IBD

Coagulation and IBD — PAI1 provides the missing link

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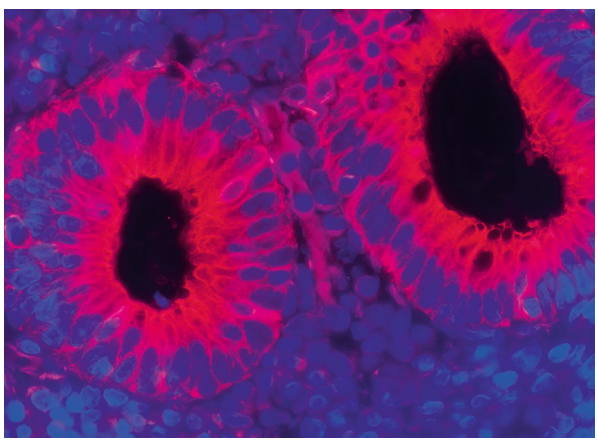
A new study implicates the coagulation pathway in the development of IBD. The research, published in *Science Translational Medicine*, pinpoints plasminogen activator inhibitor-1 (PAI1), a notable factor in coagulation, as having an important role in controlling key inflammatory modulators during mucosal damage in colitis.

IBD is a complex disease with heterogeneous pathophysiology in both Crohn's disease and ulcerative colitis. Multiple interacting factors including, among others, the environment, genetics, microbiota and immune system contribute to intestinal inflammation and the development of IBD. This complexity means there is an ongoing need to better understand IBD pathogenesis to help monitor disease activity and identify new therapeutic approaches, as well as which patients might benefit from targeted therapy.

"We were interested in new targets for IBD therapy that were not directly related to inflammation," explains author Thaddeus Stappenbeck. "We [were] especially interested in molecules that were overproduced by the intestinal epithelium in most patients with IBD." The researchers used both bioinformatics analysis (including Bayesian network analysis) and experimental research in animal IBD models as part of their investigations.



PAI1 expression in colonic biopsy sample from patient with IBD. Image courtesy of G. E. Kaiko and T. S. Stappenbeck, Washington University School of Medicine, USA.

First, global gene expression data sets from patients with IBD were analysed, derived from 91 colon biopsy samples from both patients with active ulcerative colitis and Crohn's disease versus controls, encompassing three separate cohorts. Of 1,773 genes that were altered across the cohorts, gene pathways linked to coagulation–haemostasis were consistently highly enriched. Crucially, further analyses revealed *SERPINE1* (encoding PAI1) as a candidate gene for further validation, as it linked genes expressed in the intestinal epithelium and those associated with myeloid cell-driven inflammation. Indeed, *SERPINE1* expression was specifically increased in IBD-related colon biopsy samples from active, inflamed areas compared with samples taken from uninflamed or uninvolved regions, patients in remission or non-IBD samples. Moreover, immunofluorescence showed increased numbers of PAI1-positive cells in colon tissue from regions with active ulcerative colitis, mainly within epithelial cells.

Next, the investigators explored the role of PAI1 in experimental colitis. *Serpine1* intestinal expression was markedly increased in wild-type mice with colonic injury and inflammation as a result of treatment with dextran sodium sulphate (DSS). Moreover, PAI1 was shown to promote intestinal damage and inflammation, worsening the features of DSS-induced colitis (such as weight loss, mucosal damage and crypt hyperplasia). The direct target of PAI1, the fibrinolytic protease tissue plasminogen activator (tPA, which PAI1 is known to bind and inhibit) also had a role in regulating intestinal inflammation in vivo, suppressing colitis and mucosal damage in mouse models of IBD.

Further investigations found that treatment with a small-molecule inhibitor targeting PAI1 reduced the severity of experimental colitis (including decreased mucosal damage and inflammation) via increased amounts of active tPA. Interestingly, experimental evidence indicated that the PAI1–tPA axis exerted its effects in colitis via the regulation of anti-inflammatory transforming growth factor β.

Finally, the functional insights into PAI1 were linked back to clinical settings by examining *SERPINE1* expression in a subset of difficult-to-treat patients with IBD. Crucially, *SERPINE1* expression was increased in active, severe disease and in patients with moderate-to-severe disease who failed to respond to anti-TNF agents.

"The strong link to coagulation was the most interesting and surprising finding that came out of this analysis," notes Stappenbeck, adding that this novel connection opens up new avenues for treatment. "We hope to target this pathway therapeutically," says Stappenbeck, "there is a lot of work to do here, but we feel this is an exciting target for potential therapy".

Katrina Ray

ORIGINAL ARTICLE Kaiko, G. E. et al. PAI-1 augments mucosal damage in colitis. *Sci. Transl. Med.* **11**, eaat0852 (2019)
FURTHER READING de Souza, H. S. P. et al. The IBD interactome: an integrated view of aetiology, pathogenesis and therapy. *Nat. Rev. Gastroenterol. Hepatol.* **14**, 739–749 (2017)