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enhancing cell sensitivity to 5-FU. Furthermore, 5-FU exposure markedly decreased the levels of endogenous ERK5 and MEK5 expression ($p<0.05$), while inducing p53 and p21 expression ($p<0.05$).
CONCLUSION: Overall, our results indicate that overactivation of MEK5/ERK5 pathway may contribute to CC aggressiveness and chemoresistance, suggesting that ERK5-targeted inhibition, via siRNA, miRNA or small-molecule inhibitors, may provide a promising therapeutic approach for CC treatment, warranting further investigation.
(Supported by PTDC/SAU-ORG/119842/2010, PEstOE/SAU/UI4013/2011, Sociedade Portuguesa de Gastrenterologia, SFRH/BD/88619/2012 and SFRH/BD/79356/2011. The authors thank Dr. Robert Doebele for the kind gift of pWPI-MEK5AA and pWPI-MEK5DD constructs.)
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Disclosure of Interest: None Declared
Keywords: 5-Fluorouracil, Chemosensitization, Colon Cancer, MEK5/ERK5 Signalling

TUESDAY, OCTOBER 15, 2013 11:00–12:30
Nutrition and gut function – Hall 8

OP246 PPARGAMMA IS A MASTER REGULATOR OF LACTASE PRODUCTION BY INTESTINAL EPITHELIAL CELLS

M. Fumery[1], A. Langlois[1], S. Speca[1], C. Dubuquoy[1], M. Figeac[2], R. Christel[3], L. Dubuquoy[1], S. Bellinvia[4], P. Desreumaux[1], B. Bertin[1,*]. [1]*Inserm U995,* [2]*Genomic platform IFR-114,* [3]*Inserm U995, Université Lille-Nord de France, Lille, France,* [4]*GiulianiSpA, Milano, Italy*

INTRODUCTION: Lactose intolerance is a frequent condition that causes abdominal discomfort and diarrhea, resulting from lactase (LCT) enzyme deficiency produced by intestinal epithelial cells (IEC). Except for lactose free diet, no treatment can cure lactose intolerance and the regulation of LCT enzyme expression remains unknown. Peroxisome proliferator-activated receptor γ (PPARγ) is a nuclear receptor highly expressed by IEC playing a key role in gut homeostasis and metabolism regulation.
AIMS&METHODS: Aim: To evaluate the roles of PPARγ in the regulation of lactase production *in vitro* in IEC and *in vivo* in rodents. **Methods**: Caco2 cells were treated 24 hours with Pioglitazone (Pio; 1µM) and with a new PPARγ modulator named GED (amino-phenyl-methoxy-propionic acid; 1mM) or 5-aminosalycilate (5ASA; 30mM). Transcriptomic profiling was done using Agilent 2-colors 44K Gene Expression Microarrays. LCT mRNA and protein expression was assessed by quantitative RT-PCR and immunostaining. LCT activity was evaluated *in vitro* by standard method measuring the amount of glucose after lactose digestion. Involvement of PPARγ was confirmed using RNA interference, antagonist treatment (GW9662) and intestine-specific PPARγ knock-out C57BL/6 mice ($PPAR^{\Delta IEC}$). *In vivo*, LCT expression and activity were determined in the duodenum and jejunum of wild-type rodents orally treated with GED.
RESULTS: Both in microarray and qRT-PCR analysis, LCT mRNA expression was upregulated by GED, Pio and 5ASA compared to control cells with a mean fold of 5.7 ($p<0.0001$), 14.7 ($p<0.0001$) and 9.5 ($p<0.0001$) respectively. LCT protein upregulation was also observed by immunostaining of stimulated Caco-2 cells. Importantly, GED and Pio treatments significantly increased LCT enzyme activity of Caco-2 cells (2.5 to 3 fold; $p<0.05$). LCT mRNA ($p=0.0022$), protein expression and lactase activity ($p=0.0043$) were decreased in PPARγ knock-down Caco2 cells. In $PPAR^{\Delta IEC}$ mice, LCT mRNA expression was significantly decreased both in duodenum ($p=0.028$) and jejunum ($p=0.05$) compared to control mice. Both LCT expression and activity were increased in the duodenum ($p<0.05$) and jejunum ($p<0.01$) of weaned C57BL/6 mice and Sprague-Dawley rats treated one week with GED compared to animals receiving vehicle.
CONCLUSION: PPARγ agonists are able to increase lactase expression and activity *in vitro* and *in vivo*. These findings identify PPARγ as a new master regulator of LCT production by IEC and suggest that modulating PPARγ activity may be a new therapeutic strategy for the management of lactose intolerance.
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Disclosure of Interest: M. Fumery Financial support for research from: Giuliani SpA, A. Langlois Financial support for research from: Giuliani SpA, S. Speca Financial support for research from: Giuliani SpA, C. Dubuquoy Financial support for research from: Giuliani SpA, M. Figeac: None Declared, R. Christel Financial support for research from: Giuliani SpA, L. Dubuquoy Financial support for research from: Giuliani SpA, S. Bellinvia Directorship(s) for: Giuliani SpA, P. Desreumaux Financial support for research from: Giuliani SpA, B. Bertin Financial support for research from: Giuliani SpA
Keywords: instestinal epithelial cells, lactase gene, lactose intolerance, PPARgamma, small intestine

