Genetic and small-molecule modulation of STAT3 in mouse models of inflammatory bowel disease

Background & Aims: Ulcerative colitis (UC) and Crohn's disease (CD) are inflammatory bowel diseases (IBD) of unclear etiology that cause substantial morbidity and predispose to colorectal cancer (CRC). There are two isoforms of STAT3-α and β; STAT3α is pro-inflammatory and anti-apoptotic, while STAT3β has opposing effects on STAT3α. We determined the contribution of STAT3 to UC and CD pathogenesis by comparing disease severity caused by dextran sodium sulfate (DSS; UC model) or 2, 4, 6-trinitrobenzenesulfonic acid (TNBS; CD model) in mice expressing only STAT3α (Δβ/Δβ) and in wild-type (WT) mice treated with TTI-101, a small-molecule inhibitor of both isoforms of STAT3.

Methods: Seven days following administration of DSS in drinking water or two days following a single intra-rectal administration of TNBS, Δβ/Δβ mice, cage-control (+/+ ) mice and WT mice given TTI-101 or vehicle were examined for IBD manifestations; their colons were evaluated for apoptosis of CD4+ T cells, levels of STAT3 activation, IL-17A protein expression and transcriptome alternations.

Results: IBD manifestations were increased in Δβ/Δβ transgenic vs. cage-control WT mice and were accompanied by decreased apoptosis of colonic CD4+ T cells. Complementing and extending these results, TTI-101 treatment of WT mice prevented IBD, markedly increased apoptosis of colonic CD4+ T cells, reduced colon levels of IL17A-producing cells and down-modulated STAT3-gene targets involved in inflammation, apoptosis-resistance and colorectal-cancer metastases.

Conclusion: STAT3, especially in CD4+ T cells, contributes to the pathogenesis of UC and CD and its targeting may provide a novel approach to disease treatment.

Biography
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