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Vancomycin-specific T Cell responses in allergic and non-allergic individuals

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Background

The association between specific HLA alleles and risk of severe cutaneous drug hypersensitivity reactions is increasingly recognised. Vancomycin mediated pseudo-allergic 'red man syndrome' is well recognised, yet urticaria/angioedema is uncommon and some clinical reactions are delayed. Although this may suggest the presence of vancomycin initiated T cell responses, no predisposing vancomycin HLA association has been identified. Therefore we set out to examine the role of T cell responses in vancomycin hypersensitivity reactions.

Methods

Of our tested cohort of 103 individuals who suffered delayed skin drug hypersensitivity reactions, vancomycin was deemed the culprit in 17, who developed drug exanthems (59%), DRESS (35%), or SJS/TEN (18%). We used ELISpot and $[^3\text{H}]$ -Thymidine assays to measure vancomycin-specific *ex-vivo* IFN- γ /IL-4 and proliferation above background.

Results

Individuals with drug hypersensitivity showed a mean circulating PBMC frequency of vancomycin-specific cells of 470.0×10^{-4} (IFN- γ) / 33.5×10^{-4} (IL-4) and SI 4.08 if tested within 30 days, whilst those tested after 30 days showed 316.0×10^{-4} (IFN- γ) / 20.0×10^{-4} (IL-4) and SI 3.43. Individuals never previously exposed to vancomycin (n=11) showed a lower mean circulating frequency: 2.1×10^{-4} (IFN- γ , $p < 0.005$) / 1.7×10^{-4} (IL-4, $p = 0.27$) and SI 1.28. In controls who had been exposed to vancomycin (without any evidence of a hypersensitivity reaction, n=6) detectable frequencies were also lower than allergics: 11×10^{-4} (IFN- γ) / 7.1×10^{-4} (IL-4) and SI 0.98. We co-cultured non-allergic PBMC with vancomycin for

two-weeks in vitro. In two lines, we saw expansion of vancomycin-specific T cells in ELISpot to an average frequency of 954×10^{-4} (IFN- γ) and 1130×10^{-4} (IL-4) which was confirmed by ELISpot and intracellular cytokine staining.

Conclusion

These data confirm that robust Th1 responses target vancomycin in cutaneous hypersensitivity reactions, which supports the use of T cell inhibition such as steroids and ciclosporin. Vancomycin-specific responses appear reduced with time which advocates early diagnostic testing, but the clinical possibility of loss of sensitisation is intriguing. The finding that vancomycin-specific T cells can be artificially expanded from individuals without clinical reactivity, suggests that both immune predisposition and potentially adaptive regulation may be important in development of hypersensitivity responses to vancomycin.

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