Results: at diagnosis, 2446 disease-specific CpG sites in rectal tissue (FDR<0.05) were identified. At baseline, the disease-associated DNAm signature in rectal tissue is distinct from our previous study from blood as only 15 CpGs were common between rectal tissue DNAm and blood DNAm. In contrast to what was observed in blood DNAm where the initial DNAm signature reverted back to control levels upon treatment, rectal tissue DNAm signatures remained consistent during follow-up (Figure 1). The majority of the disease-specific CpG sites identified in rectal biopsies showed a strong positive correlation with CRP. This evidence suggests that the treatment affects systemic measures of inflammation more strongly than disease tissues.

Conclusion: When studied longitudinally, the UC-specific DNA methylation patterns in rectal tissue are distinct from blood samples. In contrast to blood DNAm which normalizes after therapy during follow-up, rectal tissue DNAm changes persist after treatment in UC. This suggests the currently available therapies control the systemic inflammation effectively, but have less direct effect on the disease itself. Future therapies targeting disease-specific DNAm may be more effective in disease management and long-term remission.

Figure 1. The disrupted methylation patterns in blood DNA and rectal biopsies of UC patients at diagnosis and during course of the disease. (A) In blood, DNAm differences observed between IBDD cases and controls (x-axis) reverted back to normal after treatment (Gastroenterology, 2019, 156 (B): 2254–2265), evidenced by a strong negative correlation in case-control effect sizes (x-axis) and baseline-follow up differences (y-axis), R=−0.93; P < 2.2e-16 (B) In contrast, the majority (1828) of the 2446 CpGs showing case-control differences in rectal biopsies at baseline did not show even nominally significant differences between baseline and follow-up in cases, suggesting that they persist during treatment and over the course of disease.

P135
MAJOR GENE REGULATORS AFFECTED IN COLON AND BLOOD OF DEXTRAN SODIUM SULFATE ACUTE COLITIS MURINE MODEL

Reza Yarani, Oana Palasca, Nadezhda Tsankova Doncheva, Christian Anthon, Bartosz Pilecki, Thomas Litman, Uffe Holmskov, Lars Juul Jensen, Jan Gorodkin, Flemming Pociot

Background: Dextran sulfate sodium (DSS) ulcerative colitis (UC) murine models have long been used for in vivo studies. DSS is a negatively charged polysaccharide with colitogenic properties. Although the mechanisms by which DSS induces intestinal inflammation are not fully understood, there are several good reasons why the DSS chemical colitis model is of interest for investigating the immunopathogenesis of UC is widely used. These include strong phenotypic clinical manifestations which emulate numerous clinical and histopathological features of human UC, ease of use, low mortality rate and high reproducibility. Here, by using high-throughput RNA sequencing analysis we set to investigate the major predicted gene regulators (GRs) affected by differentially expressed genes in the DSS treated UC model in order to obtain regulatory insights into the pathogenic mechanisms of UC development.

Methods: A DSS-induced mouse model of UC was established. Total RNA from colon tissue and blood of 3 healthy and 3 DSS-treated mice was extracted and sequenced by Illumina HiSeq 4000. Gene expression levels were obtained by mapping and quantification to the annotated mouse genome. Subsequently, differential gene expression analysis between DSS-treated and control mice both in colon and blood was performed. Ingenuity pathway analysis software (IPA®,Qiagen) was used to predict/identify major GRs affected by significantly differentially expressed genes (SDEGs, FC > 2; p < 0.05) in both colon and blood.

Results: Our analysis revealed how many and which major GRs are affected in DSS- treated mice and also the direction of change as compared to healthy (untreated) mice. In colon, 595 activated and 198 inhibited major GRs (p-value of overlap <0.05) in relation to ~ 3180 SDEGs were identified, while in blood, we identified 205 activated and 62 inhibited GRs (in relation to ~650 SDEGs). Colon and blood share 181 activated and 41 inhibited GRs. Identified GRs include transcription regulators, cytokines, transmembrane receptors and enzymes that mainly contribute to the development of inflammatory/immune responses. In colon and blood, the top 10 activated and inhibited regulators with the highest positive and negative activation z-score with target molecules as well as expression in the datasets are indicated in Figure 1a and 1b, respectively.

Conclusion: In this study, we analyzed linkage of GRs to SDEGs through coordinated expression and identified potential major regulators that have significant effect on UC pathogenic-related gene expression. These GRs seem to be the key regulators of transcriptomic changes induced by inflammation. These findings expand our molecular understanding of putative new targets that may be important in the pathophysiology of UC and provide biological insights into the observed expression changes between the UC and healthy controls.

Downloaded from https://academic.oup.com/ibdjournal/article-abstract/26/Supplement_1/S32/5714392 by guest on 06 February 2020

SCGN DEFICIENCY RESULTS IN COLITIS SUSCEPTIBILITY

Luís Sifuentes-Dominguez, Haying Li, Ernesto Llano, Zhe Liu, Li, Amika Singh, Ashish Patel, Mahesh Kathania, Areen Khoury, Nicholas Norris, Jonathan Rios, Petró Starokadomskyy, Jason Park, Purva Gopal, Ql Liu, Shuai Tan, Lillennie Chan, Theodora Ross, Steven Harrison, K. Venuprasad, Linda Baker, Da Jia, Ezra Burstein

Inflammatory bowel disease (IBD) affects 1.5–3.0 million people in the United States. IBD is genetically determined and many common risk alleles have been identified. Yet, a large proportion of genetic predisposition remains unexplained. In this study we report the identification of an intronic missense variant (NM_006998.3:c.230G>A;p.Arg77His) in the SCGN gene causing Mendelian early-onset ulcerative colitis. SCGN encodes a calcium sensor that is exclusively expressed in neuroendocrine lineages, including enteroeendocrine cells and gut neurons. SCGN interacts with the SNARE complex, which is required for vesicle fusion with the plasma membrane. We show that the SCGN mutation identified impacted the localization of the SNARE complex partner, SNAP25, leading to impaired hormone release. Finally, we show that mouse models of SCGN deficiency recapitulate impaired hormone release and susceptibility to DSS-induced colitis. Altogether, these studies demonstrate that functional deficiency in SCGN can result in intestinal inflammation and implicates the neuroendocrine cellular compartment in IBD.

Innate and Mucosal Immunology and Immunity

12
A FUNCTIONAL TL1A/DR3 SYSTEM IS CRUCIAL FOR OPTIMAL GENERATION OF PATHOGENIC TH9 CELLS IN MURINE CROHN’S DISEASE-LIKE ILEITIS

Ludovica Buttò, Paola Menghini, Natalia Aladyshkina, Kristine-Ann Buel, Carlo De Salvo, Abdullah Osm, Theresa Pizarro, Fabio Cominelli

Background: Despite numerous therapeutic advancements, inflammatory bowel disease (IBD) remains a major health burden due to the inefficiency of conventional approaches. The cytokine DR3 plays a role in autoreactive T lymphocyte expansion in human IBD. The role of the soluble TNF superfamily member TL1A, which binds to DR4 and DR3, in the pathogenesis of IBD is still unknown. Here, we report that a functional TL1A/DR3 system is crucial for optimal generation of pathogenic Th9 cells in a murine model of Crohn’s disease-like ileitis.

Downloaded from https://academic.oup.com/ibdjournal/article-abstract/26/Supplement_1/S32/5714392 by guest on 06 February 2020

© 2020 by the Crohn’s & Colitis Foundation and the AGA Institute.