MUCOSAL IMMUNOLOGY – A TRANSLATIONAL VIEW INTO THE CLINIC

July 6-8, 2023

Symposium 234

POTSDAM, GERMANY

13 CME CREDITS

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13 credit hours (CME) have been awarded for Symposium 234 by the European Union of Medical Specialists (UEMS).

PREFACE

Dear colleagues,

It is an extraordinary pleasure to be able to offer a discussion and exchange forum for translational mucosal immunology in Potsdam this year and by this introduce a novel meeting format.

“Mucosal Immunology - A Translational View Into The Clinic” is a meeting that is dedicated to provide plenty of room for discussion and exchange in particular. In addition to classical key note lectures designed to introduce a thematic block, followed by further lectures on this topic, method discussions and poster pitches will set the frame for intense exchange.

Thematically, the most current topics for translation in the field of inflammatory bowel diseases will be addressed during the three days. This includes the intestinal barrier, the importance of single cell populations, systems biology, the enteric nervous system, fibrosis, environmental factors, organoid techniques as well as nutritional strategies. We are pleased that we have been able to attract international experts for these topics, who will undoubtedly contribute to the success of this format in the wonderful surroundings of Potsdam.

We are looking forward to welcoming you all in Potsdam in July.

Raja Atreya Axel Dignass Gerhard Rogler Britta Siegmund

MUCOSAL IMMUNOLOGY – A TRANSLATIONAL VIEW INTO THE CLINIC

July 6-8, 2023

Scientific Organization:
Prof. Dr. Raja Atreya, Erlangen
Prof. Dr. Axel Dignass, Frankfurt
Prof. Dr. Gerhard Rogler, Zurich
Prof. Dr. Britta Siegmund, Berlin

Start of Registration:
Thursday, July 6, 2023
12:30-18:30 h
at the congress office

Congress Venue:
Dorint Hotel Sanssouci
Jägerallee 20
14469 Potsdam
Germany

For admission to scientific events your name badge should be clearly visible. Accompanying persons are not permitted during the conference at any time.

Thursday, July 6, 2023

13:45 Welcome and opening remarks
Raja Atreya, Erlangen; Axel Dignass, Frankfurt; Britta Siegmund, Berlin; Gerhard Rogler, Zurich

SESSION I

Epithelial Barrier – Microbiome a delicate interplay

Chairs: *Claudia Günther, Erlangen; Holm Uhlig, Oxford*

14:00 Keynote lecture I: Tryptophan metabolites as central regulators in IBD
Harry Sokol, Paris

14:30 Inflammation, microbiota and colorectal cancer formation
Michael Scharl, Zurich

14:50 The intestinal microbiome in IBD – target or biomarker
Melanie Schirmer, Freising

15:10 Failing repair mechanism in intestinal inflammation
Konrad Aden, Kiel

15:30 **Coffee break with poster session**

SESSION II

Poster pitches session

Chairs: *Jay Patankar, Erlangen; Melanie Schirmer, Freising*

16:20 10 poster pitches (each 3' pitch plus 2' discussion)

Thursday, July 6, 2023

SESSION III

Methods and challenges

Chairs: *Eva Rath, Freising; Michael Scharl, Zurich*

17:15 Overview talk: Intestinal organoids
Claudia Günther, Erlangen

17:30 Panel discussion

POSTER AWARD SESSION

18:00 **Presentation of poster awards**

SESSION IV

Exposome

Chairs: *Konrad Aden, Kiel; Julian Schwärzler, Innsbruck*

18:15 Keynote lecture II: Exposome – regulating IBD
Gerhard Rogler, Zurich

18:45 **Welcome dinner with light refreshments**

Friday, July 7, 2023

SESSION V

Dietary strategies

Chairs: *Michael Schumann, Berlin; Harry Sokol, Paris*

09:00	Keynote lecture III: Environmental factors shaping the gut microbiome *Rinse K. Weersma, Groningen*
09:30	Dietary-factors driving gut inflammation *Julian Schwärzler, Innsbruck*
09:50	Celiac disease and other inflammatory food sensitivities *Detlef Schuppan, Mainz*
10:10	Diet as modulator of intestinal inflammation *Hans Herfarth, Chapel Hill*
10:30	**Coffee break with poster session**

Friday, July 7, 2023

SESSION VI

The enteric nervous system is there more

Chairs: *Timothy W. Hand, Pittsburgh*

11:20	IBD-mediated changes in the ENS, cause or consequence *Jay Patankar, Erlangen*
11:40	ENS-mediated changes in intestinal barrier *Michael Schumann, Berlin*
12:00	Enteric nervous system and interaction with intestinal macrophages *Guy E. Boeckxstaens, Leuven*
12:20	Choroid plexus and intestinal inflammation – a novel connection? *Sara Carloni, Milan*
12:40	Panel discussion
13:00	**Lunch break with poster session**