OP247 DISTURBED INTESTINAL INTEGRITY IN PATIENTS WITH COPD; EFFECTS OF ACTIVITIES OF DAILY LIVING

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INTRODUCTION: Chronic obstructive pulmonary disease (COPD) is accepted to be a multicomponent disease with various comorbidities. The contribution of the gastrointestinal tract to the systemic manifestation of COPD has never been investigated. This metabolically active organ may experience recurring local oxygen deficits during daily life, leading to disturbed intestinal integrity in COPD patients.
AIMS&METHODS: 18 patients with moderate COPD (mean FEV1: 55±3%pred) and 14 matched healthy controls were tested on two occasions, a baseline measurement at rest and, at another day, during the performance of activities of daily living (ADLs). To assess enterocyte damage, plasma intestinal fatty acid binding protein (IFABP) levels were determined, whereas urinary excretion of orally ingested sugar probes was measured using liquid chromatography and mass spectrometry to assess gastrointestinal permeability.
RESULTS: Plasma IFABP concentrations were not different between COPD patients and healthy controls at rest. In contrast, 0-3h urinary lactulose/rhamnose and sucralose/erythritol ratios and 5-24h urinary sucralose/erythritol ratios were significantly higher in COPD patients compared to controls, indicating increased permeability of the small intestine and colon. Furthermore, the performance of ADLs led to significantly increased plasma IFABP concentrations in COPD patients but not in control subjects. In line, the intestinal permeability difference between COPD patients and controls was intensified.
CONCLUSION: Besides an altered intestinal permeability in COPD patients at rest, performing ADLs led to enterocyte damage in addition to intestinal hyperpermeability in COPD patients but not in controls, indicating functional alteration in the gastrointestinal tract. Hence, intestinal compromise should be considered as a new component of the multisystem disorder COPD.
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Disclosure of Interest: None Declared
Keywords: Chronic disease, Intestinal epithelial barrier, Intestinal epithelial cells, Intestinal injury, Physical activity

OP248 FOLATE PRODUCTION IN BIFIDOBACTERIA FROM INFANT AND ADULT HUMANS

M. R. D'Aimmo[1], M. Modesto[2], P. Mattarelli[2,*], B. Sgorbati[2], B. Biavati[2], T. Andlid[1]. [1]*DEPARTMENT OF CHEMICAL AND BIOLOGICAL ENGINEERING, Chalmers University of Technology , Goteborg, Sweden,* [2]*DIPSA, BOLOGNA UNIVERSITY, Bologna, Italy*

