection is the initiator of Chagas disease [1]. There are, however, few, if any, examples in humans where molecular mimicry is known to give rise to an autoimmune disease. Epitope mimicry may indeed be involved in the pathogenesis of several diseases such as post-viral myocarditis [reviewed by Lawson, and Rose and Mackay, in this issue] or Chagas disease, but for many other diseases in which it has been implicated, such as IMD or RA, convincing evidence is still lacking. The progression from benign autoimmunity to pathogenic autoimmune disease appears to depend on the balance of the cytokines produced during the inflammatory process resulting from an infection [2].

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Microbial agents can induce autoimmune responses by a variety of unique mechanisms and several of these might occur during an infection: polyclonal activation of B lymphocytes [3], enhanced expression of major histocompatibility complex (MHC) class I or class II molecules on immune cells [4], bystander activation [5], alteration of immunoregulatory cells [6], and/or virus-induced molecular mimicry.

For most of the current theories, potentially autoreactive T cell clones are presumed to exist in the immunocompetent peripheral T cell pool, but activation of autoimmunity is considered not to take place unless a triggering or inductive event occurs.

Antigenic molecular mimicry is defined by cross-reactive immunity due to structural homologies shared by molecules encoded by dissimilar genes. Either linear amino acid sequences of the molecules or their conformational epitopes may be shared, even though their origins are separate. Regardless of the methods used for identification, it is now abundantly clear that molecular mimicries between proteins encoded by numerous microbes and host 'self' proteins are common events. The induction of cross-reactivity does not require the persistence of a replicating agent, and immune-mediated injury can occur after the immunogen has been eliminated, as in a hit-and-run event. Hence, the viral or microbial infection that initiates the autoimmune phenomenon may no longer be present by the time overt autoimmune disease develops. Thus, the microbes can induce cellular injury and release microbial antigens, which in turn generate immune responses that cross-react with structurally similar distinct self-antigens. Molecular mimicry depends on interactions between the three major components of the immune system involved in antigen recognition: MHC gene products expressed on the surface of antigen-presenting cells, T cell receptors (TCRs) of responding T cells and immunoglubulin receptors of reactive B cells.

Examples of epitope mimicry were first described in the early 1980s by investigators who found that monoclonal antibodies raised against SV40 T antigens could cross-react with host proteins inside cells [7]. The contacting residues of peptides involved in the binding to MHC are different from those involved in the binding to the TCR. This suggests that mimicking epitopes recognized by T cells requires sharing of additional residues involved in the binding of MHC-peptide complexes to the TCR for T cell activation.

Encephalitis, myelitis, and neuritis are complications of viral diseases, which often involve autoimmune reactions. Such complications may occur even after vaccination with attenuated or killed viral vaccines [8]. These clinical observations have stimulated a search for molecular mimicry between viral and host antigens in order to explain the activation of self-reactive T cell clones in these diseases. Subsequent to the development of hybridoma technology, information about antibodies specific for viral proteins that can bind to mammalian cells has increased vastly.

Immune mediated (type 1) diabetes (IMD)

IMD is the result of chronic autoimmune pancreatic β cell ablation, a process that usually begins early during childhood and is associated with a lifelong requirement for insulin replacement treatment, a reduced life span, and serious long-term complications [9]. Whereas IMD is the most common form of diabetes during childhood, there are multiple other forms of diabetes in children, e.g., non-insulin-dependent diabetes, maturity onset diabetes in the young (MODY), and insulin-resistant diabetes associated with a decreased function of insulin receptors. IMD is HLA-DR and -DQ associated, similar to RA and MS. The occurrence of IMD in identical twins is only 40–60% concordant [10], while in humans carrying the disease-associated HLA-DR/DQ phenotypes, the disease most often does not occur. Accordingly, it is believed that environmental factors must contribute to the disease, i.e., there is a multifactorial etiology [11]. However, low penetrance of disease in carriers of the disease-associated HLA phenotypes could also be explained by the need for additional susceptibility genes, which are non-MHC linked. The presence of such genes for type 1 diabetes in humans has been shown by microsatellite gene mapping in extensive family studies [12]. In the following, we discuss the findings of molecular mimicry between virus proteins and autoantigens in IMD.

