# FOXA2 prevents hyperbilirubinaemia in acute liver failure by maintaining apical MRP2 expression

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## Abstract

Objective: Multidrug resistance protein 2 (MRP2) is a bottleneck in bilirubin excretion. Its loss is sufficient to induce hyperbilirubinaemia, a prevailing characteristic of acute liver failure (ALF) that is closely associated with clinical outcome. This study scrutinises the transcriptional regulation of MRP2 under different pathophysiological conditions.

Design: Hepatic MRP2, farnesoid X receptor (FXR) and Forkhead box A2 (FOXA2) expression and clinicopathologic associations were examined by immunohistochemistry in 14 patients with cirrhosis and 22 patients with ALF. MRP2 regulatory mechanisms were investigated in primary hepatocytes, Fxr -/- mice and lipopolysaccharide (LPS)-treated mice.

Results: Physiologically, homeostatic MRP2 transcription is mediated by the nuclear receptor FXR/retinoid X receptor complex. Fxr-/- mice lack apical MRP2 expression and rapidly progress into hyperbilirubinaemia. In patients with ALF, hepatic FXR expression is undetectable, however, patients without infection maintain apical MRP2 expression and do not suffer from hyperbilirubinaemia. These patients express FOXA2 in hepatocytes. FOXA2 upregulates MRP2 transcription through binding to its promoter. Physiologically, nuclear FOXA2 translocation is inhibited by insulin. In ALF, high levels of glucagon and tumour necrosis factor α induce FOXA2 expression and nuclear translocation in hepatocytes. Impressively, ALF patients with sepsis express low levels of FOXA2, lose MRP2 expression and develop severe hyperbilirubinaemia. In this case, LPS inhibits FXR expression, induces FOXA2 nuclear exclusion and thus abrogates the compensatory MRP2 upregulation. In both Fxr -/- and LPS-treated mice, ectopic FOXA2 expression restored apical MRP2 expression and normalised serum bilirubin levels.

Conclusion: FOXA2 replaces FXR to maintain MRP2 expression in ALF without sepsis. Ectopic FOXA2 expression to maintain MRP2 represents a potential strategy to prevent hyperbilirubinaemia in septic ALF.

Keywords: ACUTE LIVER FAILURE; CHOLESTASIS; SEPSIS.