INTRODUCTION: Folates – the natural chemically reduced forms of folic acid (vitamin B9) - are cofactors in essential metabolic pathways such as DNA synthesis and methylation pathways. Humans cannot synthesize folate and depend on intake both from the diet (green vegetables, cereals, rice, milk, fermented milk products, etc.) and from indigenous folate synthesizing bacteria of the intestinal microbiota. Low folate levels increase the risk for neural tube defects and may increase the risk for e.g. certain cancer forms, cardiovascular disease and Alzheimer's.
AIMS&METHODS: Screening for folate production of the bifidobacteria isolates from human adult and infant (1-6 month old) was performed. Strains typical of infants, such as *Bifidobacterium longum* subsp. *infantis* and *B. breve,* and of adults (*B. adolescentis*) were selected for characterization. The aim of the present work was to investigate bifidobacteria from human host of different age with different feeding habits in order to establish a possible correlation between diet and the folate production. Folate is present in many different forms in humans. The detectable forms studied in the present work are 5-CH3-H4, H4 and total folate content. Bifidobacteria strains were cultivated in folate free synthetic media. Validated HPLC method was used to analyze deconjugated folates extracted from bacterial biomass.
RESULTS: All bifidobacteria tested (both from adult and infant) were able to produce folate. Strains derived from adults were the higher producer of total folate (range from 580 to 935 μg/g dry matter) with the predominance of 5-CH3-H4 folate and a low amount of H4 folate. In infants we obtained the opposite results with strains typical of infant habitat producing low amounts of total folate (range from 35 to 200 μg/g dry matter) and an inverted ratio of 5-CH3-H4/H4 folate in respect to adults.
CONCLUSION: In agreement with idea of coevolution of host-gut microbiome (Ley et al., 2008) we find that bifidobacteria present in the adult gut were able to produce high amount of folate whereas strains derived from infants were less able to produce folate. These findings correlate with the diet and the folate requirement of the host: in infants, in fact, milk feeding is able per se to fulfill the folate needs of the individuals whereas in adults a more complex diet is sometime not able to cover all the folate need. The relevance of the different ratio of 5-CH3-H4/H4 folate production in adults and infants has being studied only in few strains and further studies are requested in order to complete this finding and provide an ecological explanation.
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Disclosure of Interest: None Declared
Keywords: Bifidobacterium adolescentis, Bifidobacterium breve, Bifidobacterium longum subsp. infantis, Folate production, Gut microbiota

OP249 UNDISSOCIATED GELATIN TANNATE REDUCES INTESTINAL LEAKINESS AND MUCOSA INFLAMMATION BY FORMING A PROTECTIVE BIOFILM: RESULTS FROM IN-VITRO AND IN-VIVO STUDIES

L. Bueno[1,*], S. Sekkal[1], V. Theodoru[1], M. Dattilo[2]. [1]*INRA, Tolouse, France,* [2]*Biogem, Ariano Irpino, Italy*

INTRODUCTION: Gelatine (GEL) stabilised by cross-linking with tannic acid (TA) forms gelatine tannate (GT). GT is approved as medical device for the oral treatment of diarrhoea as Tasectan®. GT is considered as a protective biofilm on the gut mucosa and has been shown to cure diarrhoea but the mechanism of action needs further investigation.
AIMS&METHODS: We aimed at investigating the effect of GT and its components (GEL and TA) on the intestinal mucosa using both *in-vitro* and *in-vivo* models.

The *in-vitro* "filming" activity was evaluated by Corrositex®, a standard measure of chemical aggression, and on Caco-Goblet monolayers. The effect of GT (5 or 20 mg/ml) on Caco-Goblet cell permeability was assessed by Trans-Epithelial Electrical Resistance (TEER) and Lucifer Yellow (LY) before and after apical *S. typhimurium*. The tight-junction (TJ) proteins acquaporin-3 (AQP3) and occludin (OCL) were assayed by RT-PCR as markers of TJ integrity.
In-vivo, Wistar rats received orally either GT (250 mg/kg), Gel (125 mg/kg), or TA (125mg/kg), and 2 h. later were injected IP with LPS from *E. coli*. Jejunal strips were collected 6 hours later for *in vitro* TJ permeability measurement using FITC-dextran and mucosal myelo-peroxidase (MPO) activity as a marker of inflammation.
RESULTS: GT increased the corrosion time (hydrochloric ac. 37%) from 400 to 699 sec ($p < 0.001$) suggesting a chemical biofilm protection. In addition, GT(5 mg/ml) increased TEER of CACO-goblet at 4 hours (from 180.1 to 269.2 ohm*cm2, $p < 0.05$) and decreased the basal permeability to LY in basal conditions at both 2 and 4h. The LY permeability increased from 1.18 to 7.54 after 2 hours of exposure to *S. typhimurium* however a pre-treatment with GT suppressed this increase and decreased bacterial invasion by 72%, such been associated with overexpression of AQP3 and OCL at 4 hours (350 and 200% respectively for GT at 20mg/kg.
Six hours after LPS injection in rats, both jejunal TJ permeability and MPO activity were dramatically increased. Oral pretreatment with GT reduced by 78.1% the jejunal increase of permeability whereas GEL and TA did not affected it and subsequently reduced significantly the LPS-induced increase in MPO.
CONCLUSION: Our results confirm that GT acts by mechanical protection of the gut mucosa. The protective biofilm formed by GT prevents the leakiness of the tight Junctions both in basal conditions and after insult by bacteria (in-vitro) and by LPS (in-vivo). These effects cannot be replicated by either tannic acid or gelatine confirming that GT is the active form to prevent gut leakiness and subsequent inflammation.
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Disclosure of Interest: None Declared
Keywords: Diarhoea, Gelatin tannate, inflammation, LPS, paracellular permeability

