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INSIGHTS

Lectin recruits pathogenic bugs

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Colitis is an irritable bowel disorder affecting about 7 million patients worldwide, but the causes are diverse and not fully understood. In this issue, Matute et al. (2022. *J. Exp. Med.* https://doi.org/10.1084/jem.20211938) found that a stress-induced lectin, intelectin-1, recruits pathogenic bacteria to the gut and exacerbates colitis.

The causes of ulcerative colitis (UC), an inflammatory bowel disorder caused by inflammation in the colon or rectum, are not well known. Both the unfolded protein response (UPR) and the expression of Intelectin-1 (ITLN1), a lectin that binds to microbes (Wesener et al., 2015), are increased in UC patients (Nonnecke et al., 2021). Therefore, Matute et al. (2022) investigated the extent the UPR is associated with ITLN1 and how both are associated with UC pathology.

From colonic biopsies, the authors show the expression of *ITLN1* and signature genes of the UPR were increased in UC patients. Furthermore, there was a positive association between UPR and *ITLN1*, suggesting upregulation of ITLN1 is a byproduct of upregulation of the UPR. To test this hypothesis, mouse organoids were treated tunicamycin to induce the UPR, which increased *Itln1* expression along with other markers of the UPR. Inhibition of separate arms of the UPR—PKR-like ER kinase, IRE1α, and ATF6—each suppressed tunicamycin-induced *Itln1* expression and UPR, thus confirming that ITLN1 expression is controlled by the UPR.

Next, the authors generated ITLN1-deficient and -overexpressing mice to determine the role of ITLN1 in the gut in vivo. Using a flow cytometry–based assay, the authors identified that both human and mouse ITLN1 bound to a relatively small subset of gut flora, most noticeably *Akkermansia muciniphila*. Because *A. muciniphilia* has mucolytic properties, and mucous layer thinning occurs in UC, the authors sought to methodically test mucous layer thickness. Using two different fixation methods, methanol-Carnoy and methacrylate, to preserve the mucous layer, ITLN1-overexpressing mice had a significantly thinned mucous layer as demonstrated by both methods, while no changes were identified in the ITLN1-deficient mice. Mucous layer thinning was reversed in germ-free mice, but monoclonization of *A. muciniphilia* in germ-free mice was sufficient to restore the decrease in mucous layer thickness.

Lastly, to determine the role of ITLN1 and *A. muciniphilia* in colitis, Matute et al. (2022) tested the sensitivity and severity of ITLN1-deficient or ITLN1 transgenic mice in the dextran sodium sulfate (DSS) colitis model. Despite having similar abundance of *A. muciniphilia*, there was an increase in colitis severity in the ITLN1 transgenic mice. This was recapitulated in a T cell adoptive transfer model of colitis where ITLN1 transgenic mice had increased severity. Depleting *A. muciniphilia* with tetracycline prevented the increased severity in the DSS colitis model and limited pathology. The increased colitis severity may be due to increased TNF expression from gut macrophages, which is diminished in the absence of *A. muciniphilia*. Thus, increased UPR stress increases ITLN1 expression, and ITLN1-bound *A. muciniphilia* thin the mucous layer and then are taken up into macrophages. As a result, the gut epithelial cells become more sensitive to inflammatory damage worsening UC (see figure).

Insights from Charles R. Schutt and Sho Yamasaki.

This research project is important because it highlights a novel mechanism that ties the gut microbiome, ITLN1 expression, and the UPR to the pathology of UC. *A. muciniphilia* is mucolytic, so discovering how this bacterium can be brought close to the epithelium to thin the mucus layer may be important for understanding the pathology in UC. As metagenomic analysis of IgA-captured microbes, called IgA-seq, is well established (Palm et al., 2014), this method can be expanded to its teleological prototype, soluble lectins, as "lectin-seq." The current study pioneered a way for future extensive study, as lectins represent a large diverse family.

However, some unsolved questions remain. It is unclear what ligand(s) from *A. muciniphilia* is recognized by ITLN1. It is also unknown which receptor(s) mediates the internalization of ITLN1–*A. muciniphilia* complex (Lin et al., 2021; Kobayashi et al., 2022). It remains to be determined how the

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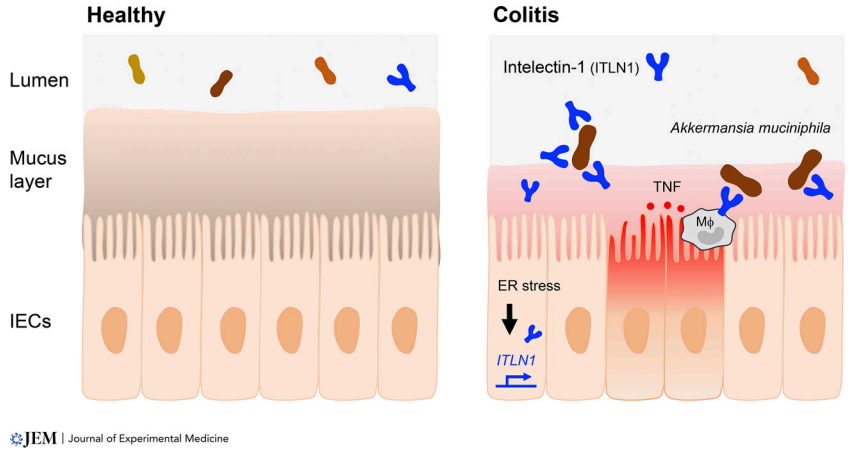

ITLN1-coated pathogenic bacteria thin the mucus layer, worsening colitis. In the healthy gut, a there is limited expression of the lectin ITLN1 and a thick mucus layer keeping the microbiota away from the intestinal epithelial cells (IECs). During colitis, the increase in ER stress increases the expression of ITLN1, which binds to *A. muciniphila*, an organism that can degrade the mucus layer in the gut. ITLN1-bound *A. muciniphilia* can be taken up into intestinal macrophages that produce TNF, increasing gut inflammation and worsening colitis.

ITLN1–*A. muciniphilia*–macrophage axis is reducing the thickness of the mucus layer. As this axis is unlikely to exist only for causing UC, understanding its physiological advantage could further clarify soluble lectin–mediated maintenance of homeostasis. Clinically, a new therapy that can allow for regeneration of the mucus layer might be promising.

Additionally, this study is of interest because of the establishment of a mouse model where *Itln1*, but not the other paralogs of ITLN, is overexpressed from the Villin promoter. In this model, the increased ITLN1 is localized to goblet cells, which is the location of ITLN1 expression in humans. As this model can recapulate human colitis, it would be useful for further studies of ITLN1 in colitis or other gastrointestinal disorders. As the ITLN1 expression is not restricted to gut epithelial cells (Kerr et al., 2014; Watanabe et al., 2017), a similar approach could also be used to investigate the role of ITLN1 in other disease settings in the different tissues.

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