Clinical and Translational Allergy

POSTER PRESENTATION Open Access

HLA class I-drug-T-cell receptor interactions in SJS/TEN

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From 6th Drug Hypersensitivity Meeting (DHM 6)
Bern, Switzerland. 9-12 April 2014

Background

Carbamazepine (CBZ) is associated with the severe cutaneous drug reaction Stevens-Johnson Syndrome/toxic epidermal necrolysis (SJS/TEN). CBZ-SJS/TEN has been associated with HLA-B*15:02 carriage and specific T-cell clonotypes. We aimed to characterize the interactions between specific T-cell receptor (TCR) clonotypes, HLA-B*15:02 and CBZ.

Methods

Peripheral blood mononuclear cells (PBMCs) were isolated from patients with CBZ-SJS/TEN and healthy controls, stimulated with 10ug/mL CBZ (Sigma, cat. no. C4024-5G) and cultured over a 9-14 day period. RNA was isolated at various time points and TCR V subtypes were assessed using digital droplet PCR (Bio-Rad QX100 droplet digital PCR system). Drug specific T-cell INF and granulysin responses were assessed by ELISpot and ICS. *In silico* modelling was used to examine the interaction between the known specific TCR V and V chains, CBZ and HLA-B*15:02.

Results

CBZ specific T-cell INF and granulysin responses were detected many years following the original SJS/TEN reaction. Expansion of specific TCR CDR3 sequences was confirmed in CBZ SJS/TEN patient cultures. *In silico* modelling of the CBZ-HLA-B*15:02-TCR interaction suggests that CBZ binds non-covalently in the P4 binding pocket of the HLA-B*15:02 antigen binding cleft in a site that is typically occupied with bound peptide.

Conclusions

These findings raise two non-mutually exclusive possibilities: 1) CBZ may block peptide binding and be presented by HLA-B*15:02 in a solvent exposed manner available for direct recognition by the TCR, 2) CBZ binding the central portion of the HLA-B*15:02 antigen binding cleft may permit long peptides to bind conventionally at the peptide termini (in the A and F pockets) and bulge over the drug in the central residues to permit indirect recognition of CBZ (peptide mediated TCR contact).

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Published: 18 July 2014

doi:10.1186/2045-7022-4-S3-P2
Cite this article as: Rive *et al.*: HLA class I-drug-T-cell receptor interactions in SJS/TEN. *Clinical and Translational Allergy* 2014 4(Suppl 3):P2.

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