OP250 DIABETES AND GASTROINTESTINAL DISORDERS: THE EFFECT OF INTESTINAL METHANE PRODUCTION ON GLYCEMIC CONTROL

V. Cesario[1], T. A. Di Rienzo[1], D. Pitocco[2], M. Campanale[1], G. D'Angelo[1], S. Pecere[1], F. D'Aversa[1], A. Tortora[1], F. Barbaro[1], G. Vitale[1], G. Gigante[1], G. Caracciolo[1], A. Gasbarfrini[1], V. Ojetti[1,*]. [1]*Internal Medicine,* [2]*Diabetology, POLICLINICO GEMELLI, Rome, Italy*

INTRODUCTION: At the state of art it isn't known the correlation between diabetes and lower gastrointestinal disorders. Some studies show a significantly higher prevalence of small intestinal bacterial overgrowth (SIBO) in patients with type I diabetes. No data exists about gastrointestinal methane (CH4) production in patients with diabetes.
AIMS&METHODS: Aim of our study was to evaluate the effect of methaogenic flora eradications on glycemic control and daily insulin requirements in patients with type 1 diabetes in order to identify a possible role of CH4 production on diabetes severity.
30 consecutive patients (9 males, 21 females; mean age 45 +/-7yrs) affected by type 1 diabetes underwent H2/CH4 lactulose breath test to evaluate the presence of SIBO and CH4 production (CH4 concentration at least 3 ppm over that of room air). The glycemic control was evaluated trought glycated hemoglobin and daily insulin requirement (ratio between total insulin units in a day and body weight). CH4 producers were treated with metronidazole (500 mg bid for 10 days) and underwent a control breath test 8 weeks after the end of therapy. Data were analyzed using paired-data t-test.
RESULTS: 12/30 patients (40%) were methane-producers (mean baseline value 6+/-2ppm; mean peak 25+/-8ppm); the mean glycemic control was 7,6% and the daily insulin requirements was 0.68+/-0.12 UI/kg. 9/12 patients (75%) showed a significant ($P < 0.001$) reduction of their glycemic control (mean HbA1c 7.6% vs 6.8%) and daily insulin requirements (0.68+/-0.12 vs 0.49+/-0.08 UI/kg) after metronidazole therapy.
CONCLUSION: Our study showed for the first time a possible role of CH4 production in diabetes metabolic control. In particular, the most interesting data is that poorly controlled diabetes seems to be related to a gut CH4 production as confirmed by its significant improvement after eradication therapy.
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Disclosure of Interest: None Declared
Keywords: diabetes mellitus type 1, glycemic control, methanogenic flora

OP251 MEDIUM-CHAIN TRYGLICERIDE INDUCED LEUKOCYTE ACTIVATION IS NOT MEDIATED BY TOLL-LIKE RECEPTOR 4

E. D. Olthof[1,*], A. F. Guelich[1], L. A. Joosten[2], H. M. Schaap - Roelofs[1], G. J. Wanten[1]. [1]*Department of Gastroenterology and Hepatology,* [2]*Department of General Internal Medicine, RADBOUD UNIVERSITY NIJMEGEN MEDICAL CENTRE, Nijmegen, Netherlands*

INTRODUCTION: Lipids, as part of parenteral nutrition formulations modulate the function of the immune system. For instance, medium-chain triglycerides (MCTs), but not long-chain triglycerides (LCT), as part of parenteral lipid emulsions activate leukocytes *in vitro* by mechanisms that are still unknown. It has been shown that saturated fatty acids can activate Toll-like receptor 4 (TLR-4) mediated pro-inflammatory signaling pathways in leukocytes.
AIMS&METHODS: Aim of our study was to investigate whether TLR-4 is also involved in MCT-induced leukocyte activation. We assessed the *in vitro* effect of the parenteral mixed lipid emulsion LCT/MCT, at a clinically relevant triglyceride concentration of 5 mmol/l, on the expression of leukocyte surface membrane activation markers in the presence or absence of the specific TLR-4 inhibitors TAK-242 (0.5 and 5 μmol/l) and *Bartonella quintana* LPS (0.1, 1 and 2.5 μg/ml).
RESULTS: As expected, LCT/MCT activated leukocytes, with an increase in expression of adhesion (55% and 41% in granulocytes and monocytes, respectively), azurophilic and specific degranulation (19% and 22%, respectively in granulocytes) markers, and a decrease in L-selectin (14% and 20% in granulocytes and monocytes, respectively). Inhibition of TLR-4 by TAK-242 and *Bartonella quintana* LPS did not alter the LCT/MCT-induced decrease in L-selectin and increase in adhesion marker expression in granulocytes and monocytes. Furthermore, in granulocytes *Bartonella quintana* LPS did not change the MCT-induced increased expression of specific and azurophilic degranulation markers. The LCT/MCT induced increase in expression of both degranulation markers in granulocytes was abolished during TLR-4 inhibition with 5 μmol/l TAK-242. However, a similar decrease in degranulation marker expression was found after incubation with 5 μmol/l TAK-242 alone.
CONCLUSION: MCT-induced immune activation is not mediated by TLR-4 signaling.
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Disclosure of Interest: None Declared
Keywords: immune activation, medium chain triglyceride, parenteral nutrition, toll like receptor-4

