Identification of a Novel function of Corticotropin Releasing Factor (CRH) in the Repair of Intestinal Epithelium in DSS Colitis.

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Background: Corticotropin Releasing Hormone (CRH), a major mediator of the stress (adaptive) response in mammals, is implicated in the development and progress of Inflammatory Bowel Disease (IBD). We have previously shown the requirement of Crh in the regulation of the responses to innate immune challenges such as DSS, using the Crh-null (Crh -/-) mice. Based on the severely compromised ability of Crh-/- mice to reconstitute the intestinal epithelial cell barrier, in this study we set up to identify the exact role of this secreted homeostatic factor Crh in the epithelial repair and regeneration.

Methods: C57/Bl6 adult male mice, Crh-/- or wild-type (wt) were exposed to 3% DSS via their drinking water for 7 days. Mouse colon tissues were collected 7 days after initiation of DSS treatment and 4 days after the termination of the DSS administration and processed for histology by hematoxylin and eosin (H&E) staining for disease scoring, immunohistochemistry for epithelial cell characterization, gene expression by Q-PCR and cytokine levels by ELISA.

Results: We confirmed that Crh-/- mice exhibited a more severe DSS-induced inflammation, as evidenced by histology and cytokine levels in the media of colonic explants ex vivo. In particular, levels of interleukin 12p70, 1beta and TNFalpha were significantly upregulated in Crh-/- tissues at the end of DSS treatment. The compromised repair of the epithelial barrier was reflected in the limited formation of new crypts. To understand the exact level of CRH involvement in this process, we assessed the activation of Wnt pathway and identified downregulation of Wnt5alpha and its downstream target Math1, together with upregulation of the Wnt pathway inhibitor DKK1.

Conclusions: This is the first demonstration that Crh is required for intestinal epithelial repair via direct effects in the activation of Wnt5alpha, previously reported as the stromal-derived factor critical for epithelial regeneration. Our results provide a link between the hormonal mediator of the adaptive response to stressors and the regeneration of intestinal epithelia. Our findings raise the possibility for therapeutic potential of topical CRH in the resolution of inflammation and the restitution of the epithelial barrier.

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