The key factor that identifies IMD as an autoimmune disease is the presence of autoantibodies and autoreactive T cells directed against islet cells or their antigenic constituents [13]. A number of autoantigens have been identified in human IMD including insulin, GAD65, and the protein tyrosine phosphatases IA-2 and IA-2β. Non-obese diabetic (NOD) mice, a widely used animal model for human IMD, develop lymphocytic infiltration of the pancreas around 4–6 weeks of age, beginning as periductal and perivascular accumulation. By 6–8 weeks of age, the lymphocytes begin to invade the islets and specifically destroy the insulin-secreting β cells. Overt diabetes is observed around 3–4 months of age and female mice have significantly higher diabetes rates ($\sim$80%) than male mice ($\sim$20%). In NOD mice, autoimmunity appears to begin first against GAD, followed by epitope spreading to involve other antigens such as insulin [14]. In humans, autoimmunity to insulin and/or GAD develops early in the course of the disease and tends to extend to IA-2 later [15]. Progressive development of autoantibodies against multiple anti-

gens (epitope spreading) appears to be strongly associated with the risk for clinical disease [see Farris et al. in this issue].

Pathogenesis of IMD

IMD is a T-cell-mediated autoimmune disease resulting from specific autoimmune destruction of the pancreatic β cells through cytotoxic T-cell-induced apoptosis. The immunological mechanisms underlying human IMD are still not fully known. Strong evidence, both in humans and NOD mice, suggests that T cells are important contributors to the pathogenic process and that islet autoantigen-specific T cells play a key role. A number of studies have shown that both CD4+ and CD8+ T cells are required for optimal disease transfer. T cells from diabetic NOD mice induce diabetes in irradiated young NOD mice within 3–4 weeks of adoptive transfer [16]. This conclusion has been confirmed and extended in NOD mice with the severe combined immunodeficiency (SCID) phenotype. Islet-cell-specific CD4+ or CD8+ T cell clones alone can cause diabetes in NOD mice [17]. Furthermore, studies in this animal model have suggested a role for several proinflammatory and immunoregulatory cytokines, including interferon-γ (IFN-γ), interleukin-2 (IL-2), IL-4, IL-10 and tumor necrosis factor (TNF-α). Studies by Qin et al. [18] have shown that there is significant lymphocytic infiltration of the pancreatic islets in complete Freund's adjuvant (CFA)-treated NOD mice, yet these animals are protected from IMD. These studies suggest that a proportion of T cells within islets after such treatments must down-regulate the anti-self immune response, as opposed to causing β cell destruction. This balance in the immune response between destruction and protection may be maintained by the ratio of the T helper (Th)1 to Th2 cells. Various studies in NOD mice have shown that the β cell destruction is observed in conjunction with local IFN-γ-positive T cells, while lesions dominated by IL-4-producing T cells do not result in islet cell destruction. Furthermore, diabetes has been transferred by CD4+ T cells expressing a Th1 cytokine profile, while treatments with IL-4 or IL-10 protected mice from the disease. Furthermore, a Th1-dominated infiltration of T cells in the islets has also been observed in type 1 diabetes patients who died at disease onset. A study by Kallmann et al. [2] demonstrated a systemic bias of Th1/Th2 balance in the cytokine network towards cell-mediated immunity in IMD patients by determining ratios among several cytokine markers characteristic of cellular (Th1) or humoral (Th2) immune responses.

Recently, a subset of mature CD4−CD8− TCR$\alpha\beta$+ T lymphocytes with some phenotypic markers of natural killer (NK) cells, characterized by their restricted usage of Vα and Vβ chains in their expressed TCRs, positive selection by non-polymorphic molecules such as CD1, and expression of activated/memory and NK markers have been described [19]. These CD3+, CD4−CD8− TCR$\alpha\beta$+ lymphocytes together with a minor CD4+ T cell subset sharing similar features are usually referred to as natural killer T (NK T) cells [20]. This population has the particularity of secreting large amounts of cytokines, such as IL-4, after primary stimulation in vitro or in vivo [21]. The incomplete concordance in identical twins and the presence of autoreactive T cells and autoantibodies in individuals who do not develop diabetes suggest that other abnormalities may occur in the immune system for the onset of clinical disease. One group showed that diabetic siblings had lower frequencies of CD4−CD8−Vα24JαQ+ T cells compared with their non-diabetic siblings [22]. Furthermore, all Vα24JαQ+ T cell clones developed from the peripheral blood of diabetic twins/triplets secreted only IFN-γ upon stimulation, whereas clones from at-risk non-progressors and normals secreted both IL-4 and IFN-γ. They postulated a model for IMD in which Th1-cell-mediated tissue damage is initially regulated by Vα24JαQ+ T cells producing both cytokines, while their loss of capacity to secrete IL-4 predisposes subjects to IMD.