TUESDAY, OCTOBER 15, 2013 11:00–12:30
Pancreatitis: Lessons from animal models – Salon 11/12

OP252 IMPROVEMENT OF ENDOPLASTIC RETICULUM STRESS BY ENHANCED PERK PATHWAY REDUCES MURINE EXPERIMENTAL ACUTE PANCREATITIS

T. Okazaki[1,*], A. Nishio[1], T. Masahiro[2], T. Inoue[2], Y. Sakaguchi[1], T. Fukui[2], K. Uchida[2], K. Okazaki[2]. [1]*Gastroenterology and Hepatology, Kansai Medical University, Moriguchi,* [2]*Gastroenterology and Hepatology, Kansai Medical University, hirakata, Japan*

INTRODUCTION: Endoplasmic reticulum (ER) stress causes the accumulation of misfolded proteins inside the ER and initiates unfolded protein response (UPR). UPR is activated during pancreatitis to restore ER homeostasis. Although protein kinase RNA-like ER kinase (PERK) is associated with the UPR through phosphorylation of eukaryotic initiation factor 2-alfa (eIF2-a), the role of PERK signaling pathway in pancreatitis is not fully clarified. We investigated the significance of PERK signaling pathway in severe acute pancreatitis in mice using an eIF2-a dephosphorylation inhibitor, salubrinal.
AIMS&METHODS: Severe acute pancreatitis was induced by intraperitoneal injection of cerulein (CER) at a dose of 50 mg/kg six times at 1 hour intervals. Moreover, LPS was administered at a dose of 10mg/kg as the septic challenge immediately after the completion of CER injections. Salubrinal was administered intraperitoneally immediately after LPS injection and six hours later. Mice were sacrificed at 24 hours after the first injection of CER and the severity of pancreatitis was histologically graded with a scoring system. Serum amylase and proinflammatory cytokine levels were measured. Expression of ER stress-related proteins was examined by western blotting.
RESULTS: The severity of pancreatitis in mice treated with salubrinal was significantly attenuated compared with control mice. Serum amylase and proinflammatory cytokine levels were lower in salubrinal-treated mice than those of control mice. Expression level of 78kDa glucose regulated protein (GRP78), activating transcription factor 4 and phosphorylated eIF2-a protein were elevated in mice treated with salubrinal compared with control groups.
CONCLUSION: Inhibition of eIF2-a dephosphorylation decreased ER stress and reduced severe acute pancreatitis in mice. Augmentation of PERK signaling pathway could be a potential therapeutic option for the treatment of acute pancreatitis.
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Disclosure of Interest: None Declared
Keywords: ER stress, pancreatitis, PERK signaling, Salubrinal

OP253 SEROTONIN REGULATES PROGENITOR CELL-BASED BUT NOT CLONAL REGENERATION IN THE ADULT PANCREATIC ACINAR CELL

E. Saponara[1,*], S. Sonda[1], K. Grabliauskaite[1], Y. Tian[1], T. Reding[1], R. Graf[1]. [1]*Swiss HPB Center, University Hospital Zurich, Zurich, Switzerland*

INTRODUCTION: Progenitor cell-based regeneration of acinar cells is activated during cerulein-induced pancreatitis. This process requires a preliminary acinar de-differentiation via secretion of zymogens, followed by expression of progenitor cell markers and formation of acinar-to-ductal metaplasia (ADM). Clonal regeneration without loss of zymogens and cell de-differentiation is observed following 60% pancreatectomy. Previously, we demonstrated that