T CELL RECOGNITION

A hidden heavy metal

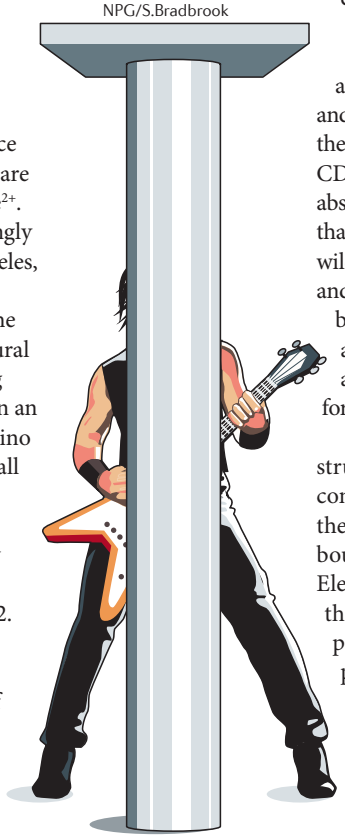
Industrial workers who handle the metal beryllium commonly develop chronic beryllium disease (CBD), which is a lifelong $CD4^+$ T cell-mediated inflammatory lung condition. T cell recognition of this metal depends on Be^{2+}-capturing peptides that bind MHC class II molecules, but exactly how T cell receptors (TCRs) recognize beryllium has been unclear. Now, Kappler and colleagues show that the TCR does not interact directly with the Be^{2+} cation but instead recognizes changes to the surface of MHC class II molecules that are induced by internally bound Be^{2+}.

Susceptibility to CBD is strongly associated with MHC class II alleles, such as HLA-DP2, that have a glutamic acid at position 69 of the β-chain (β69E). Previous structural analysis with HLA-DP2-binding peptides showed that β69E lies in an acidic pocket with two other amino acids (β26E and β68E) and that all three residues are important for Be^{2+} presentation. In addition, the structure showed a relatively large gap (11 Å) between the peptide backbone and HLA-DP2.

Kappler and co-workers decided to test whether two conserved acidic amino acids of Be^{2+}-capturing peptides might influence the ability of the MHC pocket to bind Be^{2+}.

> "the presence of Be^{2+} led to conformational changes"

NPG/S.Bradbrook



They examined two mutated forms of a complex between the Be^{2+}-capturing peptide mimotope-2 (M2) and HLA-DP2: one complex in which the two conserved acidic amino acids of M2 were changed to nearly isomorphous amides, and another complex in which the HLA-DP2 glutamic acid at β69E was changed to lysine, which is the amino acid found at position 69 in MHC class II alleles that are not associated with CBD. The wild-type and mutated complexes were tested for their ability to stimulate Be^{2+}-specific $CD4^+$ T cells in the presence or absence of Be^{2+}. The authors found that the T cells only responded to the wild-type HLA-DP2–M2 complex and only in the presence of Be^{2+}. Thus, both β69E in HLA-DP2 and the acidic side chains of the conserved amino acids of M2 were required for Be^{2+} presentation.

Next, the authors solved the structures of the HLA-DP2–M2 complex in the absence of Be^{2+} and the HLA-DP2–M2–Be^{2+} complex bound by a Be^{2+}-specific TCR. Electron density mapping showed that the side chains of the M2 peptide entered the acidic MHC pocket both before and after the addition of Be^{2+}. The presence of Be^{2+} led to conformational changes in the acidic pocket, which indicates that Be^{2+} was bound within the pocket. Furthermore, the electron density map suggested the presence of an additional large atom, so the authors included Na^+ in their structural model. The structure revealed two unexpected features of the complex: first, the Be^{2+} cation itself is bound; and second, neither Be^{2+} nor Na^+ are accessible on the surface of the complex. Thus, Be^{2+}-specific TCRs must recognize changes in the surface of the complex that are induced indirectly by Be^{2+} and Na^+.

In summary, this study shows that metal ions, such as Be^{2+}, can join the internal structure of a peptide–MHC complex and indirectly cause structural and biophysical changes to the surface of the complex that is recognized by the T cell. Interestingly, the immune response to beryllium not only resembles allergic hypersensitivity — due to the metal ion causing an allergic reaction — but also resembles autoimmunity, as the immune system mounts a response against a self-peptide. Furthermore, particular MHC class II alleles can confer susceptibility to autoimmune disease and this is also the case for CBD.

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