the tralokinumab and placebo groups was not statistically significant. Safety and tolerability were acceptable and consistent with previous tralokinumab trials.

OP012
Epigenetic control of colonic inflammation via the methyl-binding protein Mbd2
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Background: Methyl-CpG binding protein domain protein-2 (Mbd2) is a transcriptional co-repressor that binds to methylated DNA. Mbd2 can recruit a nucleosome remodelling complex which contains chromatin remodelling and histone deacetylase properties. Mbd2 deficient mice are viable and fertile but display a dysregulated T cell cytokine response. The impact of Mbd2 deficiency on innate immune cell function and the immunological phenotype in the GI tract is unknown.

Methods: Mbd2+/− or Cre negative control (WT) mice were given 2% Dextran Sulphate Sodium (DSS) in drinking water for 7-10 d. CD45RbHi T cells were adoptively transferred by intra-peritoneal injection into Rag−/− in a T cell model of chronic enterocolitis. Both models were assessed for weight loss, symptom score, colon histology score and mRNA expression of selected cytokines. Single cell suspension of colon lamina propria (LP) (leucocytes were isolated and assessed by FACs for CD4+, FoxP3, CD8, CD25, CD11b, CD11c, CD103, CD64, MertK, F4/80, Ly6C, MHC-II, SiglecF, Ly6G. Intracellular cytokines (IL1b, TNF-alpha, IL-10, IL-17 and IFN-gamma) were assessed by FACs post 4hrs ex vivo Golgistop or PMA/ionomycin incubation.

Results: Mbd2+/− and CD11cCre mice had equivalent proportions of all myeloid subsets in the LP compared to WT in the steady state. Mbd2+/− displayed significantly worse colitis post-DSS compared to WT, with greater weight loss, histology score, and mRNA expression of IFN-gamma and IL-17. CD11cCre mice similarly displayed significantly greater weight loss with increased proportion of LP neutrophils and Ly6C+ MHC-II +/- inflammatory monocytes after 8 days of DSS compared to WT. CD11cCre DSS treated LP inflammatory monocytes also had significantly greater TNF and IL-1b producing ability than WT as assessed by FACs suggesting for the first time epigenetic processes can regulate this cell type, which is previously shown to be the dominant pathogenic lineage in this model.

Mbd2+/− adoptively transferred T cells produced a significantly greater colitis with increased weight loss, histology score and mRNA expression of IL-17 and IFN-gamma. Mbd2+/− CD4+ LP T cells also had significantly greater proportion of double positive IL-17 and IFN-gamma producing cells demonstrating epigenetic regulation of T cells is critical in this established Th17 model of colitis.

Conclusions: These data reveal for the first time that Mbd2 is of critical importance in the orchestration of a T cell dependent and independent model of murine colitis in vivo. They also identify methyl-binding proteins and/or genes that they regulate as exciting new targets for therapeutic modulation of GI inflammation.

OP013
Status of ER stress and autophagy in Crohn’s disease: From genetics to functional read-outs
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Background: The imminent introduction of new therapeutic classes for inflammatory bowel disease patients emphasizes the need for efficient personalized medicine. Large-scale studies have identified several stress and inflammatory signaling pathways to be important during Crohn’s disease (CD) and ulcerative colitis (UC) pathogenesis. However, it remains unclear if and how the identified genetic variants correlate with a functional response. Therefore, we aimed to study the association of CD-associated genetic variants with deficiencies in myeloid cell function isolated from patients samples.

Methods: Peripheral blood-myeloid cells, isolated from 182 individuals (36 healthy controls and 146 CD patients), all genotyped by immunochip, were exposed to an inflammatory stimulus (LPS), ER stress (thapsigargin) or autophagy modulation (inhibition with chloroquine). We assessed the correlation of immune function, ER stress and autophagy of the myeloid cells with CD-associated genetic variants linked to innate immunity (NOD2), ER stress (XBP1, ORMDL3) and autophagy genes (ATG16L1, IRGM, ULK1, MTMR-3, LRRK2) in patients and controls.

Results: Compared to healthy individuals, CD patients showed an increase of LPS-induced cytokine levels [TNF, IL-6/10/1beta secretion: 29.4-139% median increase, p = 0.01 – 0.04]; increased levels of Bip (300% basal median increase, p = 0.02; 173.1% median increase with added stress, p = 0.02), an important ER chaperone, and 22.1% increased accumulation of p62 (p = 0.04), an autophagy-related tagging protein, after autophagy inhibition. When comparing patients according to their genetic risk load, “high genetic risk” patients (>7 risk alleles, corresponding to Q4 of the distribution of risk alleles; n = 98) had a 4.6-45.1% increased release of TNF and IL-6/10/1beta after LPS exposure, increased ER stress (21.7% basal; 39.9% with added stress) and 14.6% decreased autophagic activity (p = 0.03) compared to “low genetic risk” patients (<4 risk alleles, corresponding to Q1 of the distribution of risk alleles; n = 84). Moreover, for individual risk loci such as ATG16L1, IRGM, MTMR-3, XBP1, ORMDL3 and NOD2 an augmented LPS-induced cytokine release was observed with increasing risk alleles.

Conclusions: Our data suggest that blood-myeloid cells from CD patients typically show a more severe LPS-induced cytokine response, increased unresolved ER stress and increased autophagic demand. Our study also indicates that the burden of risk alleles, in these pathways or in individual susceptibility loci, correlates with the LPS-induced cytokine response, the level of ER stress and the autophagic rate. These findings highlight the promising potential of using these functional read-outs for personalized management of Crohn’s disease.