Friday, July 7, 2023

SESSION VII

Systems biology, single cell analysis – guiding the future

Chairs: *Raja Atreya, Erlangen; Judy Cho, New York*

14:00	Keynote lecture IV: Life time consortium – single cell analysis & more *Philip Rosenstiel, Kiel*
14:30	The transcriptional landscape in IBD *Geert D'Haens, Amsterdam*
14:50	Artificial intelligence – supporting diagnosis of IBD? *Sebastian Zundler, Erlangen*
15:10	Single cell approaches in predicting response to therapy *Ahmed N. Hegazy, Berlin*
15:30	Genomics of responses to targeted therapies *Stefan Schreiber, Kiel*
15:50	**Coffee break with poster session**

Friday, July 7, 2023

SESSION VIII

Poster pitches session

Chairs: *Lea M. Haag, Berlin; Alison Simmons, Oxford*

16:20 10 poster pitches (each 3' pitch plus 2' discussion)

SESSION IX

Fibrosis

Chairs: *Hans Herfarth, Chapel Hill; Gerhard Rogler, Zurich*

17:15 Overview talk: Fibrogenesis in IBD – From mechanism of action to therapeutic approaches
Florian Rieder, Cleveland

17:30 Panel discussion

POSTER AWARD SESSION

18:00 **Presentation of poster awards**

SESSION X

Preventive Strategies

Chairs: *Axel Dignass, Frankfurt; Britta Siegmund, Berlin*

18:15 Keynote lecture V: Preclinical disease and preventive strategies in IBD
Jean-Frederic Colombel, New York

18:45 **Networking with light refreshments**

Saturday, July 8, 2023

SESSION XI

Cell populations – clinical

Chairs: *Ahmed N. Hegazy, Berlin; Carl Weidinger, Berlin*

09:00	Keynote lecture VI: Impact of stromal cells for IBD *Alison Simmons, Oxford*
09:30	Targeting B cells in IBD: An overlooked cell population? *Saurabh Mehandru, New York*
09:50	Unique cellular modules identified in IBD *Judy Cho, New York*
10:10	Targeting the vascular and lymphocytic endothelium *Michael Stürzl, Erlangen*
10:30	Regulation of tissue-resident memory T cells by the Microbiota *Timothy W. Hand, Pittsburgh*
10:50	Tregs on the way to the clinic *Caroline Bosch-Voskens, Erlangen*
11:10	**Coffee break with poster session**

Saturday, July 8, 2023

SESSION XII

Last but not least: the organizers pick!

Chairs: *Raja Atreya, Erlangen; Britta Siegmund, Berlin*

11:40	Impeding lymph flow – driver of IBD? *Gwendalyn J. Randolph, St. Louis*
12:00	Mitochondria – therapeutic target in IBD *Eva Rath, Freising*
12:20	Very early onset IBD - can we translate diagnostic and therapeutic concepts? *Holm Uhlig, Oxford*
12:40	Final discussion
13:00	Closing words

LIST OF SPEAKERS, MODERATORS AND SCIENTIFIC ORGANIZERS

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REGISTRATION

You can register for the event via our homepage:
www.falkfoundation.org
Registration is only possible online.

CONGRESS FEES

Scientific Program of Symposium 234	EUR 300
Students (copy of student ID required)	EUR 150

The congress fees include:

- Refreshments during coffee breaks
- Welcome dinner on Thursday, July 6, 2023
- Lunch on Friday and Saturday, July 7-8, 2023
- Snacks during networking on Friday, July 7, 2023
- A copy of the final program

CONGRESS OFFICE AND REGISTRATION

Opening Hours:

Thursday, July 6, 2023	12:30 - 18:30
Friday, July 7, 2023	8:00 – 18:30
Saturday, July 8, 2023	8:30 – 12:45

ARRIVAL

Dorint Hotel Sanssouci
Jägerallee 20
14469 Potsdam
Germany

By car
Parking space in the garage of the hotel.

By plane
From Berlin airport BER you can get to the Dorint hotel by taxi.
The drive takes about 45 min (approx. 50 km).

By train
The main train station Potsdam is located 3,5km from the Dorint hotel. You can take bus line 695 direction “Pirschheide”. From the stop “Reiterweg/ Jägerallee” it’s a 100m walk to the hotel (15 min in total).

