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IMMUNOLOGY

Ironing out mucosal healing

Dendritic cell (DC)-derived hepcidin is required for mucosal healing in the mouse intestine after experimental damage, according to new research. Moreover, hepcidin production by DCs was induced by microbial stimulation and promoted local iron sequestration from the microbiota to facilitate intestinal repair.

Gastrointestinal bleeding and altered iron distribution are common in a range of gastrointestinal diseases as a result of infection, inflammation and cancer. "Our focus was on hepcidin, a well-defined master regulator of systemic iron homeostasis that is abundantly produced by the liver, but its role in intestinal damage and inflammation was previously unknown," explain authors Carole Peyssonnaux and Gregory Sonnenberg.

Mice lacking hepcidin exhibited impaired mucosal healing in the dextran sodium sulfate (DSS)-induced experimental model of intestinal damage and inflammation. Hepcidin was essential for tissue repair but, surprisingly, this process occurred independently of the liver and systemic iron regulation. Crucially, conventional DCs local to the intestine were the dominant source of hepcidin in the DSS mouse model, and bacteria and their products were potent inducers of hepcidin expression in DCs. Importantly, increased hepcidin expression was also observed in intestinal biopsy samples from patients with ulcerative colitis and Crohn's disease versus healthy controls, and conventional DCs were confirmed to be a major producer of hepcidin in the inflamed intestine of patients with inflammatory bowel disease.

Finally, DC-derived hepcidin acted on ferroportin-expressing phagocytes (macrophages and/or neutrophils) to facilitate mucosal healing in experimental models. DC-produced hepcidin also promoted local iron sequestration from the gut microbiota. This change in local iron bioavailability shaped the gut microbiota, shifting its composition and promoting colonization of tissue-protective microorganisms (such as *Bifidobacterium* spp.) and inhibition of tissue-infiltrating bacteria.

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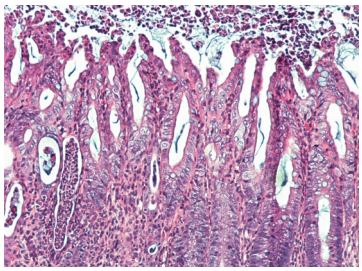

Severe damage, inflammation and impaired mucosal healing in mouse intestine (section stained with haematoxylin and eosin). Image courtesy of G.F. Sonnenberg, Weill Cornell Medicine, USA.

"Our research identifies a new pathway that is important to promote mucosal healing, a major unmet need in inflammatory bowel disease, gastrointestinal infections and colorectal cancers," say Peyssonnaux and Sonnenberg, who plan to test local delivery of hepcidin as a novel therapeutic strategy to promote or boost mucosal healing in experimental mouse models. "Our research also identifies a new pathway controlling local iron distribution in the gut and outlines the ability to employ nutritional immunity for shaping the microbiota," they add.

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ORIGINAL ARTICLE Bessman, N. J. et al. Dendritic cell-derived hepcidin sequesters iron from the microbiota to promote mucosal healing. *Science* **368**, 186–189 (2020)