MFI, p = 0.002), whereas GCSF-primed ROS production was unaffected (p = 0.79) indicating a specific GMCSF receptor signaling defect. E. coli uptake was not different, whereas a trend towards diminished killing was observed in C allele patients. In C-allele patients, GMCSF stimulation induced less activation of STAT3 (n = 5, 1.8 ± 0.8 vs 3.5 ± 1.1 vs); AKT (11.1 ± vs 23 ± 13) and ERK (30 ± 20 vs 40 ± 10) in C allele carriers. IL5 induced lower STAT5 (n = 4, 0.2 ± 0.1 vs 0.5 ± 0.2) and AKT signaling (0.03 ± 0.06 vs 0.7 ± 0.04).

Conclusions: We show a specific defect in CSFR2B signaling in patients carrying the NCF4 risk allele. The CSFR2B receptor is used by both GMCSF and IL5, and both cytokines induce reduced signaling in C-allele patients. In contrast, priming of PMN by GCSF, which signals through a different receptor, was normal. Thus, the NCF4 risk allele confers a defect in CSFR2B signaling, and may identify a subset of CD patients whose inflammation is influenced by impaired innate immunity induced by neutrophils. GM-CSF treatment, which is beneficial for some patients, may be limited by NCF4 genetic background of patients.

P095
Dipotassium glycyrrhizate ameliorates DSS-induced colitis in mice by HMGBl inhibition
R. Vitali1, F. Palone1, L. Stronati1, A. Negroni1, E. Prete1, A. Di Lillo2, G. D’Arcangelo2, M. Aloi2, S. Cucchiara2. 1ENEA, Department of Radiobiology and Human Health, Rome, Italy, 2Sapienza University of Rome, Department of Pediatrics, Pediatric Gastroenterology & Liver Unit, Rome, Italy

Background: Inflammatory bowel diseases (IBD) are chronic immune-mediated disorders of the gastrointestinal tract. Since IBD are currently not curable, it is crucial to identify innovative therapies.

High mobility group box 1 (HMGB1) is a DNA-binding nuclear protein that can be released into extracellular milieu in response to stress or damage and subsequently activate the immune system and promote inflammation. HMGB1 has been implicated in several inflammatory and auto-immune disorders.

We previously showed that HMGB1 is secreted by inflamed intestinal tissues and is abundantly present in the feces of IBD patients, therefore it was proposed as a novel marker of intestinal mucosal inflammation.

Glycyrrhizin, a glycoconjugated triterpene produced by the root of licorice plant Glycyrrhiza glabra, exhibits anti-inflammatory properties and has been shown to importantly inhibit the cytokine activity of HMGB1. Thus, the aim of the present study is to assess the efficacy of a glycyrrhizin-derived compound, the dipotassium glycyrrhizinate (DPG), in the treatment of chemical-induced murine colitis.

Methods: DPG (3–8 mg/kg) was administered to C57Bl/6 mice after induction of chemical colitis by DSS. Body weight, clinical score, histological score, colon length/weight were evaluated in treated mice and compared to controls. Expression levels of pro-inflammatory cytokines (TNF-alpha, IL-1beta, IL-6) and HMGB1 receptors (RAGE, TLR4) were also measured by RT-PCR. Fecal HMGB1 was analyzed by Western blot.

Results: Mice exposed to DPG had a dramatic recovery of body weight (60%), total clinical score, histological score and large intestine length. Moreover, mice treated with DPG showed a significantly decrease in the mRNA levels of pro-inflammatory cytokines and HMGB1 receptors (p < 0.001). Finally, HMGB1 was found to be abundantly present in the feces of mice with DSS-induced colitis, but this amount was strongly reduced following DPG treatment (p < 0.01).

Conclusions: DPG showed excellent therapeutic properties for the treatment of DSS-induced murine colitis. We believe that these findings may open new perspectives in the setting of alternative strategies for the treatment of human IBD.

P096
Circulating components of the alternative renin–angiotensin system are upregulated in patients with inflammatory bowel disease
M. Garg1 *, L. Burrell1, E. Velkoska2, K. Griggs2, P. Angus3, P. Gibson4, J. Lubel1. 1Monash University, Gastroenterology, Eastern Health, Box Hill, Australia, 2University of Melbourne, Departments of Medicine and Cardiology, Heidelberg, Australia, 3University of Melbourne, Austin Hospital Liver Transplant Unit, Heidelberg, Australia, 4Monash University, Gastroenterology, The Alfred Hospital, Prahran, Australia

Background: There is accumulating evidence that the renin–angiotensin system (RAS) is active within the gastrointestinal tract, but its influence in intestinal inflammation, especially inflammatory bowel disease (IBD), is poorly understood.

Aim: To measure the circulating concentration of RAS enzymes and peptide products in patients with IBD and healthy controls, and to correlate these with markers of disease activity.

