Corticotropin-releasing Hormone Receptor 2 Promotes Mucosal Repair Following Colitis: Implications for Treatment of IBD

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Background: Inflammatory Bowel Disease (IBD) is a chronic relapsing inflammatory disorder of the gastrointestinal tract. The corticotropin-releasing hormone (CRH) family mediates functional responses in many organs, including the intestine. Activation of CRH receptor 2 in the colonic mucosa promotes inflammation during the acute phase of colitis, but inhibits inflammation during chronic colitis. Here, we hypothesized that specific modulation of CRHR2 signaling in the colonic mucosa can also promote restoration of the epithelial barrier through stimulation of cell proliferative, migratory and wound healing responses.

Methods: Mucosal repair was assessed following dextran sodium sulfate (DSS)-induced colitis in mice receiving intracolonic injections of a CRHR2 antagonist or vehicle and in CRHR2 knockout mice. Histological damage and proinflammatory cytokine expression were evaluated, as well as TUNEL and Ki-67 immunoreactivity. Cell viability, proliferation and migration were compared between parental and CRHR2-overexpressing colonic epithelial cells. Protein lysates were processed for phosphoprotein assays and a wound healing assay was used to assess healing in vitro.

Results: Administration of a CRHR2 antagonist following DSS colitis increased disease activity, delayed healing and decreased epithelial cell proliferation in vivo. Colons from these mice also showed increased apoptosis and proinflammatory cytokine expression. Compared to controls, CRHR2 knockout mice showed increased mortality in the DSS-associated healing protocol. CRHR2-overexpressing cells had increased proliferation and migration rates compared to parental cells. Wound healing and STAT3 activity were elevated in CRHR2-overexpressing cells following Ucn2 and IL-6 treatment, suggesting advanced healing progression.

Conclusion: CRHR2 signaling promotes mucosal repair following experimental colitis in vivo and in human colonocytes in vitro. We suggest that selective CRHR2 activation may provide a targeted therapeutic approach to enhance mucosal repair pathways following colitis.

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