Several studies have reported a viral etiology associated with IMD [23–25]. The disease pathogenesis may involve multiple factors including the genetics of the host, viral strain, activation status of the autoreactive T cells, up-regulation of pancreatic MHC class I antigens, molecular mimicry between viral and β cell epitopes, and direct islet cell destruction by viral cytolysis. Viruses, as one of the environmental factors affecting the induction of IMD, may act as triggering agents of autoimmunity or as primary injurious agents, which directly damage pancreatic β cells.

Moreover, direct evidence for virus-induced diabetes largely comes from experiments in animals [26]. Several studies in humans also point to viruses as triggers of the disease [25, 27, 28]. These studies suggest that viruses play an important role in the pathogenesis of diabetes on the basis of:

1. The presence of viral-specific antigens in the islets of Langerhans and destruction of β cells in the pancreas of diabetic patients [29].
2. The presence of viral antibodies with rising titers in paired sera from newly diagnosed IMD patients [30].
3. A high frequency of Coxsackie-B-virus-specific IgM antibody in newly identified diabetic children [31].
4. cell damage in children who died of overwhelming viral infections [27].
5. The isolation of viruses from patients with acute-onset diabetes and the demonstration that these isolated viruses can cause diabetes in mice [32].

6. The association of antibody production with certain viral infections, e.g., congenital rubella and persistent cytomegalovirus infection [33].

Coxsackie B virus and rubella virus have been linked with IMD and in a few instances, Coxsackie B virus has even been isolated from pancreatic tissues of individuals with acute IMD. Inoculation of this virus into mice then produced IMD, fulfilling Koch's postulates [32]. The possibility that viruses might cause some cases of IMD by infecting and destroying pancreatic β cells has received considerable attention. However, it is difficult to demonstrate in vivo that viruses replicate in human β cells and/or produce diabetes in humans. An in vitro system was therefore developed to determine whether viruses are capable of destroying human β cells in culture [34, 35]. By this method, several common human viruses, including mumps virus, Coxsackie B3 virus [36], Coxsackie B4 virus [37], and reovirus type 3 [34] were clearly shown to be able to infect human β cells. In addition, radioimmunoassay demonstrated that the infection markedly decreased the insulin content of the β cells.

A strong correlation was found between the cytomegalovirus (CMV) genome in the immunocytes and the islet cell autoantibodies in the serum from diabetic patients [38]. About 15% of newly diagnosed IMD patients have been reported to have persistent CMV infections. Furthermore, molecular mimicry between protein 2C (p2-C) of Coxsackie virus B4 and the autoantigen GAD65 has been proposed to play a role in the pathogenesis of IMD. Kaufman et al. [39] and Vreugdenhil et al. [25] showed that the amino acid sequence of p2-C shares striking homology with a sequence in GAD65 (PEVKEK) and is highly conserved in Coxsackie virus B4 isolates and in other viruses of the subgroup of Coxsackie B-like viruses. These are the most prevalent enteroviruses and therefore exposure to the mimicry motif should be a frequent event throughout life. Furthermore, they suggested that molecular mimicry might be limited to the HLA-DR3 subpopulation of IMD patients suggesting that the presentation of the homologous peptides by HLA molecules is essential for T cell reactivity. In addition, this specific region of GAD65 contains a T cell epitope involved in the GAD cellular autoimmunity in humans with IMD [40] and this region is an early target of cellular immunity in NOD mice [41, 42].

In humans, cellular proliferative responses to determinants common to GAD have been noted [43] and a similarly shared proliferative response marked 25% of 16 newly diagnosed IMD patients but none of the 13 healthy matched control subjects [40]. Many studies have demonstrated GAD autoantibodies in patients with IMD as well as in those at risk for the disease [44]. Another study further supports a link between Coxsackie virus and IMD, associating IgM antibodies to Coxsackie B virus as a marker of recent exposure to the virus in newly diagnosed IMD patients and age/sex-matched controls [45]. In that report, humoral immunity to Coxsackie virus and GAD appeared to cluster, even in people without diabetes. A set of overlapping synthetic GAD65 peptides was used to study the most reactive T cell determinants in individuals at increased risk for IMD, i.e., autoantibody-positive, first-degree relatives of IMD patients. Elevated in vitro T cell responses were observed to GAD65 peptides (amino acids 247–266 and 260–279) in newly diagnosed IMD patients and autoantibody positive at risk individuals [46]. The sequence of this region of GAD65 (amino acids 250–273) is significantly similar to the p2-C protein of Coxsackie B virus (fig. 1). Furthermore, in a study by Lonnrot et al. [47], substantial cross-reactivity between p2-C and GAD65 peptides was seen, when they raised hyperimmune serum in rabbits against the seven different synthetic peptides of the 2-C protein of Coxsackie B4.

