Published in final edited form as:
Curr Opin Immunol. 2013 December ; 25(6): . doi:10.1016/j.coi.2013.07.012.

T Cell Recognition of Beryllium

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Abstract

Chronic beryllium disease (CBD) is a granulomatous lung disorder caused by a hypersensitivity to beryllium and characterized by the accumulation of beryllium-specific $CD4^+$ T cells in the lung. Genetic susceptibility to beryllium-induced disease is strongly associated with HLA-DP alleles possessing a glutamic acid at the 69^{th} position of the β-chain (βGlu69). The structure of HLA-DP2, the most prevalent βGlu69-containing molecule, revealed a unique solvent-exposed acidic pocket that includes βGlu69 and represents the putative beryllium binding site. The delineation of mimotopes and endogenous self-peptides that complete the αβTCR ligand for beryllium-specific $CD4^+$ T cells suggests a unique role of these peptides in metal ion coordination and the generation of altered self-peptides, blurring the distinction between hypersensitivity and autoimmunity.

Introduction

The characterization of ligands recognized by αβ T cell receptors (TCRs) has predominantly focused on peptide antigens. However, in addition to peptides, αβ TCRs recognize a variety of other ligands, including lipids, superantigens, small organic haptens and metal ions [1]. In this regard, repeated exposure to metals such as beryllium (Be), nickel (Ni) and gold (Au) may result in hypersensitivity. Be-induced hypersensitivity is one of the best characterized hypersensitivity syndromes. Approximately 2–16% of Be-exposed workers develop Be sensitization [2–6], and a subset of Be-sensitized subjects progress to chronic Be disease (CBD) [7]. The diagnosis of CBD hinges on the detection of a Be-specific adaptive immune response in blood and/or lung and the presence of noncaseating granulomatous inflammation on a lung biopsy specimen [8]. The histopathology of CBD is identical to that seen in sarcoidosis, a more common granulomatous lung disease of unknown etiology [9,10]. With the persistence of Be in the lung years after exposure cessation [11,12], the natural history of disease is characterized by a gradual decline in lung function, with one-third of untreated patients progressing to end-stage respiratory insufficiency [13]. Current therapeutic approaches include the use of immunosuppressive medications, such as prednisone, but no evidence exists that any treatment regimen altered the natural history of the disease.

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Despite the presence of a small subset of Be-responsive T cells in blood, the majority of Be-specific $CD4^+$ T cells are compartmentalized to the lung [14] and express a polarized Th1 phenotype [14,15]. These cells also express an oligoclonal TCR repertoire [16], are predominantly composed of effector memory T cells [17] and recognize Be in a CD28 independent manner [18]. Conversely, $CD8^+$ T cells do not respond to Be stimulation in culture [17,19], suggesting that $CD4^+$ T cells are the critical T cell subset involved in the immunopathogenesis of CBD.

This review focuses on recent advances in our understanding of the immunopathogenesis of Be-induced disease, in particular those involving the recognition of the MHCII-peptide/Be complex by pathogenic $CD4^+$ T cells derived from the lungs of CBD patients.

Genetic Susceptibility to Beryllium-Induced Disease

In addition to workplace exposure to Be, genetic susceptibility plays a key role in the immunopathogenesis of Be-induced disease. Susceptibility has been most strongly associated with MHCII molecules, in particular HLA-DP [20–24]. Richeldi et al. [20] showed that *HLA-DPB1* alleles with a glutamic acid (E) at position 69 of the β-chain (βGlu69) were strongly linked to disease susceptibility, with the most prevalent βGlu69-containing allele being *HLA-DPB1*02:01* [20]. Multiple studies have corroborated these findings, documenting the presence of βGlu69-containing *DPB1* alleles in 73–95% of CBD patients compared to 30–48% of exposed controls [21–26]. In addition, differential risk of disease development has been associated with certain βGlu69-containing *DPB1* alleles [22–24,26].

Approximately 15% of CBD patients do not possess a βGlu69-containing HLA-DP allele, suggesting that other MHCII molecules may be important in genetic susceptibility to Be-induced disease [23,24]. In this population of CBD patients, an increased frequency of HLA-DR13 alleles, which possess an analogous glutamic acid residue at position 71 of the β-chain (βGlu71), was seen [24]. In CBD subjects without a βGlu69-containing HLA-DP allele, Rosenman et al. [27] showed that all of these subjects possessed at least one βGlu71-expressing HLA-DR allele. Collectively, the genetic studies suggest an important role of this negatively-charged glutamic acid in conferring risk of disease development in Be-exposed workers.

