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Targeting the Trimolecular Complex

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Abstract

Class II major histocompatibility molecules (MHC) confer disease risk for multiple autoimmune disorders including type 1 diabetes. The interaction between the components of the trimolecular complex (CD4⁺ T cell receptors, self-peptide, and MHC class II molecules) plays a pivotal role in autoimmune disease pathogenesis. The development of therapies targeting various components of the trimolecular complex for the prevention of type 1 diabetes is actively being pursued. This review focuses on the components of the anti-insulin trimolecular complex, registers of insulin peptide binding to 'diabetogenic' MHC class II molecules, and therapies targeting each component of the trimolecular complex.

Keywords

diabetes; autoimmunity; immune therapies; insulin; autoreactive T cells; antigen presentation

1. Introduction

Type 1 diabetes (T1D) is a T cell mediated autoimmune disorder specific for the beta cells within the islets of the pancreas [1;2]. T1D is now a predictable disease in humans by measuring islet autoantibodies (directed against epitopes of insulin, GAD, IA-2, and ZnT8) [3]. Having two or more islet autoantibodies predisposes a significant risk to developing abnormal glucose homeostasis and eventually persistent hyperglycemia requiring insulin treatment [4]. Despite T1D being a predictable disease, safely preventing the disease is currently not possible. Furthermore, the incidence of T1D in many industrialized countries is increasing dramatically, doubling every 20 years [5;6]. Even more concerning is that age group most affected by the increasing incidence is children less than 5 years of age [7]. Over the last decade, many immune intervention trials at disease onset or in at risk populations have been attempted but with minimal to no sustained effect on preserving endogenous insulin secretion [8]. There is a clear need for safe and specific therapies to stop the underlying autoimmune destruction of pancreatic beta cells.

There is strong evidence from the non-obese diabetic (NOD) mouse, which spontaneously develops autoimmune diabetes and insulinitis, that the fundamental cause of disease is the

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recognition of insulin peptides in specific registers presented by polymorphic “diabetogenic” alleles and recognized by T cell receptors (TCR) with germline encoded conserved sequences [9–11]. The components of this trimolecular complex (MHC class II molecule – insulin B chain amino acids 9–23–CD4+ T cell receptor) provide a framework to understand CD4+ T cell autoreactivity in T1D pathogenesis and specific targets for disease intervention.

2. The anti-insulin trimolecular complex

2.1 Major histocompatibility complex molecules

The major genetic determinant of T1D is encoded by genes in the human leukocyte antigen (HLA) complex. Within the HLA region, the major histocompatibility (MHC) class II alleles confer T1D risk. In humans, MHC II alleles are divided into DP, DQ, and DR with specific alleles predisposing both disease risk and prevention. Approximately 90% of all individuals with autoimmune T1D have DQ8 (DQA1*0301, DQB1*0302) and/or DQ2 (DQA1*0501, DQB1*0201) alleles. Genome wide association studies indicate that the odds ratio for developing T1D with these alleles ranges from 6.5 to 11 [12;13]. Not only do MHC class II molecules predispose risk but also protect from disease with DQ6 (DQB1*0602) conferring protection with an odds ratio of 0.03 for disease development [12].

MHC class II molecules function to present processed antigens to CD4+ T cells. Along the peptide binding groove of these molecules are pockets that accommodate amino acid side chains of the presented peptide. DQ8 has four structural pockets (pockets 1, 4, 6, and 9) capable of anchoring peptides in the groove for presentation to T cells [14]. Similar to humans, the murine MHC class II molecule (I-A^{g7}) predisposes risk for diabetes development in the NOD mouse [15]. I-A^{g7} is structurally similar to DQ8 with both molecules having polymorphisms leading to a unique pocket 9 in the peptide binding groove of the molecule. A polymorphism in the DQ8 beta chain at position 57 from an aspartic acid residue to a valine, leucine, or alanine disrupts a salt bridge that is formed with an arginine residue at the 76 position of the DQ8 alpha chain [16]. Loss of this salt bridge allows for a positively charged pocket 9 with the 76Arg side chain able to interact with peptide side chains. Murine I-A^{g7} has a similar substitution at 57Asp to serine, again disrupting the salt bridge with 76Arg. This polymorphism is significant in that mutating a single amino acid in the I-A^{g7} chain (57Ser → 57Asp) completely prevents all NOD diabetes [17]. Also noteworthy is the fact that the protective alleles, DQ6 in humans and the murine homolog I-A^b in the C57BL/6 mouse, maintain aspartic acid at the 57 position. In summary, subtle structural changes to MHC class II molecules, especially polymorphisms altering anchor pockets along the peptide binding groove, influence disease susceptibility for T1D.