However, not all published reports have demonstrated a linkage between immunity to GAD and Coxsackie virus. For example, one study identified a non-Coxsackie-homologous region of GAD65 as a predominant

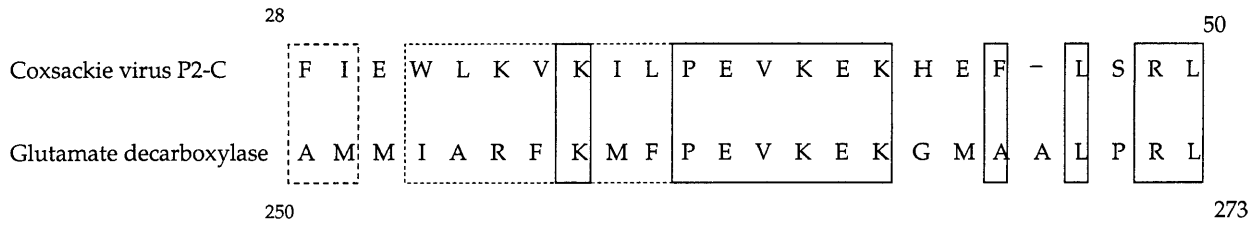

Figure 1. Sequence homology between Coxsackie virus and human GAD65. The solid lines denote identical amino acid residues. Dashed lines denote amino acid residues with similar charge, polarity, or hydrophobicity. The numbers refer to the number of amino acid residues from the N terminus of each protein. [Reproduced with permission from Elsevier Science]

cellular immune epitope while studying polyclonal human T cell responses [48].

Animal studies also provide strong support for this GAD-Coxsackie mimicry hypothesis. In NOD mice, T cell responses to GAD appear to be a key event in the induction and propagation of immunity to β cells. Immunization of NOD mice with either Coxsackie virus p2-C protein or the Coxsackie virus peptide containing the region of sequence similarity with GAD65 could induce T cell responses that cross-reacted with GAD or GAD peptides corresponding to the region of sequence similarity [43].

However, a study by Horwitz et al. [49] showed that diabetes induced by Coxsackie virus is not by molecular mimicry but is due to bystander activation. This emphasizes the complexity of the interplay between the immune responses to infection and autoimmune diseases. Furthermore, rotavirus VP7 displays 67% identity and 92% homology over 12 amino acids with a T cell epitope on GAD65, and 67% identity and 83% homology with GAD67 [50].

IA-2 is another molecular target of pancreatic islet autoimmunity in IMD. In another recent study, the epitope-spanning peptide 805–820 elicited maximum T cell responses in all at-risk relatives out of a total of 68 overlapping, synthetic peptides encompassing the intracytoplasmic domain of IA-2 [50]. This epitope was found to have 56% identity and 100% similarity over 9 amino acids with a sequence in VP7, a major immunogenic protein of human rotavirus. This dominant epitope also has 75–45% identity and 88–64% similarity over 8–14 amino acids to sequences in Dengue, CMV, measles, hepatitis C, and canine distemper viruses, and the bacterium *Haemophilus influenzae*. Furthermore, three other IA-2 epitope peptides have 71–100% similarity over a 7- to 12-amino-acid stretch to herpes, rhino-, hanta-, and flaviviruses. Two others have 80–82% similarity with dietary proteins of milk, wheat, and bean proteins. These molecular mimicries could lead to triggering or exacerbation of β-cell autoimmunity.

Besides GAD and IA-2, homologies have been detected between other β cell autoantigens and environmental agents associated with IMD [45] as listed in table 1.

Table 1. Identified homologies between β cell autoantigens and environmental/immunomodulatory agents associated with immune-mediated diabetes.