Structural Basis of CBD

To characterize the structural features of βGlu69-containing HLA-DP molecules that explain disease association, HLA-DP2 (*DPA1*01:03, DPB1*02:01*) with a bound self-peptide derived from the HLA-DR α-chain (pDRA) was crystallized and its structure solved to a resolution of 3.25Å [28]. Although the overall structure of the HLA-DP2-pDRA complex was similar to that of other MHCII/peptide complexes, several unique features were evident that might contribute to the role of this molecule in the development of CBD. For example, HLA-DP2 had one of the widest binding grooves (16.18Å) compared to 28 other published human and mouse MHCII structures in the Protein Data Base (PDB) (e.g., width averaged 15.01Å and varied from 13.59Å to 16.73Å) [28]. Importantly, this widening occurred between the peptide and β-chain α-helix (Figure 1). To confirm that the widened peptide binding groove was not a result of the crystallographic conditions, the structures of two additional HLA-DP2 molecules with different peptides in the binding groove (e.g., HLA-DP2-pRas (resolved to 2.7Å) and HLA-DP2-pA28 (1.9Å)) were solved, and nearly identical widths were documented (unpublished data). These findings suggest that the HLA-DP2 β-chain α-helix has rolled away from the peptide and the floor of the binding groove, and

recent studies have shown that this region of the β-chain may be quite flexible [29], contributing to the variation in the width of this part of the binding groove.

Another unique structural feature of the HLA-DP2-pDRA complex was the elevated position of the peptide in the binding groove. This spacing resulted in an inability of the p4Leu of pDRA to occupy the p4 pocket of HLA-DP2. Compared to two other MHC-peptide structures also having a leucine at the p4 position of the peptide [30,31], the backbone of pDRA had risen up in the binding groove at the p4 position (Figure 2A) and the side chain of the p4Leu of pDRA was surface-exposed (Figure 2B). This structure suggests that the p4Leu contributes minimally to the binding affinity of pDRA for HLA-DP2.

The net effect of these structural changes is a solvent-exposed acidic pocket that is flanked by leucines at the p4 and p7 positions of the pDRA (Figure 3A). The acidity of this pocket is due to the presence of three HLA-DP2 β-chain amino acids: βGlu68 and βGlu69 from the β-chain α-helix and βGlu26 from the floor of the peptide binding groove (Figure 3B). This cluster of glutamic acids was also solvent-exposed in the HLA-DP2-pRas and HLA-DP2-pA28 structures (unpublished data). Since βGlu69 is the most important polymorphism associated with the genetic susceptibility to CBD and solved structures of other proteins associated with Be generally show Be coordination by acidic amino acids [32], these findings strongly suggest that this acidic pocket is the Be binding site within the TCR footprint of HLA-DP2.

Beryllium Presentation to $CD4^+$ T Cells

Using antigen-specific T cell lines and hybridomas expressing Be-specific TCRs, investigators have shown that most Be presentation occurs through HLA-DP, with HLA-DR playing a minor role [33,34]. Conversely, only certain HLA-DP molecules are capable of presenting Be to pathogenic $CD4^+$ T cells [33], and the *HLA-DPB1* alleles that mediate Be presentation match those implicated in disease susceptibility, confirming that the contribution of βGlu69-containing HLA-DP molecules is based on the ability of those proteins to bind and present Be to pathogenic $CD4^+$ T cells [33,34].

In addition to βGlu69, the HLA-DP2 crystal structure suggests that βGlu26 and βGlu68 may also be involved in Be coordination and presentation (Figure 3B). Because these two amino acids are invariant among HLA-DP alleles [35], they were not identified in genetic analyses of the linkage between *HLA-DPB1* alleles and CBD, and their presence is not sufficient for Be presentation in the absence of βGlu69. Using fibroblasts expressing HLA-DP2 molecules mutated at each of these three positions, Dai et al. [28] showed that the mutant HLA-DP2 molecules were no longer able to induce Be-specific T cell activation, suggesting that these three glutamic acid residues are critical for Be coordination and T cell activation. Similarly, HLA-DR-restricted T cell recognition of Be recognition was also dependent on βGlu71 [36].