CONFLICTS OF INTEREST

Members of the scientific committee declare the following potential conflicts of interest:

Raja Atreya: InDex Pharmaceuticals, Abbvie, Biogen, BMS, Celltrion, Galapagos, Janssen-Cilag, Lilly, Takeda

Axel Dignass: Abbvie, Ferring, Roche/Genentech, Takeda, Vifor, Falk, Janssen, Pfizer, Sandoz/Hexal, Celgene/BMS, Tillotts, Fresenius Kabi, Galapagos, Pharmacosmos, Novartis, Gilead, Arena, Celltrion, Lilly, Amgen, Abivax, High5MD, Materia Prima, Streamed-Up, MedToday, Biogen, Thieme

Britta Siegmund: Arena/Pfizer, Abbvie, Abivax, Boeringer, Celgene, Cromsource, Falk, Lilly, Hoffmann-La-Roche, Index Pharma, Janssen, Parexel, Pentracor, PharmOlanReceptos, Takeda, Arena, BMS, CT- Scout, Ferring, Galapagos, Gilead, PredictImmune, PsiCro, CED Service GmbH, Chiesi, Forga Software, IBD Passport, Materia Prima, Biogen, MSD, Mylan

Gerhard Rogler: Abbvie, Ardeypharm, Arena, Astra Zeneca, Augurix, BMS, Boehringer, Calypso, Celgene, Eli Lilly, Falk, Ferring, Fisher, Flamentera, Genentech, Gilead, InDex, Janssen, MSD, Novartis, Pfizer, Phadia, Pharma-Biome, Pierre Fabre, Roche, UCB, Takeda, Tillotts, UCB, Vifor, Vital Solutions, Zeller

POSTER ABSTRACTS

1. Vedolizumab effectiveness: Real-life IBD study in Belarus
   A. Adamenka, O. Zharskaya, H. Burlo, E. Malaeva (Minsk, Gomel, BY)
2. Investigating the role of hypoxia inducible factor-1a (HIF-1a) in controlling monocyte behaviour in the intestine
   C. Adams, G. Jones, G. Ho, C. Bain (Edinburgh, GB)
3. Enteric glial cells regulate T-cell activity in inflammatory bowel diseases
   M. Bubeck, J. Patankar, M. Gonzalez Acera, C. Becker (Erlangen, DE)
4. Fiber consumption protects vascular dysfunction in mice with systemic lupus erythematosus induced by Toll-like receptor 7 activation
   J. Duarte Perez, J. Duarte, J. Moleon, C. Gonzalez-Correa, I. Robles-Vera, S. Minano, N. De la Visitacion, M. Villanueva, M. Gomez-Guzman, M. Sanchez, M. Toral, N. Martin-Morales, F. Ovalle, R. Jimenez, M. Romero (Granada, Madrid, ES; Nashville, US)
5. Does acetylation polymorphism in inflammatory bowel disease (IBD) have clinical significance?
   R. Dudkowiak, G. Szkopek, A. Wiela-Hojenska, R. Dudkowiak, K. Glowacka (Warsaw, Wroclaw, PL)
6. Bacterial outer membrane vesicles cross the mucosal barrier and might represent a novel diagnostic marker for barrier dysfunction in IBD and MS
   L. Edrich, A. Sebald, L. Krumm, M. Linnerbauer, P. Arnold, V. Rothhammer, B. Winner, R. Atreya, M. Neurath, C. Guenther (Erlangen, DE)
7. Determination of biomarkers in patients suffering from ulcerative colitis based on the microbiota composition of colonic mucosa
   J. Garcia-Garcia, P. Diez-Echave, A. Ortiz Sanchez, M. Martinez-Tirado, E. Redondo-Cerezo, J. Martinez-Cara, F. Garcia, R. Moron, J. Galvez, M. Rodriguez-Cabezas, A. Rodriguez-Nogales (Granada, ES)
8. Obesity-associated dysbiosis increases inflammation and tumorigenesis in colorectal cancer
   L. Gbati, A. Ruiz-Malagon, J. Molina-Tijeras, M. Rodriguez-Sojo, L. Hidalgo-Garcia, P. Diez-Echave, M. Rodriguez-Cabezas, E. Redondo-Cerezo, A. Rodriguez-Nogales, J. Galvez (Granada, ES)
9. Fibrostenosing Crohn's disease histological changes quantified by computational pathology image analysis using QuPath
   M. Glinka, K. Kirkwood, A. Burger, R. Baldock, D. Adams, I. Papatheodorou, S. Din, M. Arends (Edinburgh, Cambridge, GB)
10. SEPIA: A web service and database for comparative transcriptomic analysis of gut inflammation in mouse
    M. Gonzalez Acera, C. Becker, J. Patankar (Erlangen, DE)
11. Role of the intestinal microbiota in the antihypertensive effect of a calcium channel blocker in spontaneously hypertensive rats
    C. Gonzalez-Correa, C. Gonzalez-Correa, S. Minano, J. Moleon, N. De la Visitacion, I. Robles-Vera, M. Toral, A. Gamiz, A. Barranco, M. Gomez-Guzman, M. Sanchez, R. Jimenez, N. Martin-Morales, F. Ovalle, J. Duarte (Granada, ES)
12. The expression of CD69 in inflammatory bowel diseases
    K. Guzinska-Ustymowicz, K. Ustymowicz, W. Romanczyk, A. Pryczynicz, A. Mantiuk (Bialystok, Warsaw, PL)
13. Intestinal mesenchymal cells modulate inflammation and gut microbiota composition in a mouse model of inflammation-induced colorectal cancer
    L. Hidalgo-Garcia, A. Ruiz-Malagon, F. Huertas-Pena, M. Rodriguez-Sojo, J. Molina-Tijeras, B. Miron-Pozo, P. Diez-Echave, T. Vezza, L. Lopez-Escanes, R. Moron, P. Becerra-Massare, A. Rodriguez-Nogales, J. Galvez, M. Rodriguez-Cabezas, P. Anderson (Granada, ES)

