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Pregnane X receptor agonists enhance intestinal epithelial wound healing and repair of the intestinal barrier following the induction of experimental colitis.

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Abstract

The intestinal epithelial barrier plays a key role in the maintenance of homeostasis within the gastrointestinal tract. Barrier dysfunction leading to increased epithelial permeability is associated with a number of gastrointestinal disorders including the inflammatory bowel diseases (IBD) - Crohn's disease and ulcerative colitis. It is thought that the increased permeability in patients with IBD may be driven by alterations in the epithelial wound healing response. To this end considerable study has been undertaken to identify signaling pathways that may accelerate intestinal epithelial wound healing and normalize the barrier dysfunction observed in IBD. In the current study we examined the role of the pregnane X receptor (PXR) in modulating the intestinal epithelial wound healing response. Mutations and reduced mucosal expression of the PXR are associated with IBD, and others have reported that PXR agonists can dampen intestinal inflammation. Furthermore, stimulation of the PXR has been associated with increased cell migration and proliferation, two of the key processes involved in wound healing. We hypothesized that PXR agonists would enhance intestinal epithelial repair. Stimulation of Caco-2 intestinal epithelial cells with rifaximin, rifampicin and SR12813, all potent agonists of the PXR, significantly increased wound closure. This effect was driven by p38 MAP kinase-dependent cell migration, and occurred in the absence of cell proliferation. Treating mice with a rodent specific PXR agonist, pregnenolone 16α-carbonitrile (PCN), attenuated the intestinal barrier dysfunction observed in the dextran sulphate sodium (DSS) model of experimental colitis, an effect that occurred independent of the known anti-inflammatory effects of PCN. Taken together our data indicate that the activation of the PXR can enhance intestinal epithelial repair and suggest that targeting the PXR may help to normalize intestinal barrier dysfunction observed in patients with IBD. Furthermore, our data provide additional insight into the potential mechanisms through which rifaximin elicits its clinical efficacy in the treatment of IBD.

KEYWORDS: Inflammatory bowel diseases; Intestinal epithelium; Pregnane X receptor; Rifaximin; Wound healing

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