Interleukin 1 β suppresses bile acid-induced BSEP expression via a CXCR2-dependent feedback mechanism

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Abstract

Inflammation-induced cholestasis is a common problem in septic patients and results from cytokine-mediated inhibition of bile acid export including impaired expression of the bile salt export pump (BSEP) with a consecutive increase in intracellular bile acids mediating cell damage. The present study focuses on the mechanisms by which interleukin 1 β (IL-1β), as a critical mediator of sepsis-induced cholestasis, controls the expression of BSEP in hepatocytes. Notably, the treatment of hepatocytes with IL-1β leads to the upregulation of a broad chemokine pattern. Thereby, the IL-1β -induced expression of in particular the CXCR2 ligands CXCL1 and 2 is further enhanced by bile acids, whereas the FXR-mediated upregulation of BSEP induced by bile acids is inhibited by IL-1β. In this context, it is interesting to note that inhibitor studies indicate that IL-1β mediates its inhibitory effects on bile acid-induced expression of BSEP indirectly via CXCR2 ligands. Consistently, inhibition of CXCR2 with the inhibitor SB225002 significantly attenuated of the inhibitory effect of IL-1β on BSEP expression. These data suggest that part of the cholestasis-inducing effect of IL-1β is mediated via a CXCR2-dependent feedback mechanism.