β cell autoantigen	Putative environmental mimic
GAD*	Coxsackie virus P2-C protein, Ia^{g7}; HLA-DQ (IDDM-susceptible alleles); HLA-DQ (IDDM-protective alleles); adenovirus; hsp60
ICA69	Bovine serum albumin
JunB	HLA-DQβ; IA-2; human herpes virus types 1 and 4
Carboxypeptidase	HLA-DQ (IMD-susceptible alleles); Coxsackie virus; influenza virus A

GAD, glutamic acid decarboxylase; HLA, human leukocyte antigen; IDDM, insulin-dependent-diabetes mellitus; hsp60, heat shock protein 60; ICA69, islet cell autoantigen 69; IMD, immune-mediated diabetes.

* GAD also has homologies with proinsulin. Of the list above, the authors rate the mimicry involving GAD and Coxsackie virus P2-C protein as the most likely to be relevant to IMD. [Reprinted from ref. 23 with permission from Elsevier Science]

Factors governing molecular mimicry and associated virus-induced autoimmune diseases

Viral transgenes

Oldstone [51] and others [52, 53] have studied transgenic IMD mice models for autoimmune diseases to examine the molecules and events involved in virus-induced autoimmune diseases. Oldstone [51] used the rat insulin promoter to express a viral gene in the β cells of Langerhans. Diabetes did not occur spontaneously (incidence $< 1\%$ in these mice) unless tolerance was broken to the viral (self) antigen, when the incidence increased to 90–95%. When the viral transgene was expressed only in β cells, potentially autoreactive T cell clones of high antigenic affinity passed through the thymus by positive selection to reside in the periphery. Upon challenge with the virus, diabetes followed within 7–12 days. However, the situation changed when the transgene was expressed in the target cell (β cells) and also in the thymus. In this instance, high-affinity antiviral (self) T cells were removed by negative selection. Only low-affinity T cells that were anergic/unresponsive passed to the periphery. In the absence of viral infection, diabetes could be induced when such anergic cytotoxic T lymphocyte (CTL) clones (of high or low affinity) in the periphery were activated as they passed into the islet environment where IFN-γ or B7.1 were expressed. In addition, activation of low-affinity but not high-affinity CTL clones required CD4 help. For diabetes to occur in both the high- and low-affinity models, perforin and IFN-γ were required. Disallowing IFN-γ expression experimentally and/or establishing IL-4 expression in the islets aborted IMD. Expression of IFN-γ or TNF-α in the islets hastened the kinetics and/or enhanced the severity and incidence of diabetes.

These observations led to the design of various therapeutic approaches to halt virus-induced IMD. Diabetes was prevented when the cytokine profile was changed from a Th1 to a Th2 phenotype in the islet of Langerhans (IFN-γ to IL-4, IL-10 and transforming growth factor-β) [54, 55]. One interesting way by which this occurred was through the oral administration of porcine insulin [55]. However, the protective effect was lost when a single or double amino acid change was

made in the β chain of the insulin molecule that protected mice from diabetes. In the latter studies, transgenic mice developed diabetes within 1 week after lymphocytic choriomeningitis virus challenge. These studies suggest that potential autoimmune T cells exist in the periphery and once activated by cytokines such as IFN-γ or viral infection can act to break immune tolerance. The activated lymphocytes release additional cytokines in the local milieu, thus governing whether the autoimmune disease process occurs rapidly or slowly.