The unique structural features of HLA-DP2 raised the possibility that Be-responsive T cells may not recognize the HLA-DP2-peptide/Be complex in a conventional manner with a diagonal TCR orientation centered over the pMHCII complex. In this regard, unconventional binding interactions have been reported for the majority of human autoimmune complexes solved to date [37–39]. Using site-directed mutagenesis of the CDRs of Be-specific TCRs, Bowerman et al. [40] showed that Be-specific T cells recognize antigen using an unconventional binding topology, with the majority of interactions contributed by TCR Vβ CDR3 and the HLA-DP2 β1-chain. Thus, unusual docking topologies are not exclusively used by autoreactive T cells, but also for the recognition of metal antigens.

Beryllium-Dependent Peptides in Metal Ion Coordination

In addition to Be, specific peptides are required to complete the Be-specific αβTCR ligand [28]. However, a set of known HLA-DP2-binding peptides [41], including those derived from HLA-DR α-chain, Ras and HLA-A28, did not induce IL-2 secretion by T cell hybridomas expressing Be-specific TCRs [40], demonstrating that HLA-DP2-restricted T cell recognition of Be depends on a limited number of specific peptides. Falta et al. [42] identified Be-dependent mimotopes that bind to HLA-DP2 and Be, forming a complex recognized by pathogenic $CD4^+$ T cells in CBD. Important characteristics of Be-dependent mimotopes included a preference for bulky hydrophobic or nonpolar amino acids at the p1 and p6 anchor positions that match the known HLA-DP2-binding motif [43], independence of TCR recognition on the C-terminus of the peptide, and negatively-charged aspartic and glutamic acid residues at p4 and p7 of the peptide that represent potential Be coordination sites [42]. The location of these two negatively-charged amino acids in addition to the three glutamic acids contributed by the HLA-DP2 β-chain strongly suggests their role in capturing and coordinating Be for T cell recognition.

In a search for endogenously-derived peptides with homology to the mimotope sequences and an ability to bind to HLA-DP2/Be and stimulate pathogenic $CD4^+$ T cells from CBD patients, plexin A peptides were identified. Plexins are transmembrane proteins encoded by nine genes (*PLXNA1-4*, *B1-3*, *C1* and *D1*) that are involved in cell movement and response [44]. Only the plexin A family contains the stimulatory epitope for the Be-responsive TCRs that includes the acidic amino acids at both the p4 and p7 positions [44]. Several plexin A proteins are expressed in BAL fluid and lung tissue; thus, they are readily available as a source of antigen in the target organ of CBD patients [42]. Using HLA-DP2-plexin A4 tetramers soaked in Be, Falta et al. [42] showed tetramer-binding $CD4^+$ T cells in the BAL of all HLA-DP2-expressing CBD patients who possessed a Be-specific immune response in lung, strongly supporting a role of plexin A as an endogenous antigen for a set of Be-specific TCRs.

Models for Beryllium Presentation to $CD4^+$ T Cells

Currently, the mechanism(s) by which Be binds to the MHCII/peptide remains an important unanswered question. The various possibilities by which Be may interact with this complex are shown in Figure 4. Be may bind to either the MHCII/peptide complex (Figure 4A) or peptide alone (Figure 4B), and both of these models would require direct interaction between Be and the TCR. An indirect interaction between Be and TCR is shown in Figure 4C and D. The presence of Be in the binding groove may neutralize the acidic environment of the p4 pocket and alter the repertoire of peptides capable of binding to the MHCII (Figure 4C). The ability of endogenous peptides, such as those derived from plexin A, to participate in metal ion capture may result in the conversion of a self-peptide into a neoantigen with an altered conformation (Figure 4D). The creation of neoantigens that are absent in the thymus and arise in a target organ plays a key role in the genesis of autoimmunity [45] and hypersensitivity [46]. In CBD, self-peptides bound in the HLA-DP2 binding groove may be altered by the presence of Be, resulting in the conversion of these endogenous peptides into neoantigens and culminating in Be-specific adaptive immunity. Although Figure 4D depicts the preferred model, ultimate confirmation will await structural analysis of the TCR-pMHCII/Be complex.

Conclusions

The unique structural features of HLA-DP2 and the ability of particular peptides to participate in Be ion capture and coordination provides an explanation for the generation of

CBD in a genetically-susceptible host exposed to an environmental antigen. Similar to T cell recognition of self-peptide in autoimmunity, our findings suggest that Be-specific $CD4^+$ T cells utilize an altered binding topology to recognize the HLA-DP2-peptide landscape created by the addition of Be. Thus, we believe that recent findings in Be-induced hypersensitivity are relevant to autoimmune diseases and the role of neoantigens in driving both hypersensitivity and autoimmunity.

