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Pregnane X Receptor Activation Attenuates Inflammation-Associated Intestinal Epithelial Barrier Dysfunction by Inhibiting Cytokine-Induced Myosin Light-Chain Kinase Expression and c-Jun N-Terminal Kinase 1/2 Activation.

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Abstract

The inflammatory bowel diseases (IBDs) are chronic inflammatory disorders with a complex etiology. IBD is thought to arise in genetically susceptible individuals in the context of aberrant interactions with the intestinal microbiota and other environmental risk factors. Recently, the pregnane X receptor (PXR) was identified as a sensor for microbial metabolites, whose activation can regulate the intestinal epithelial barrier. Mutations in NR1I2, the gene that encodes the PXR, have been linked to IBD, and in animal models, PXR deletion leads to barrier dysfunction. In the current study, we sought to assess the mechanism(s) through which the PXR regulates barrier function during inflammation. In Caco-2 intestinal epithelial cell monolayers, tumor necrosis factor-α/interferon-γ exposure disrupted the barrier and triggered zonula occludens-1 relocalization, increased expression of myosin light-chain kinase (MLCK), and activation of c-Jun N-terminal kinase 1/2 (JNK1/2). Activation of the PXR [rifaximin and [[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]ethenylidene]bis-phosphonic acid tetraethyl ester (SR12813); 10 μM] protected the barrier, an effect that was associated with attenuated MLCK expression and JNK1/2 activation. In vivo, activation of the PXR [pregnenolone 16α-carbonitrile (PCN)] attenuated barrier disruption induced by toll-like receptor 4 activation in wild-type, but not Pxr-/-, mice. Furthermore, PCN treatment protected the barrier in the dextran-sulfate sodium model of experimental colitis, an effect that was associated with reduced expression of mucosal MLCK and phosphorylated JNK1/2. Together, our data suggest that the PXR regulates the intestinal epithelial barrier during inflammation by modulating cytokine-induced MLCK expression and JNK1/2 activation. Thus, targeting the PXR may prove beneficial for the treatment of inflammation-associated barrier disruption in the context of IBD.

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