2.2 Insulin as an autoantigen

There is convincing evidence in the NOD mouse model that insulin is a primary autoantigen with the amino acids 9–23 of the B chain (B:9–23) pathogenic. Mutating a single amino acid in the insulin B:9–23 peptide sequence (B16:Tyr → Ala) maintains euglycemia while preventing all NOD diabetes [18;19]. Recent work indicates that the insulin B:9–23 peptide can bind in multiple registers to the I-A^{g7} peptide binding groove (Fig 1A). Using register trapping techniques, numerous anti-B:9–23 T cell hybridomas, capable of inducing insulin autoantibodies and diabetes, recognize the peptide in a low affinity register, termed register 3 [9;10]. In this low affinity register 3, amino acids B:14–22 are in the p1–p9 positions with the B22Arg residue in the p9 pocket, which is an unfavorable match due to the positive charge of the arginine side chain and the positively charged p9 pocket. The separate registers of binding provide distinct epitopes for TCR interaction as depicted in figure 1B.

Along with the structural similarities between murine I-A^{g7} and human DQ8, the amino acid sequence of the insulin B:9–23 peptide is identical in mice and humans [20]. With the

significant homology, human insulin specific T cells may respond to the B:9-23 peptide in a similar low affinity register. Our preliminary studies support this concept with peripheral blood mononuclear cells (PBMCs) from newly diagnosed T1D patients having more robust IFN- γ Elispot responses to insulin B:9-23 register 3 mimotope peptides than compared to the native peptide (unpublished data).

2.3 T cell receptors

The third component of the trimolecular complex is T cell receptors on CD4⁺ T cells. Most TCRs interact with peptide/MHC through six complementarity determining regions (CDR) with the alpha and beta chains having three each. The CDR3 region is most crucial for peptide recognition [21]. In the NOD mouse, approximately 70% of TCRs reacting with the insulin B:9-23 peptide utilize a single alpha chain, TRAV5D-4 [22;23]. TRAV5D-4 containing TCRs are able to induce insulin autoantibodies, insulinitis, and diabetes when the specific alpha chain is introduced into an α -chain only retrogenic mouse [11]. In these mice, individual CD4⁺ T cells contain the specific alpha chain sequence which pairs with endogenously derived beta chains in vivo. The human ortholog of TRAV5D-4 is TRAV13-1. Using the same experimental system of α -chain retrogenic mice, chimeric TCRs (TRAV13-1 with murine beta chains) were able to induce insulin autoantibodies and diabetes. This evidence suggests that TCR recognition to the insulin/MHC complex in the NOD mouse may be comparable in humans.

3. MHC class II specific therapies

With the strong MHC class II association in T1D, blocking or altering allele specific antigen presentation provides a defined target for disease intervention (Fig 2). In our initial work, we hypothesized that small organic molecules predicted to occupying pockets along the murine I-A^{g7} peptide binding groove would block anti-B:9-23 T cell reactivity [24]. Using in silico molecular modeling and docking, a library of 140,000 ‘drug-like’ small molecules from the National Institute of Health Developmental Therapeutics Program was screened to bind pockets 1, 4, 6, and 9. Several of the top 40 scoring compounds predicted to bind pocket 1 and pocket 6 inhibited B:9-23 stimulated T cell activation. Furthermore, one compound, tetraazatricyclododecane (TATD), predicted to occupy pocket 6 blocked stimulation of T cells responding to whole insulin, necessitating protein processing along the MHC class II pathway. The compound also inhibited T cell hybridoma activation in the presence of whole NOD islets, which have been shown to contain insulin peptides including B:9-23. TATD was also predicted to bind pocket 6 of the DQ8 peptide binding groove and blocked activation of a human B:9-23 responsive TCR restricted to DQ8. Blocking MHC class II antigen presentation may lead to a delay in diabetes onset or prevention.

