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Human leukocyte antigen-associated drug hypersensitivity.

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Abacavir hypersensitivity syndrome (AHS) is a T-cell mediated drug hypersensitivity triggered by the antiretroviral drug abacavir, used in the treatment of HIV infection. It is one of an increasing number of adverse drug reactions found to be associated with specific Human Leukocyte Antigen (HLA) alleles. Occuring exclusively in individuals possessing HLA-B*57:01, this is one of the strongest associations between an HLA and disease found to date and provides an attractive candidate for exploring the general basis for allotype-specific drug presentation by the HLA. In this study, we detail that abacavir alters the repertoire of endogenous peptides that can bind HLA-B*57:01. By use of the MX2 beamline at the Australian synchrotron we determined the high resolution X-ray crystallographic structure of HLA-B*57:01 in complex with abacavir. This enabled as to map the molecular details underlying the exquisite specificity of abacavir for HLA-B*57:01. Furthermore, we were able to show that abacavir changes the shape and chemistry of the HLA-B*57:01 antigen-binding cleft. In this way, abacavir guides the selection of new endogenous peptides, inducing a marked alteration in 'immunological self'. The resultant peptide-centric 'altered self' activates abacavir-specific T-cells, thereby driving polyclonal CD8+ T-cell activation and a systemic reaction manifesting as AHS.

Reference: Illing, P., Vivian., et al
Nature. 2012 Jun 28;486(7404):554-8
Immune self-reactivity triggered by drug-modified HLA-peptide repertoire.

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Summary

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