Acknowledgments

This work was supported by the following NIH grants: HL062410, ES011810, HL102245 (to A.P.F) and TR000156 (to SD). SD is also supported by the Boettcher Foundation.

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• of special interest

•• of outstanding interest

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Highlights

- CBD is a classic example of a disorder resulting from a gene-environment interaction.
- HLA-DP2 is linked for the generation of beryllium-induced hypersensitivity.
- HLA-DP2 possesses unique structural features, including a beryllium-binding site.
- Beryllium's binding to MHCII-peptide generates an abnormal landscape for TCR interaction.

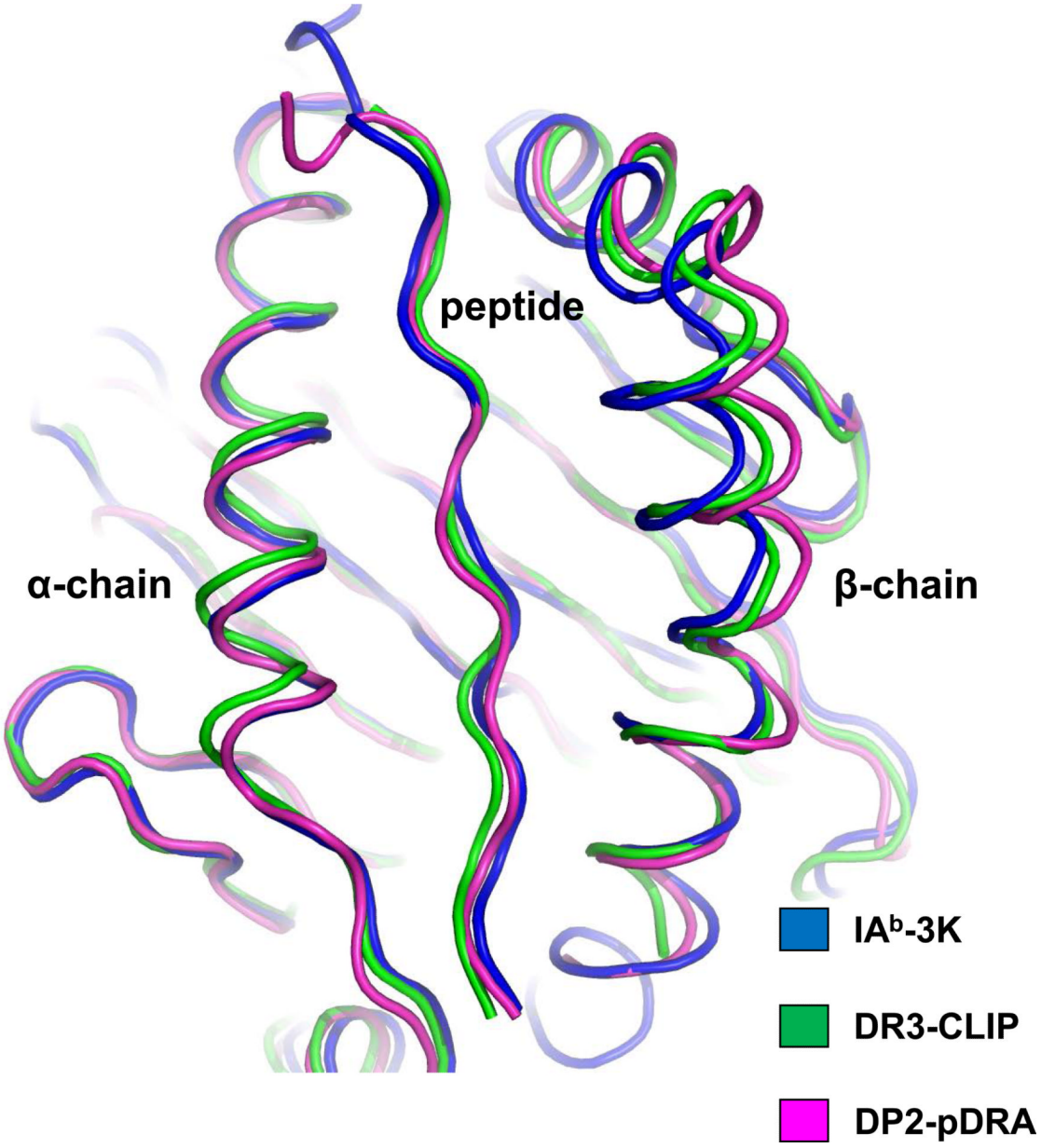

Figure 1. HLA-DP2 possesses a widened peptide binding groove

Three MHCII structures were overlaid on the basis of their α1 domains: DP2-pDRA (PDB ID code 3LQZ, magenta), HLA-DR3 bound to the invariant chain CLIP peptide (PDB ID code 1A6A, green) and mouse IA^b bound to 3K peptide (PDB ID code 1LNU, blue). Human or mouse MHCII with a bound peptide were analyzed for