Methods: Healthy controls, and patients with Crohn’s disease (CD) and ulcerative colitis (UC) were studied. Demographic and clinical data together with plasma concentrations of the classical RAS components – angiotensin converting enzyme (ACE) and angiotensin II (Ang II) – and alternative RAS – ACE2 and Ang (1–7) – were analysed by radioimmuno- and enzymatic assays. Systemic inflammation was assessed using serum C-reactive protein, white cell count, platelet count, and albumin and intestinal inflammation by faecal calprotectin. Participants taking ACE inhibitors and angiotensin receptor blockers were excluded.

Results: 19 healthy controls (11 female; mean age 38, range 23–68 y), 19 patients with CD (11 female; aged 45, range 23–76 y) and 15 with UC (6 female; aged 42, 26–64 y) were studied. The 3 groups were demographically similar. The classical RAS components were not significantly different across the three groups, whereas ACE2 activity and Ang (1–7) concentrations were higher in patients with IBD compared to controls, (ACE2; 21.5 vs 13.3 pmol/ml/min; p < 0.05, Ang (1–7); 22.8 ± 14.1 pg/ml; p < 0.001). Ang (1–7) demonstrated a weak correlation with platelet count and white cell count, but not calprotectin or C-reactive protein in patients with IBD.

Conclusions: The alternative RAS axis is upregulated in patients with IBD, and Ang (1–7) correlates with some markers of disease activity. Further research into this novel pathway in IBD is indicated.
was to evaluate the effects of B-98, a newly synthesized benzoxazole derivative and a novel 5-lipoxygenase inhibitor, in mice model of IBD induced by dextran sulfate sodium (DSS). We also investigated the effect of B-98 on the Th (helper T) cell and Treg (regulatory T) cell profiles.

Methods: Seven to eight week old C57BL/6 mice were randomly assigned to 3 groups: normal control, DSS colitis group (DSS + saline), B-98 group (DSS + B-98 20 mg/kg). For the induction of acute colitis, the mice were treated with 3% DSS for seven days. B-98 diluted in dimethyl sulfoxide was administered simultaneously with DSS from day 1 to 7 by intraperitoneal route. On day 8, the mice were sacrificed and proximal and distal colonic specimens were obtained. The severity of the colitis was assessed via the disease activity index (DAI), colon length, and histopathologic grading. The production of cytokines IL-6 and TNF-α was determined by RT-PCR. Th cells from the lamina propria were examined for the expression of polymorphism among CD and control subjects (P = 0.21 and P = 0.26, respectively), whereas TT genotype and T allele seem to have a protective role against UC (P = 0.017 and P = 0.007 respectively). The presence of miR-146a rs2910164 and miR-196a2 rs11614913 SNPs did not influence disease phenotype.

Results: Our results demonstrate that the miR-146a rs2910164 polymorphism has major role in genetic susceptibility to CD but no in genetic susceptibility to UC, since miR-196a2 rs11614913 polymorphism found to have a protective role against UC, at least in the population studied here. Independent studies are needed to validate our findings in a larger series, as well as in patients of different ethnic origins.

P099 Anti-TNF-alpha treatment improves carbohydrate metabolism in patients with inflammatory bowel disease

K. Lorinczy1*, P. Miheller1, A. Patócs1, H. Székely1, P. Reismann1, Á. Csontos1, B. Fekete1, O. Terjék1, L. Herszényi1, A. Somogyi1, Z. Tulassay1. 1Semmelweis University, 2nd Department of Internal Medicine, Budapest, Hungary

Background: TNF-alpha has an important role in metabolic profile and insulin resistance. Adipose tissue has been recognized as an immune organ that secretes numerous immunomodulatory factors and seems to be a significant source of inflammatory signals known to cause insulin resistance. However, the regulation of carbohydrate metabolism by TNF-alpha in inflammatory bowel disease (IBD) is poorly understood. Previous studies have shown increase endogenous ghrelin production among patients suffering from IBD. The aim of our study was to assess the changes of serum ghrelin levels and progress of anti-TNFα therapy in IBD.

Methods: 17 IBD patients (4 with ulcerative colitis [UC], 13 with Crohn’s disease [CD]) were treated with biological therapy (5 mg infliximab per kg at week 0, 2, 6 and then in every 8 weeks; or adalimumab 160/80 as an induction and 40 mg/2 weeks as a maintenance therapy). Mean age of the patients was 34.2±9 years. Oral glucose tolerance test were performed and markers of carbohydrate metabolism (ghrelin), inflammatory and routine parameters were measured at the first visit than 3 and 12 month later. Insulin resistance calculated by homeostatic model assessment (HOMA-IR). Ghrelin levels were measured by radioimmunoassay using polyclonal rabbit-antibody. Calculations were performed using SPSS statistics 15.0 software.

Results: The insulin resistance significantly decreased to the 3th and 12nd month of the therapy (HOMA-IR at week 0.: 1.40±1.02 vs. week 12.: 0.27±0.24, and month 12.: 0.20±0.38, respectively; p < 0.01). Oral glucose tolerance improved at the end of the study (Figure 1.).

Figure 1. Oral glucose tolerance.

We observed decreasing trend in ghrelin concentrations (at week 0.: 1044.60±427.95 vs. week 12.: 957.77±170.33 vs.