It has recently been shown by two independent groups of investigators that a small molecule drug, abacavir used to suppress HIV replication [25], can bind a specific MHC class I allele HLA-B*57:01. Abacavir was crystalized binding to the middle of the peptide binding groove with a mimotope peptide and further shown to alter repertoire of peptides presented to CD8 T cells [26;27]. Although abacavir binds a class I allele, these studies indicate it is possible for small molecule drug to bind and alter MHC antigen presentation to T cells.

In addition to identifying compounds that block antigen presentation to T cells, we also made an unexpected discovery that small molecules predicted to occupy pocket 9 of the I-A^{g7} peptide binding groove result in T cell stimulation in the presence of the insulin B:9-23 peptide. Half of the 40 screened compounds resulted in an enhanced T cell hybridoma response only in the presence of insulin B:9-23 [24]. Glyphosine, a pocket 9 compound studied in detail, led to robust IL-10 responses in the presence of insulin B:9-23 both in vitro and in vivo. There was little to no increase in IFN- γ production. Allele specificity was shown

in that glyphosine did not stimulate I-A^d and I-A^b restricted T cells. When administered to NOD mice, glyphosine prevented diabetes onset as long as the compound was administered. Furthermore, glyphosine was able to induce IL-10 responses from PBMCs in human T1D patients with DQ8. This response was not observed in HLA matched controls. We hypothesize that glyphosine binds pocket 9 changing the charge of the pocket, allowing B:9-23 to be presented in the low affinity register 3, leading to a T cell mediated IL-10 response.

4. Peptide/MHC specific therapies

4.1 Monoclonal antibodies against insulin B:9-23/I-A^{g7}

More specific therapies involve targeting defined peptide/MHC complexes to prevent diabetes. A monoclonal antibody to the insulin B:9-23/I-A^{g7} complex may block insulin specific T cell activation or potentially delete antigen presenting cells with insulin B:9-23 on the cell surface. Treating NOD mice with recombinant B:9-23/I-A^{g7} with the peptide trapped in register 3 is able to delay diabetes onset [28]. Monoclonal antibodies specific for the B:9-23 peptide in register 3 of I-A^{g7} were generated from these mice capable of inhibiting trimolecular complex formation and blocking in vitro T cell activation to B:9-23 responsive hybridomas (personal communication with Li Zhang). Conceptually, a monoclonal antibody to any peptide/MHC complex could be generated for disease intervention as long as the pathogenic peptide and relevant register of binding to a specific MHC allele are known.

4.2 Antigen specific therapy with a strong insulin mimotope

Antigen specific therapies have been used to delay and reverse diabetes in clinical trials with limited success [29]. With the knowledge of registers of insulin B:9-23 peptide binding to I-A^{g7}, Von Boehmer and colleagues used an insulin mimotope peptide to induce tolerance in NOD mice. In the B:9-23 amino acid sequence, the native B22 arginine was changed to glutamic acid (B:9-23 R22E) [30]. Administering the peptide through intraperitoneal osmotic pumps at a low dose (5ug/day) resulted in regulatory T cells and dominant tolerance. NOD diabetes was completely prevented both early (4 to 6 weeks of age) and late (12 weeks of age) in the disease process even when mice had moderate levels of insulin autoantibodies present. These results were not seen with low doses of the native amino acid sequence of the insulin B:9-23 peptide. Hyperglycemia reversal with the B:9-23 R22E mimotope was unable to reverse diabetes as monotherapy. These studies indicate that the use of a strong insulin mimotope may improve the efficacy of antigen specific therapy when administered at an appropriate time in the T1D disease course.

5. T cell specific therapies

The third element of the trimolecular complex which can be targeted are CD4⁺ T cells and specific T cell receptors. Specific T cells have been targeted in autoimmune diabetes rat models (BB rat and Lew1.WR1). In these models, the MHC class II allele (RT1/Du) predisposes diabetes risk similar to humans and the NOD mouse [31]. A germline encoded TCR, V 13, predisposes diabetes risk in the diabetes animal models, while rat models with different polymorphisms in the V 13 gene are resistant to diabetes [32]. Dominant usage of the V 13 TCR is found in CD4⁺ T cells but not CD8⁺ with an abundance of V 13 T cells identified in pre-diabetic islet infiltrates. An anti-rat V 13 depleting monoclonal antibody is able to prevent diabetes in Poly I:C and spontaneous autoimmune diabetes rat models, while a specific anti-V 16 antibody did not change disease frequency [33]. Although the epitope recognized by V 13 CD4⁺ T cells is yet unknown, it is possible to prevent diabetes by targeting a limited segment of the T cell repertoire.

