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Tissue Factor and Protease-Activated Receptor 2 associated genes are upregulated in patients with Inflammatory Bowel Disease

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Background: Tissue Factor (TF) is well known for its role in coagulation, but it is also a key mediator of inflammatory cellular signaling relating to myeloid cell migration and kinase activation. TF is upregulated during inflammation and has been implicated in IBD pathology. Its role as a therapeutic target has not been well characterized, due to concerns that inhibition may induce a coagulopathy. When activated, TF cleaves protease-activated receptor 2 (PAR2) and induces multiple intracellular signaling pathways. Our aim was to investigate TF gene expression and PAR2 activated genes by colonic segment with inflamed tissue in patients with IBD compared to non-inflamed regions, and tissue from healthy controls.

Methods: RNA seq data from colon biopsy samples taken from The Mount Sinai Crohn’s and Colitis Registry (MSCCR) cohort containing 1188 subjects (431 UC, 505 CD and 252 healthy controls) were downloaded from GEO (GSE193677) and preprocessed by the Endpoint Health RNA seq Analysis Pipeline. Tissues from patients with UC and CD were included in the analysis if the endoscopic score indicated moderate to severe inflammation. Differential gene expression analysis was performed using the Wilcoxon rank test. Gene set enrichment analyses (GSEA) was performed for PAR2 associated genes.

Results: 1,030 tissue samples, including 161 UC, 409 CD and 460 healthy control samples, were analyzed from 90, 174 and 252 subjects respectively. TF was found to be upregulated in inflamed tissue compared to non-inflamed tissue in patients with UC and CD, supporting a role for TF in inflamed lesions (Figure 1). Furthermore, PAR2-induced inflammatory related gene expression was observed in the inflamed tissue biopsies from patients with UC and CD compared to health control samples. Genes involved in inflammation, which include chemokines such as CXCL8 and chemokine receptors CXCR1, were consistently upregulated in all inflamed tissue regions isolated from patients with UC and CD (Table 1).

Conclusion: TF was found to be upregulated in inflamed tissue compared to non-inflamed tissue in patients with UC and CD, which may indicate TF contributing to tissue inflammation. TF represents a novel therapeutic target for IBD, but safety concerns with inhibiting coagulation have limited its clinical utility for inflammatory disease. To address this safety concern, EP004, a human IgG1 monoclonal antibody, targets the extracellular domain of human TF, inhibiting PAR2-induced inflammatory signaling while not altering coagulation activity. Clinical studies are required to elucidate its therapeutic effect.