the distance (Å) between the Cα of the p5 amino acid position of the peptide and the Cα of the MHCII β71 amino acid (equivalent to β69 of DP2): 7.62 Å (IA^b-p3K), 9.00 Å (DR3-pCLIP), and 10.94 Å (DP2-pDRA). The distance between the peptide and DP2 β-chain α-helix is among the widest of all MHCII molecules.

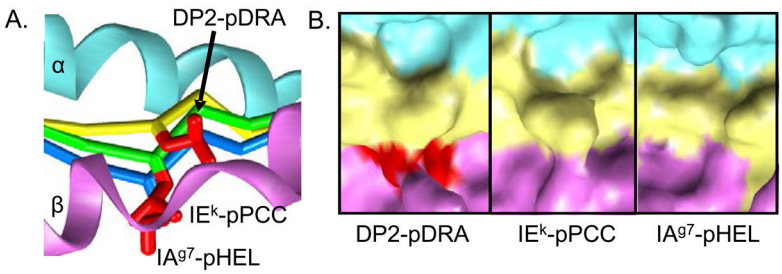

Figure 2. Unusual configuration of the HLA-DP2 peptide binding groove

A, A side view of the DP2 β1 helix (magenta) toward the α1 helix (cyan) is shown. The pDRA backbone is shown as a Cα trace (yellow). Two other MHCII/peptide structures, which also have leucines at p4, were overlaid on the DP2-pDRA structure: IE^k-pPCC (PDB ID code 1KTD) and IAg7-pHEL (PDB ID code 1F3J). Their peptide Cα traces are shown in green and blue, respectively. For all three peptides, the side chain of the p4Leu is shown as a red wireframe. **B**, For the same three structures shown in **A,** the solvent exposed surface of the MHC/peptide complex is shown in the region of p4Leu, α1 - cyan, β1 - magenta and peptide - yellow, expect for the side chain of p4Leu -red.