14. Dysmotility associated by colonic inflammation is attributed to preferential neurogenesis of nitrergic neurons in the myenteric plexus of DSS colitis mouse colon
M. Kadowaki, K. Miyata, T. Yamamoto, S. Hayashi (Toyama, JP)
15. Development of 3D immunocompetent epithelial model combining colon epithelium monolayer with CD4+ T cells to study mucosal inflammation
I. Larafa, O. Thoma, C. Gunther, M. Neurath, M. Waldner (Erlangen, DE)
16. Evaluation of the Lavandula stoechas L. extract in the experimental model of irritable bowel syndrome
L. Lopez-Escanez, F. Algieri, A. Rodriguez-Nogales, T. Vezza, J. Garrido-Mesa, M. Gonzalez-Tejero, M. Casares-Porcel, J. Molero-Mesa, M. Rodriguez-Cabezas, J. Galvez (Granada, ES)
17. Comparison expression of Bcl-xl in ulcerative colitis and Crohn's disease
A. Mantiuk, W. Romanczyk, A. Romanczyk, K. Ustymowicz, K. Guzinska-Ustymowicz, A. Pryczynicz (Warsaw, Bialystok, PL)
18. Bioelectrical impedance analysis and hematological scales – A brand new combination for the evaluation of IBD patients?
A. Michalak, K. Szczygiel, H. Cichoz-Lach, B. Kasztelan-Szczerbinska, A. Rycyk-Bojarzynska (Lublin, PL)
19. Effects of hydrochlorothiazide on intestinal dysbiosis in spontaneously hypertensive rats
S. Minano, C. Gonzalez-Correa, J. Moleon, N. De la Visitacion, I. Robles-Vera, M. Toral, A. Barranco, M. Gomez, M. Sanchez, R. Jimenez, N. Martin, F. O'Valle, M. Romero, J. Duarte (Granada, Madrid, ES; Nashville, US)
20. Dietary fibers: Prebiotics to prevent the development of cardiovascular complications linked to systemic lupus erythematosus
J. Moleon, C. Gonzalez, S. Minano, I. Robles, N. De la Visitacion, A. Barranco, N. Martin, F. O Valle, L. Mayo, A. Garcia, M. Gomez, R. Jimenez, M. Sanchez, M. Romero, J. Duarte (Granada, Madrid, ES; Nashville, US)
21. Limosilactobacillus fermentum modulates the gut microbiota and produces anti-cancer metabolites to protect against inflammation-associated colorectal tumorigenesis
J. Molina-Tijeras, A. Ruiz-Malagon, L. Hidalgo-Garcia, M. Rodriguez-Sojo, J. Garcia-Garcia, P. Diez-Echave, T. Vezza, L. Lopez-Escanez, M. Rodriguez-Sanchez, O. Banuelos, M. Olivares, M. Rodriguez-Cabezas, A. Rodriguez-Nogales, J. Galvez (Granada, ES)
22. Impact of processing of wheat flours on their ATI-induced TLR4 stimulating bioactivity
M. Neerukonda, V. Curella, M. Sielaff, S. Neufang, S. Koch, E. Bockamp, M. Afzal, K. El Hassouni, S. Tenzer, F. Longin, D. Schuppan (Mainz, Hohenheim, DE)
23. The TLR4-activating potential of dietary wheat amylase trypsin inhibitors (ATIs) depends on their interaction with other wheat proteins
M. Neerukonda, M. Sielaff, Y. Kim, S. Koch, S. Neufang, E. Bockamp, F. Longin, S. Tenzer, D. Schuppan (Mainz, Hohenheim, DE)
24. TLR4 stimulating bioactivity of wheat ATIs depends on the location of cultivation
M. Neerukonda, V. Curella, M. Sielaff, S. Neufang, S. Koch, E. Bockamp, M. Afzal, K. El Hassouni, S. Tenzer, F. Longin, D. Schuppan (Mainz, Hohenheim, DE)
25. The oral tissue transglutaminase inhibitor ZED1227 prevents gluten-induced enteropathy in the humanized NOD-DQ8 mouse model of celiac disease
A. Pesi, H. El Mard, M. Encalada, J. Ruhnau, P. Frankenbach, K. Sajko, F. Roehr, R. Krini, R. Surabattula, M. Hils, B. Tewes, R. Pasternack, R. Greinwald, S. Steven, V. Zevallos, E. Verdu, D. Schuppan (Mainz, Darmstadt, Freiburg, DE; Hamilton, CA)
26. SEFA-1024, a structurally engineered EPA derivative reduces intestinal inflammation in mice by restoring intestinal mucosal barrier function
G. Pickert, J. Matzner, D. Thies, D. Fraser, D. Schuppan (Mainz, DE; Naarden, NL)

