2018

"Epigenetic silencing of SOCS3 expression contributes to fibrosis in Crohn’s disease"

Emily T. Marshall  
Virginia Commonwealth University

Chao Li  
Virginia Commonwealth University

John F. Kuemmerle  
Virginia Commonwealth University

Follow this and additional works at: https://scholarscompass.vcu.edu/mds_posters  
Part of the Medicine and Health Sciences Commons

Downloaded from  
https://scholarscompass.vcu.edu/mds_posters/14

This Poster is brought to you for free and open access by the School of Medicine at VCU Scholars Compass. It has been accepted for inclusion in MD Student Summer Research Fellowship Program Posters by an authorized administrator of VCU Scholars Compass. For more information, please contact libcompass@vcu.edu.
Abstract/Background

Identified risk polymorphisms affecting the Jak-STAT3 pathway in patients with Crohn's disease could affect TGF-β1 and collagen I expression in the pathogenesis of fibrostenotic disease. This data demonstrates one of the mechanisms of epigenetic silencing of SOCS3 that allow the sustained Jak-STAT3 activity that drives excess TGF-β1 and collagen expression and characterizes fibrostenotic Montel B2 and B3 phenotype Crohn's disease.

Introduction

Cytokines, including IL-6, are pivotal modulators of responses in inflammatory diseases and are secreted by numerous cells including activated intestinal subepithelial myofibroblasts.

Binding of IL-6 activates the constitutively activated Jak-1 and Jak-2 resulting in cross-phosphorylation and docking sites for STAT3. Specific STAT3 residues are acetylated and phosphorylated and STAT3 translocates to the nucleus where it regulates transcription activity, including of TGF-β1 and COL1α1.

A consensus STAT3 binding element is present in the 5'UTR region of the Suppressor of Cytokine Signaling-3 (SOCS3) gene (1).

Normally activation by IL-6, via Jak-STAT3, induces expression of SOCS3, a crucial negative regulator of cytokine-induced Jak-STAT3 signaling.

We recently demonstrated that in patients with Crohn's disease with fibrostenotic disease fibro-epithelial phenotype, that despite increased autocrine production of numerous pro-inflammatory cytokines, particularly IL-6, in mesenchymal cells of affected ileum, there is loss of the expected upregulation of SOCS3 protein.

Methods

Participants

The study included 15 individuals with fibrostenotic Crohn's disease (Montreal B2) and 14 individuals with non-fibrostenotic (Montreal B0/B1) disease. The study was approved by the VCU Institutional Review Board.

mRNA for degradation.

Results for qRT-PCR were calculated using the 2-ΔΔCt method (remains stable across Crohn's phenotypes compared to non-Crohn's subjects. In contrast, miR-15b levels were significantly elevated in SEMF of affected ileum compared to normal ileum in patients with B2 fibrostenotic disease. * denotes p<0.05 vs normal ileum.

Figure B. miR-19a and miR-19b expression was unchanged or decreased in SEMF of affected ileum of patients with fibrostenosis by transfection of miR-19b-mimic and increased when antagomiR-19b was used. Epigenetic silencing of SOCS3 in ileal SEMF of patients with fibrostenotic Crohn's disease occurs by increased miR-19b mediated degradation of SOCS3.

Figure A. Hybridization analysis of SOCS3 and miR-19b identified a conserved 8-mer seed sequences complementary for both has-miR-19a and has-miR-19b at position 1561-1568 of SOCS3 3'UTR, which targets SOCS3 mRNA for degradation.

Figure 1. SOCS3 expression decreased in affected ileum of patients with stricturing (Montreal B2) and penetrating (B3) Crohn's disease compared to normal ileum in the same patient as well as non-Crohn's subjects. The opposite occurred in patient with inflammatory (B1) Crohn's disease. Values represent the mean ± SEM of 5-6 separate experiments. *denotes p<0.05 vs normal ileum in the same patient.

Figure 8. miR-19b and miR-19b expression was unchanged or decreased in SEMF of affected ileum in patients with Montel B1 and B3 phenotype Crohn's disease, respectively, compared to non-Crohn's subjects.

Conclusions

Expression of specific miRs are altered in the fibro-epithelial organs including several members of the paralogous miR17~92 and miR106a~363 cluster gene, C13orf25 (3). Position 1561-1568 of the region of the miR17~92 cluster gene, C13orf25 (3). Position 1561-1568 of the region of the miR17~92 cluster gene, C13orf25 (3). Position 1561-1568 of the region of the miR17~92 cluster gene, C13orf25 (3). Position 1561-1568 of the region of the miR17~92 cluster gene, C13orf25 (3).

Acknowledgments

Special thanks to John F. Kuemmerle and Chao Li for their continued guidance and direction in both this experiment and current endeavors.

References