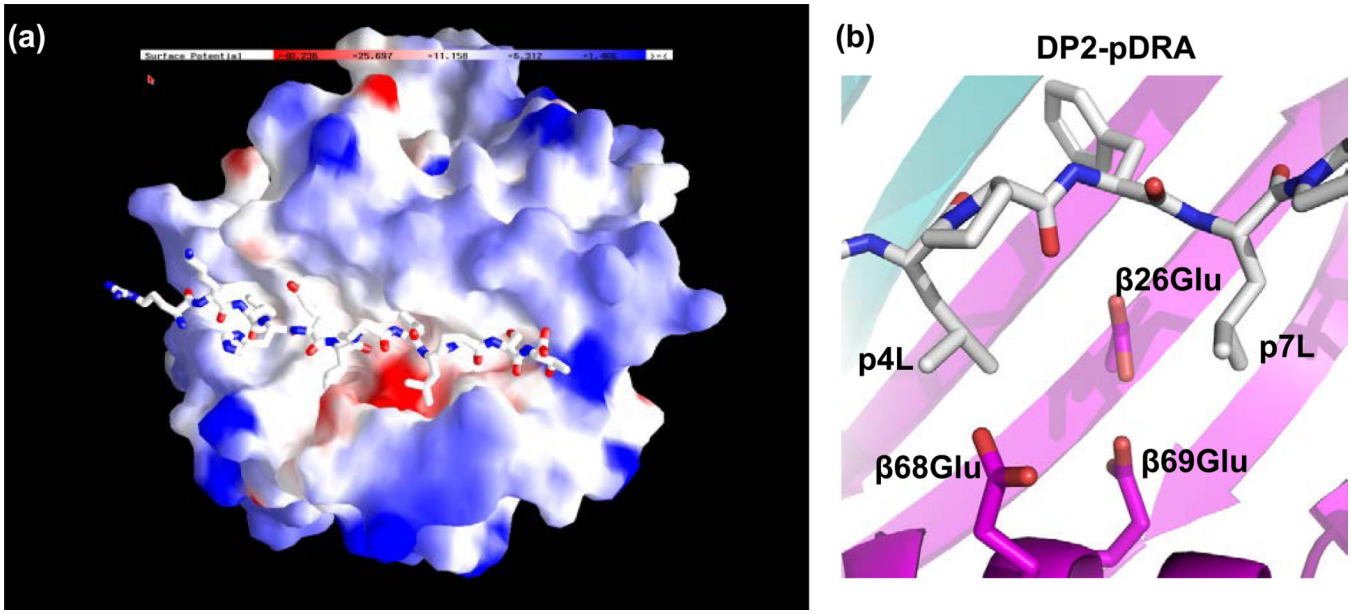

Figure 3. βGlu69 lies in a solvent-exposed acidic pocket

A, The electrostatic surface charge of the HLA-DP2 molecule (with bound pDRA) is shown colored by the relative charge of the surface atoms (red - negative and blue - positive). A wireframe representation of the peptide is also shown with CPK coloring. **B**, View from above the surface-exposed acidic pocket of the HLA-DP2-pDRA structure. The β strand floors of DP2 α- and β-chain domains are colored light cyan and light magenta, respectively. Wireframe representations of the side chains of β26Glu, β68Glu, and β69Glu are shown with magenta carbon and red oxygen. The wireframe representations of p4 to p7 of the peptides are shown with white carbon, red oxygen and blue nitrogen.

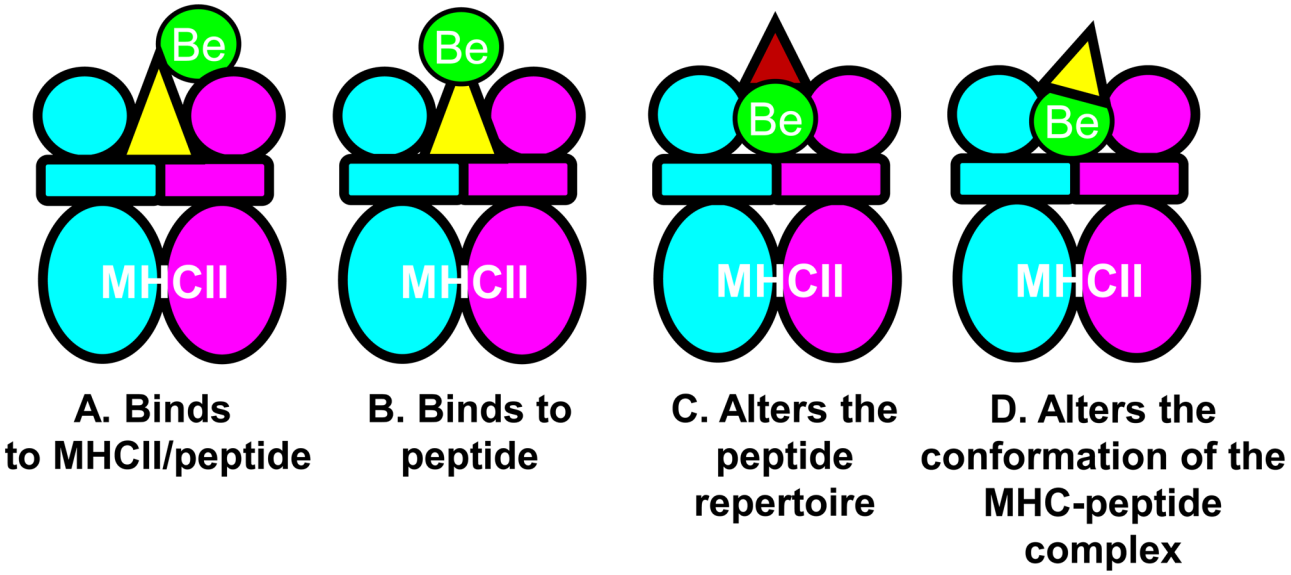

Figure 4.

Models of Be presentation to $CD4^+$ T cells in the context of MHCII molecules. **A**, A schematic model for the direct binding of Be to the MHCII/peptide complex is shown. **B**, A direct model of interaction is depicted where the metal binds to the antigenic peptide alone. **C**, The potential ability of Be to alter the MHCII peptide repertoire that is capable of bindings due to the presence of Be in the peptide-biding groove is shown. **D**, The preferred model depicting the ability of Be to alter the conformation of self-peptides that are subsequently recognized as neoantigens by the TCR is shown. It remains unknown whether the Be-specific TCR directly contacts Be or recognizes an altered self-peptide with no direct contacts between the metal and the TCR (as shown in Figure 4D).