27. The inflammatory role of IL-4Rα signaling in IBD is limited to monocytes at the onset of colitis
G. Pickert, B. Weigmann, K. Johanna, J. Matzner, D. Thies, B. Seeger, N. Fittler, S. Weng, J. Crosby, E. Bockamp, D. Schuppan (Mainz, Erlangen, DE; Taipei City, TW; Carlsbad, US)
28. Epithelial c-MET expression is associated with active inflammatory bowel disease and IBD-associated colorectal cancers
R. Porter, G. Halliday, M. Arends, C. Black, S. Din (Edinburgh, GB)
29. Increased epithelial HMGB1 expression is associated with inflammatory bowel disease and associated colorectal cancers
R. Porter, G. Murray, S. Hapca, D. Brice, A. Hay, S. Berry, M. McLean (Edinburgh, Aberdeen, Manchester, Dundee, GB)
30. Characterization of gut microbiota in the colonic mucosa in Crohn's disease patients as a tool for developing new therapeutic approaches
A. Rodriguez Nogales, J. Garcia-Garcia, P. Diez-Echave, A. Ortiz Sanchez, P. Martinez-Tirado, E. Redondo-Cerezo, J. Martinez-Cara, M. Rodriguez-Sanchez, F. Garcia, R. Moron, J. Galvez, M. Rodriguez-Cabezas (Granada, ES)
31. Beneficial effect of organosulfur compound from Allium spp. on mucosal immunology in a mouse model of colitis-associated colorectal cancer
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32. Tigecycline in the treatment of obesity-associated colorectal cancer: Impact on colon inflammation and gut dysbiosis
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1. Vedolizumab effectiveness: Real-life IBD study in Belarus

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Introduction: Vedolizumab (VDZ) is a humanized IgG1 monoclonal antibody that targets α4β7 integrin receptors and is actively used in the inflammatory bowel diseases (IBD) treatment.

The aim is to study the real effectiveness of VDZ for Crohn's disease (CD) and ulcerative colitis (UC) treatment in Belarus.

Methods: 71 patients with IBD from different regions of Belarus were prescribed VDZ. The drug effectiveness was assessed after its fourth infusion (0-2-6-14 weeks).

Results: 71 patients with IBD from different regions of Belarus were prescribed VDZ. The drug effectiveness was assessed after its fourth infusion (0-2-6-14 weeks).

To date, 44 out of 71 patients (62.0%) have received 4 infusions of vedolizumab: median age 30.5 years; 16 females, 28 males, 21 patients with CD, 23 with UC.

22 patients (50.0% [95% CI: 31.3–75.7%]) were bio-naïve before VDZ prescription. Previous treatment failure with ≥ 1 anti-TNFs occurred also in 50% (95% CI: 31.3–75.7%) cases.

In 2 cases (4.6% [95% CI: 0.6–16.4%]) CMV colitis was developed and VDZ infusions were discontinued until the infection resolved, in 1 case (2.3% [95% CI: 0.6–12.7%]) colectomy was performed. Estimation of VDZ effectiveness was completed in the rest 41 cases. 10/41 patients (24.4% [95% CI: 11.7–44.9%]) had no response to 4 VDZ infusions, while a clinical response incidence was significantly higher in the rest 31/41 cases (75.6% [95% CI: 51.4–107.3%], $p < 0.05$) with no differences between bio-naïve group and the group with previous anti-TNF treatment failure, $p = 0.99$. All the responders are currently on treatment: in 16 of them (39.0% [95% CI: 22.3–63.4%]) due to insufficient clinical response, the administration regimen was escalated to 1 infusion every 4 weeks. The need for dose escalation was significantly more frequent in the group of anti-TNF failure (13/16 patients, 81.3% [95% CI: 43.3–138.8%], $p = 0.02$) in comparison with bio-naïve group (3/16, 18.8% [95% CI: 3.9–54.8%]). Clinical and endoscopic remission was achieved in 6/41 patients (14.6% [95% CI: 5.4–31.9%]) after the 4th infusion.

