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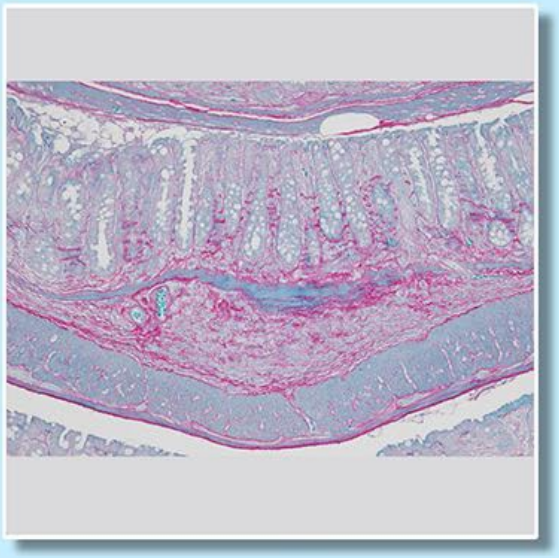

Intestinal fibrosis driven by a pathobiont-derived small molecule of the microbiota (Red = collagen)

Intestinal Fibrosis Driven by a Pathobiont-derived Small Molecule of the Microbiota

Intestinal fibrosis, defined as the excess deposition of extracellular matrix (ECM) as a result of chronic inflammation and dysregulated wound healing, afflicts more than 30% of patients with inflammatory bowel diseases (IBD), yet there is minimal understanding of the mechanisms controlling fibrosis. There is no known cause or cure; however, the microbiota provides a putative causal link between IBD associated bacteria and development of fibrosis. The bacterial siderophore yersiniabactin (Ybt) and its cognate receptor FyuA promote microbial fitness and are secreted in high quantities in non-pathogenic *Escherichia coli* overrepresented in IBD patients. The role of the Ybt:FyuA system in fibrotic development is unknown, so to investigate the impact of the Ybt:FyuA system on IBD and fibrosis, germ-free, colitis-susceptible *Il10-/-* mice and resistant WT mice were colonized with pathobiont *E. coli* NC101 or an isogenic mutant deficient in either the FyuA receptor (NC101 *ΔfyuA*), Ybt (NC101 *Δirp1*), or both Ybt and FyuA (NC101 *ΔfyuAΔirp1*). Tissue analysis revealed a subset of *Il10-/-* mice colonized with NC101 *ΔfyuA* developed a distinct submucosal colonic pathology with abnormal ECM deposition, edema, and cellular infiltration of activated fibroblasts. This pathology was independent of colonization capacity (fecal and mucosal bacterial loads), host and bacterial iron homeostasis, and Ybt uptake through FyuA. RNAseq revealed highly significant differences (2692 genes) in the colonic transcriptome of NC101 *ΔfyuA/Il10-/-* mice with the fibrotic pathology vs NC101/*Il10-/-* mice devoid of pathology. Because the most differentially regulated genes were associated with ECM and fibroblasts secrete increased ECM proteins in response to chronic inflammation/fibrosis, this lead to evaluating whether the *E. coli* strains above could directly and differentially activate fibroblasts. Swiss 3T3 fibroblasts were co-cultured with WT and mutant *E. coli* strains and assessed for fibroblast activation via real-time qPCR. When the live bacteria did not result in fibroblast activation, Swiss 3T3s were co-cultured with various bacterial small molecules and assessed for activation. Because fibrosis pathology required Ybt biosynthesis but not bacterial uptake of Ybt, this suggests a novel mechanism for the siderophore separate from its role in bacterial fitness and iron acquisition and implicates the potentiality of siderophores as therapeutic targets for IBD-fibrosis. In summary, *E. coli* NC101 *ΔfyuA* induced fibrosis in the *Il10-/-* IBD mouse model, but did not activate fibroblasts *in vitro*. These results warrant future studies evaluating an indirect mechanism of fibroblast activation.