

Characterization of TCR Repertoire Diversity and Tissue Distribution of Drug-specific T Cells in DRESS

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Abstract:

Vancomycin is now recognized as the most frequent antibiotic cause of drug reaction with eosinophilia and systemic symptoms (DRESS). DRESS is a T cell mediated adverse drug reaction (ADR) with up to 10% mortality that is characterized by fever, rash, hematologic abnormalities, and multi-organ dysfunction. We aim to describe the phenotype, repertoire diversity and tissue distribution of drug-specific pathogenic T cells and establish how long these vancomycin-reactive T cells are maintained during the recovery phase of DRESS. Following ex vivo (18 hour) stimulation with vancomycin, CD4+T cells expressing markers of T cell activation (CD137, CD69) were isolated from the peripheral blood of a vancomycin DRESS patient at three time points during the recovery phase. These activated drug-specific CD4+ T cells were shown to be of effector memory phenotype and to produce IFN-gamma and IL-2. Single CD4 +T cells were sorted for surface expression of CD137 and sequenced for paired T cell receptor (TCR) alpha and beta genes. TCR sequences from candidate pathogenic clonotypes were introduced into a Jurkat-based TCR expression system to verify drug reactivity. To define the clonotypes present in the skin during vancomycin DRESS, we performed TCR Vb repertoire (bulk) sequencing on DNA isolated from an archived formalin fixed paraffin embedded skin biopsy obtained during the acute cutaneous reaction. We compared the TCR repertoire from affected skin to that found in the recovery phase of peripheral blood following ex vivo drug stimulation to determine if common clonotypes are present in these two compartments and if these are maintained over time.