Discussion/Conclusion: Vedolizumab is effective in real clinical practice both in bio-naïve patients and in patients with previous anti-TNF therapy failure.

2. Investigating the role of hypoxia inducible factor-1a (HIF-1a) in controlling monocyte behaviour in the intestine

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Introduction: Macrophages are highly abundant in the intestinal mucosa where they play fundamental roles in tissue homeostasis. Unlike many other tissue macro-phages, those in the healthy intestinal mucosa are replenished by circulating monocytes. However, in inflammatory bowel disease monocytes accumulate in large numbers and display aggressive, pro-inflammatory behaviour. Why seemingly phenotypically identical monocytes display such distinct fates and functions during health and inflammation remains unclear.

Methods: Transcriptional profiling of blood and colonic monocytes from healthy and colitic mice using the dextran sodium sulphate model of colitis revealed that monocytes in colitis have a unique transcriptional profile, including enrichment of genes involved in cell metabolism. Parallel analysis of analogous cells in human blood and mucosal biopsies from a treatment-naïve Crohn's disease patient showed this molecular signature is evolutionarily conserved between mouse and man, in particular expression of hypoxia inducible factor 1a (HIF-1a). To assess the role of HIF-1a in controlling monocyte behaviour in the gut mucosa, we generated mice with myeloid (Lyz2)-specific deletion of Hif1a.

Results: Preliminary data show that deletion of Hif1a has no baseline effect on the composition of the monocyte-macrophage compartment in homeostasis nor in the inflamed colon after DSS-induced acute colitis. By generating competitive bone marrow chimeric mice, we found that deficiency of Hif1a conferred a competitive advantage to monocytes. However, this was also seen in circulating classical monocytes ($p = 0.0023$), suggesting there is an effect at the level of haematopoiesis. Transcriptional profiling of Ly6C+ monocytes by NanoString from chimeric mice following acute colitis revealed increased mRNA expression of monocyte/ macrophage effectors and downregulation of mRNA associated with monocyte maturation/differentiation in Hif1a deficiency.

Discussion/Conclusion: Our work identifies HIF-1a as a feature of inflammation-associated monocytes which may act to limit monocyte lifespan. Future work will seek to confirm these findings and delineate further molecular control of monocytes in colitis.

3. Enteric glial cells regulate T-cell activity in inflammatory bowel diseases

Marvin Bubeck (Erlangen, DE), Jay Patankar (Erlangen, DE), Miguel Gonzalez Acera (Erlangen, DE), Christoph Becker (Erlangen, DE)

Inflammatory bowel diseases are characterized by chronic dysregulation of immune homeostasis, epithelial demise, immune cell activation, and microbial translocation. Recent publications have highlighted the crucial role of the Enteric Glia Cells (EGC), in regulating intestinal inflammatory processes. A recent single cell study has shown an IFNγ-dependent activation that leads to EGC activation resulting in increased pro-inflammatory cytokine receptor and chemoattractant production. This study also highlights an activated state of EGC in inflammatory processes, in which their transcriptome changes significantly. We have recently shown that contrary to intestinal infection and dysbiosis, chemically induced experimental and clinical colitis causes an increase in the transcript levels of enteric neuronal and glial genes. The immunological and molecular drivers behind these contrasting findings remain poorly understood. Taking advantage of T-cell- or pathogen-driven mouse models of intestinal inflammation, we show that EGCs can be directly modulated via activated T-cells.

To uncover the direct impact of T-cell cytokines on EGCs, we stimulated plexanoids, primary cell cultures derived from longitudinal muscle myenteric plexuses with specific T-cell cytokines. RNA from stimulated cultures was isolated and subjected to bulk sequencing. Comparative transcriptomic analysis revealed IFNg and IL13 were the most profound cytokines impacting plexanoid cultures. Gene Ontology analysis shows enrichment for Cell projection organization, Neurogenesis, Cellular response to endogenous stimulus, migration and other biological processes in inflammation. Comparison of our ex vivo data with recently published data have highlighted both common and divergent IFNg driven pathways isolation associated injury versus helminth infection models. These ex vivo studies were also able to recapitulate the activated state of the EGC in inflammatory processes and upregulation of key adhesion molecules.

These findings highlight dynamic interactions between T-cells and EGC. Further research in this area could lead to the development of new therapeutic strategies targeting T-cell-EGC interaction for the treatment of IBD.

