

Defining The Signals Between Hepatocytes And Immune Cells In Idiosyncratic Drug-induced Liver Injury (DILI)

Background: An association between HLA genotype and the development of certain forms of DILI is well known. It is now apparent that drug-specific T-cells are activated in certain patients with DILI. The cross-talk signals between hepatocytes and the immune cells resident in the liver and circulation are likely to be critical in determining the outcome of drug exposure with regards to development of immune-mediated DILI. However, tissue-specific immune signalling with respect to human DILI remains largely unexplored. Thus, the aim of this study was to profile the signals released by fresh human hepatocytes upon drug exposure and to characterise the impact of these molecules on the phenotype and function of antigen presenting cells (APC).

Method: Fresh human hepatocytes were exposed to graded concentrations of four test compounds implicated in DILI (Flucloxacillin, acetyl-para-aminophenol, amoxicillin and isoniazid) and two reactive metabolites (nitroso-sulphamethoxazole [SMX-NO] and *N*-acetyl-*p*-benzoquinone imine [NAPQI]), and end-points of hepatocyte toxicity assessed.

Results: HMGB1 and LDH release as well as ATP depletion occurred in a drug- and concentration-dependent manner (figure 1). Furthermore, compound-specific activation of Nrf2 marker genes was observed with each of the test drugs. SMX-NO and NAPQI differentially induced the expression of NQO1, TXNRD1 and SRXN1 responsible for cytoprotection against chemically reactive metabolites. Also, the expression of AKR1B10 and LOC344887 were significantly increased by flucloxacillin. Drug exposure triggered the release of an array of both pro-inflammatory and anti-inflammatory cytokines from hepatocytes, including IL-12p70, IL-6 and IL-10 and numerous chemokines. Co-culture of APC with hepatocyte-conditioned supernatant resulted in the release of IFN- γ , IL-10, IL-12 IP-10 and IL-17A alongside subtle changes in the expression of MHC class II and CD86.

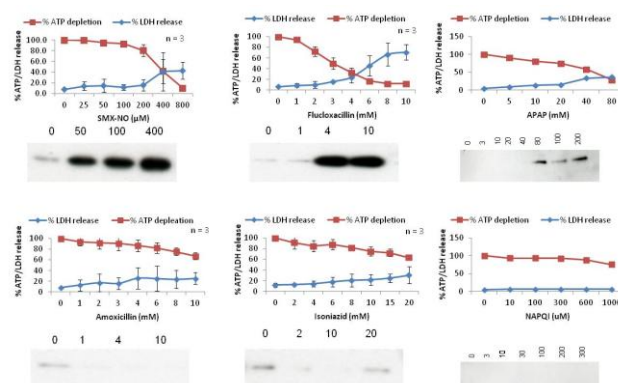


Figure 1: Toxicity profile of test drugs using ATP depletion, and LDH release and HMGB1 release as endpoints

Conclusion: In conclusion, our study begins to define the various factors that might be important in determining whether drug exposure in patients result in an immune response and tissue injury. The development of a liver/immune cell culture system will be an important step forward in advancing our understanding of the molecular mechanisms underlining idiosyncratic DILI.