Superantigens

Besides molecular mimicry, retroviral expression of superantigens (SAgs) may be able to activate clonal expansion of autoreactive T cell clones. SAgs have been implicated in the pathogenesis of various autoimmune diseases [56, 57]. Originally described as minor-lymphocyte-stimulating antigens, retroviral SAgs expressed by B cells interact with the development of T helper cells of both Th1 and Th2 subtypes in mice. This is of interest, since β cell destruction appears to be Th1 dependent. Furthermore, a glycemia-related increased expression of p73 core protein of intra-cisternal retroviral particles has been noted in genetically diabetic (db/db) and NOD/Lt mice [58]. These mice spontaneously develop insulin autoantibodies (IAAs) that cross-react with the p73 antigen, suggesting that a molecular mimicry mechanism could be involved, despite the fact that they have little linear sequence similarity. Another study in patients with IMD demonstrated that two-thirds of IAA-positive sera also reacted with p73 [59]. Conrad et al. [57] isolated a novel mouse mammary-tumor-virus-related human endogenous retrovirus (HERV) in patients suffering from acute-onset type 1 diabetes termed the HERV IDDMK$_{1,2}$22 subtype. The N-terminal moiety of the envelope (env) gene encoded an MHC-class-II-dependent SAg. They proposed that expression of this SAg, induced extra-pancreatically and by professional antigen-presenting cells, could lead to β cell destruction via the systemic activation of autoreative T cells. Furthermore, selective expansion of Vβ7+ T cells in the islet cell infiltrates from two patients with recent-onset IMD was associated with extensive junctional diversity of Vβ7+ T cell clones. These investigators demonstrated that islet cell membrane preparations preferentially expanded Vβ7+ T cells from non-diabetic peripheral blood mononuclear cells [60]. Others and we, however, were unable to confirm IMD specificity of IDDMK$_{1,2}$22, since it was equally recoverable as viremia from controls as well as patients [61]. Furthermore, both patients and controls made antibodies to env proteins. The SAg effect reported also needs confirmation. Nonetheless, this mechanism is another alternative to mimicry to account for viral instigation of autoimmunity.

To establish molecular mimicry as a mechanism responsible for autoimmune diseases, identifying the precise epitope that initiates the putative cross-reactive immune response is important. Additional complexity that has come into the limelight due to various animal studies is that of epitope spreading. Both intra-molecular and inter-molecular epitope spreading have been described in NOD mice [41, 58]. These studies demonstrated that T cell responses in NOD mice expand in vivo against a defined group of islet cell antigens in an orderly sequential manner. These responses in the young NOD mice first show a strong reactivity to the GAD enzyme and not to other islet cell antigens. Furthermore, the initial response to GAD is first limited to one region of the protein only. Gradually, this response spreads intramolecularly to involve other regions of the protein. Eventually, after the destructive islet cell inflammation (insulitis) as a result of autoimmunity to β cells, the T cell responses spread inter-molecularly to involve other islet cell proteins (e.g., heat shock protein 60, carboxypeptidase H, and insulin) [62]. This epitope spreading makes it difficult to predict which putative cross-reactions, if any, are important in terms of disease induction, and which do not give rise to autoimmune pathology, particularly in humans with differing genotypes who are exposed to many infections.

Conclusions and future directions

The concept of molecular mimicry is a useful tool in understanding the etiology, pathogenesis, treatment, and prevention of autoimmune disorders. This review has summarized the evidence that viral infection can serve to trigger autoimmune reactivity. Several mechanisms have been proposed: chronic persistence of viruses in the target cells may provoke their immune-mediated destruction in an attempt to eradicate the virus, and/or viruses may induce inflammatory responses that result in release of self-antigens and enhancement of the costimulatory activity, which may trigger autoreactive T cells; or viral determinants may mimic host antigens and directly stimulate self-reactive T cell clones to attack host tissues. HLA molecules further play a crucial role in molecular mimicry in presentation of the homologous peptides to the self-reactive T cells, e.g., the HLA-DR3 molecule in IMD. Furthermore, the clinical features of the resulting autoimmune disease would depend upon the qualitative features of the immune response, the particular cytokines produced (Th1 vs Th2), and the tissue distribution of the target self-antigens. After tissue damage begins, additional self-antigens are released which may further cross-react with an infecting virus.

Various reports showing a strong similarity between GAD65 and Coxsackie virus p2-C protein do not prove that antigenic molecular mimicry is the cause of IMD. To demonstrate a stronger link, islet autoantibody-positive (at-risk) individuals who show an increased frequency of peripheral T cell response to GAD would also need to show a positive response to Coxsackie virus protein. Follow-up studies are required in at-risk individuals with autoimmunity to GAD, other autoantigens, and/or Coxsackie virus proteins.

Various transgenic animal models designed to evaluate molecular mimicry and virus-induced autoimmune diseases have revealed that potential autoimmune-inducing T lymphocytes exist in the periphery. Specific therapies to inhibit viral replication, inactivate antiviral CD8 + CTLs or change the cytokine profile to a more protective one (Th1 or Th2) have proven successful in the treatment of these transgenic animal models. These interventions are likely adaptable to human autoimmune diseases. However, these mechanisms do not provide direct evidence that viral infection can precipitate autoimmune diseases by mechanisms that include molecular mimicry. Despite the extensive knowledge that has accumulated, the specific relationship between infections and autoimmunity is still obscure.

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