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Abstract preview

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Title: Tauroursodeoxycholic acid forces epithelial IRE1 activation and alleviates DSS-induced colitis

Abstract text:
Background
Recent data point to a direct link between the activation of the unfolded protein response (UPR) and intestinal inflammation. In inflammatory bowel disease (IBD), inflammation is associated with the induction the UPR. A fundamental question is how the balance between cytoprotective and apoptosis promoting functions of the UPR can be influenced to alleviate inflammation. We used the dextran-induced model of colitis to estimate consecutive UPR events during acute intestinal inflammation and evaluated the effect of tauroursodeoxycholic acid (TUDCA), a bile salt with chaperone-like functions that has been shown to alter the UPR.
Methods
C57BL/6 mice received 4% dextran sodium sulfate (DSS) in their drinking water for 7 days to induce colitis. Mice were matched for body weight and treated IP daily with 500 mg/kg TUDCA or PBS. Weight loss and mortality were monitored. On day 0, 3, 7 and 10, eight mice per group were sacrificed and colon length was assessed. Colonocytes were isolated and lysed for real-time PCR (qPCR) analysis of BIP, XBP1s, XBP1u, ATF4 and PDIA4. HT29 cells were treated with 10 mM TUDCA for 24 hours and lysed for qPCR analysis.
Results
Administration of DSS did not result in substantial activation of the UPR in colonic epithelial cells. A transient activation of IRE1 was seen, measured by the increased ratio of spliced to unspliced XBP1 levels at day 7 and 10. Activation of the PERK and ATF6 pathways was not observed, as ATF4 and PDIA4 expression remained unchanged. The expression of the key chaperone BIP diminished at day 3 and 7 and returned to baseline at day 10. Administration of TUDCA resulted in 100% survival as compared to 60% in vehicle treated mice ($p<0.05$). Weight loss and colon shortening was significantly less in TUDCA treated mice ($p<0.01$ and $p=0.02$ respectively). Colonocytes from these mice showed 2.6-fold XBP1 splicing increase at day 3, while BIP levels were comparable to those in non-DSS treated mice. These findings were confirmed *in vitro* by the induction of XBP1 splicing and BIP expression in HT29 cells cultured in the presence of TUDCA ($p<0.001$).

Conclusions
Acute colitis is accompanied by a transient activation of the IRE1 pathway. TUDCA alters this response by forcing IRE1 activation and inducing its downstream target gene BIP. BIP protects cells from stress to the endoplasmic reticulum and could be beneficial to epithelial cells subjected to colonic damage. Chemical chaperones such as TUDCA merit further clinical investigation for the treatment of IBD.

Keywords: -

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