4. Fiber consumption protects vascular dysfunction in mice with systemic lupus erythematosus induced by Toll-like receptor 7 activation

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Introduction: Toll-like receptors (TLRs) are involved on the onset and progression of human and spontaneous mouse models of systemic lupus erythematosus (SLE). TLR7 activation causes vascular dysfunction in non-autoimmune controls mice and accelerates cardiovascular pathology in lupus-prone mice. Western lifestyle is linked to autoimmune and metabolic diseases, driven by changes in diet and gut microbiota composition. Western diet is characterized by low dietary fiber intake. The aims of the present study were therefore to investigate the role of dietary fiber intake in the raise of BP mice with SLE induced by TLR7 activation with imiquimod (IMQ) and to explore the possible underlying mechanisms.

Methods: Female BALB/c seven- to nine-week-old mice were randomly divided into 4 experimental groups: 1) an untreated control (CTR); 2) a group treated with IMQ; 3) IMQ mice treated with resistant starch (RS) (SF11-025 diet: 72.7% insoluble fiber); and 4) IMQ treated with inulin-type fructans (ITF) (ORAFTI P95, soluble fiber). IMQ cream (1.25 mg of 5%) was administered through topical application for 8 weeks.

Results: Fiber consumption induced profound changes in gut microbiota composition. No significant change in acetate- and butyrate-producing bacteria and lower abundance of propionate-producing bacteria were found IMQ compared to CTR group. Acetate-, butyrate-, and propionate-producing bacteria were increased by RS diet whereas ITF only increased the proportion of acetate-producing bacteria. Both fiber treatments prevented the development of hypertension and cardiac hypertrophy, improved the aortic relaxation induced by acetylcholine and the vascular oxidative stress. Fiber treatments improved colonic integrity, endotoxemia, and decreased helper T (Th)17 proportion in mesenteric lymph nodes (MLNs), blood, and aorta in mice with SLE induced by IMQ. RS consumption reduced splenomegaly, hepatomegaly, and plasma anti-ds-DNA, but ITF was without effect.

Discussion/Conclusion: In conclusion, fiber consumption prevented the develop-ment of hypertension by rebalancing of dysfunctional gut-immune system-vascular wall axis in SLE induced by TLR7 activation.

5. Does acetylation polymorphism in inflammatory bowel disease (IBD) have clinical significance?

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Introduction: In the metabolism of many organic compounds, an important role is played by the acetylation process, which increases the solubility and facilitates the excretion of the transformed substances. These reactions are catalyzed by two N-acetyltransferases, type 1 and type 2, encoded by the NAT1 and NAT2 genes, respectively. The NAT1 gene is expressed

in the cells of most tissues and organs. NAT2 has a more limited expression profile – mainly in the liver, small intestine and colon.

The acetylation polymorphism affects not only the effectiveness of the applied therapy, but may also predispose to the occurrence of certain diseases. Acetyl-transferases taking part in the biotransformation of drugs, toxins and carcinogens can modify the risk associated with cancer appearance.

The potential role of the acetylation genotype in autoimmune diseases is based on the hypothesis that in the case of slow-type acetylation, xenobiotics can accumulate and transform into reactive metabolites that change the way the antigen is presented to T lymphocytes, which when activated stimulate B lymphocytes to proliferate and produce antibodies. In the case of IBD, there is little data on the impact of acetylation polymorphism on the development of these diseases, and the available research results are inconclusive.

Methods: Isolation of genomic DNA from peripheral blood leukocytes was performed in 29 pts with ulcerative colitis (UC; 15 female, 14 male) and 25 pts with Crohn's disease (CD; 13 F, 12 M). The average age was 37 years.

All patients took 5-aminosalicylic acid preparations. The control group (CG) included 100 people (52 F, 48 M), aged 20–89 years. There were no acute or chronic autoimmune diseases, including IBD, in CG.

Results: The analysis of acetylation type, both in the entire group of IBD pts and in individual subgroups of pts with UC and CD, showed no significant differences in the frequency of slow and fast acetylators compared to CG. The analysis of genotypes showed that NAT2*4/5 variant was significantly more common among the entire group of IBD pts ($p = 0.0277$; OR = 2.567; CI: 1.090–6.046) and in the subset of CD pts ($p = 0.0041$; OR = 4.125; CI: 1.495–11.385). It was also found that the relative risk of IBD development, which was expressed by the odds ratio, was over 2.5 times higher (OR = 2.576, CI: 1.127–5.887) for the carriers of NAT2*5 alleles in comparison to the carriers of other variants. In the case of CD the same risk was almost 6 times higher in pts with this allele (OR = 5.924, CI: 1.318–26.630).