6. Future directions and conclusions

As previously mentioned, T1D is a predictable disease but not yet preventable in humans. In animal models of autoimmune diabetes, it has become clear that the components of the trimolecular complex (MHC class II – autoantigen – TCR) lead to specific targeting of beta cells, insulinitis, and eventual metabolic abnormalities. Therapeutic intervention at each component of the anti-insulin trimolecular complex is able to prevent disease and abrogate autoimmunity (Fig 2). In human clinical trials in which new onset T1D patients are treated with immune therapies, only therapies targeting components of the trimolecular complex have had limited success in preserving endogenous insulin producing ability. Anti-CD3 monoclonal antibodies target T cells (both CD4+ and CD8+) leading to a delay in the loss of C-peptide area under the curve after a mixed meal tolerance test when therapy is administered within the first three months after diabetes diagnosis [34–37]. Rituximab, an anti-CD20 monoclonal antibody that depletes memory B cells, targets antigen presenting cells capable of presenting epitopes to CD4+ T cells. Rituximab therapy was able to delay the loss of endogenous insulin production, similar to anti-CD3, when used shortly after diagnosis [38]. Furthermore, insulin autoantibody levels were reduced in treated responders compared to treated non-responders [39]. The other islet autoantibody (GAD, IA-2, or ZnT8) levels did not differ, nor were they able to discriminate treatment response. A final therapy used in new onset T1D, abatacept (CTLA-4 Ig) which blocks CD80/86 on MHC class II expressing antigen presenting cells, led to a delay in the loss of C-peptide [40]. Antigen specific therapies and other immune modulatory/suppressive therapies have not had effects on preserving endogenous insulin production in new onset T1D individuals.

Targeting disease specific trimolecular complex formation, especially those focused on insulin, appears to be a rational approach. The individual components of these trimolecular recognition units provide more defined therapies for diabetes prevention. Having more specific therapies may allow for greater safety and immunologic biomarkers for monitoring therapeutic responses. However, these novel therapies have their own theoretical risks including potential activation of immune responses to neo-antigens with small molecules, possible creation of gaps in the immune repertoire, inconvenience of delivering monoclonal antibodies, and disease induction with antigen specific therapies. Despite these theoretical risks, the logic and reasoning behind developing these therapies is sound. Tailoring therapies to specific HLA alleles, autoantigen, and register of epitope presentation to autoreactive T cells is truly personalized medicine which we believe will ultimately prevent type 1 diabetes. The lessons learned from T1D are broadly applicable to general immune function and designing therapies for other autoimmune disorders.

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Abbreviations

T1D	type 1 diabetes
TCR	T cell receptor
NOD	nonobese diabetic mouse

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Highlights

- The trimolecular complex (MHC–peptide–T cell receptor) is a target for therapies in diabetes.
- Small molecule drugs can block allele specific peptide presentation to T cells.
- Small molecule drugs with insulin B:9-23 lead to IL10 production and diabetes prevention.
- A monoclonal antibody specific for an insulin/MHC complex blocks T cell activation.
- Specific T cell receptor antibodies can prevent autoimmune diabetes in rat models.

Figure 1.

Registers of insulin B:9-23 peptide binding to I-Ag⁷. (A) Four different registers of insulin B:9-23 binding to I-Ag⁷ with amino acids in red being MHC contact residues and amino acids in black potential T cell receptor contacts. (B) Models of insulin B:9-23 binding to I-Ag⁷ in two different registers. Register 2 is the conventional register with the B21 glutamic acid binding in pocket 9, while register 3 has B22 arginine occupying pocket 9. Note the different amino acid side chains available for T cell receptor recognition in the different registers of peptide binding. The insulin B:9-23 peptide is depicted in yellow. The models were provided courtesy of David Ostrov and constructed using Pymol software.

Figure 2.

The trimolecular complex and multiple approaches for therapeutic targeting. The trimolecular complex consisting of T cell receptor – peptide – MHC class II molecule is depicted. In order to block interactions: (1) a small molecule (red circle) can occupy a pocket in an allele specific MHC peptide binding groove altering presentation, (2) monoclonal antibody can bind a specific peptide/MHC complex, or (3) monoclonal antibody targets a specific T cell receptor chain.