

INVOLVEMENT OF METABOLIC AND IMMUNE RESPONSES IN THE PATHOGENESIS OF ABACAVIR HYPERSENSITIVITY REACTION

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Background: Abacavir is an effective therapeutic nucleoside analogue used in the treatment of HIV infection that is associated with hypersensitivity reactions in ~8% of individuals. Susceptibility to abacavir hypersensitivity (ABC-HSR) is highly predicted by the presence of alleles on the 57.1 ancestral haplotype including *HLA-B*5701*, *TNF -238A*, and *Hsp70Hom-493T*.

Objective: To examine the metabolic and immune responses in the pathogenesis of ABC-HSR.

Methods: Cellular HSP70, CD40 and IFN- γ expression were measured by immunofluorescence staining using confocal microscopy, intracellular flow cytometry (ICS) and ELISA. Alcohol dehydrogenase activity was determined by spectrophotometric analysis of NADH production.

Results: Confocal microscopy revealed significantly increased HSP70 expression in endosomal compartments of antigen presenting cells within 3 hours of abacavir stimulation in cultured PBMCs from *HLA-B*5701*⁺ ABC-HSR and *HLA-B*5701*⁺ ABC-naive individuals, compared with ABC-tolerant patients ($P=0.023$). Blockade of cell surface receptors with CD14, HSP70 or TLR4 antibodies reduced HSP70 redistribution in susceptible individuals to basal levels ($P<0.004$). CD40 expression, an activation and maturation marker, was significantly higher in CD14⁺, CD83⁺ cells from HSR versus tolerant patients ($P=0.0008$). Abacavir stimulation resulted in increased T1 cytokine expression including monocyte TNF- α (ICS, $P=0.0003$) and IFN- γ (ELISA, $P=0.001$) associated in ABC HSR compared with tolerant patients. The IFN- γ response was observed in CD8⁺ T cells (ICS). Inhibiting abacavir bioactivation via ADH with 4-MP decreased both HSP70 redistribution and IFN γ production.

Conclusions: Both innate and adaptive immune responses are critical in the pathogenesis of ABC-HSR, providing abacavir-specific activation and maturation signals to antigen presenting cells, whilst the generation of abacavir-specific immune responses also appears to be contingent on ADH-mediated bioactivation. The exquisite *HLA-B*5701*⁺ restriction of abacavir modified ligands provides the most clinically relevant basis for genetic screening, although the involvement of toll-like receptors may also have therapeutic implications.