Discussion/Conclusion: A significant advantage in the frequency of the NAT2*4/5 genotype compared to healthy individuals (CG) may indicate a relationship between the possession of this N-acetyltransferase variant and an increased risk of developing inflammatory bowel disease, in particular Crohn's disease.

6. Bacterial outer membrane vesicles cross the mucosal barrier and might represent a novel diagnostic marker for barrier dysfunction in IBD and MS

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Introduction: Multiple sclerosis (MS) is the most prevalent chronic inflammatory disease of the central nervous system. Recently, a bidirectional link between the gut microbiome, intestinal inflammation and neuroinflammation, in accordance with the idea of the microbiome-gut-brain-axis has gained increasing attention. In line with this idea, alterations in gut microbial composition have been identified as a key environmental element influencing both IBD and MS.

Recently, we have shown that beside bacterial metabolites, the gut resident microbiota release bacterial extracellular vesicles (BEVs) that are capable of crossing not only the mucosal but also blood-brain-barrier (BBB) to target CNS-resident glial cells. These BEVs are highly immunogenic and act as biological shuttle systems. Thus, microbial dysbiosis might affect MS pathogenesis significantly through BEVs shuttling across the BBB modulating immune processes within the CNS.

Methods: To investigate whether BEVs can cross the gut barrier and translocate to distant sites, including the brain, and whether this translocation is enhanced in the context of IBD and MS, we isolated EVs from serum samples of healthy controls, IBD patients, and MS patients.

Moreover, we stimulated macrophages and human iPSC-derived microglia-like cells with BEVs from an E. Coli BL21 strain either carrying a wildtype or a modified LPS (not causing any endotoxic response).

Results: Our translational approach detected higher levels of EV-bound LPS derived from IBD patients compared to healthy controls, indicating elevated BEV levels in their bloodstream. Similar experiments are currently underway using MS patient samples to evaluate the potential correlation between inflammatory activity and BEV levels in the blood.

The stimulation experiments revealed a strong LPS mediated upregulation of pro-inflammatory genes emphasizing the potential impact of BEVs on neuroinflammation.

Discussion/Conclusion: In summary, our data suggest that BEVs might represent a critical new environmental factor interacting with other disease factors to cause mucosal- and neuroinflammation and further might be used as a diagnostic marker.

7. Determination of biomarkers in patients suffering from ulcerative colitis based on the microbiota composition of colonic mucosa

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Introduction: The inflammatory status that characterises ulcerative colitis (UC) has been associated with gut dysbiosis. Most frequently, the microbiota composition has been determined in faeces, mainly corresponding to the luminal contents, and less information is available about the microbiota adhered to the mucosa. In the present study, we have assessed the microbiota composition of colonic mucosa in UC patients and compared it to that from colonic lumen. This approach could be used for developing new treatments based on microbiota composition.

Methods: In the present pilot study, 15 patients suffering from UC were enrolled and their clinical variables were collected. The day before colonoscopy, a sample from faeces was obtained, which constituted the material to characterise the intestinal lumen microbiota. During colonoscopy, different samples were taken by scraping the colonic mucosa from damaged areas, and these will constitute the mucosa-associated microbiota. Microbiota composition was determined by Next Generation Sequencing.

Results: Bioinformatic analysis showed changes in both alpha and beta diversity for stool and mucosa samples. At genus level, microbiota in the damaged mucosa was enriched in E. shigella and Lachnospiraceae, while healthy mucosa presented an enrichment in Sutterella. On the other hand, a high abundance of Prevotella was observed in stool samples. Furthermore, a differential expression analysis revealed the increased presence of Coprococcus

comes in the damaged mucosa. Finally, a correlation analysis between microbiota composition and clinical variables was performed. For stool and healthy mucosa, the high presence of Prevotella and Sutterella negatively correlated with those variables used for measuring UC damage. On the contrary, in damaged mucosa, Lachnospiraceae showed strong correlations against post-surgery recurrence and disease extension.

Discussion/Conclusion: There are clear differences in microbiota composition between luminal and mucosa-associated microbiota of the colonic tissue, being Coprococcus comes specifically present in the latter location. In addition, the presence of some bacteria in damaged mucosa were correlated with a bad prognosis of UC. As a result, the identification of specific bacteria in the inflamed areas of the colonic tissue could be used for developing new therapeutic approaches.

8. Obesity-associated dysbiosis increases inflammation and tumorigenesis in colorectal cancer

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Introduction: Obesity is considered a risk factor for the development of colorectal cancer (CRC). Both diseases share altered metabolic pathways, a chronic inflammatory status and a gut dysbiosis situation. The aim of this study was to evaluate the impact of the obesity-associated dysbiosis on the development of colitis-associated CRC (CAC) and how the modulation of this gut microbiota through fecal microbiota transplantation (FMT) affected to this type of cancer.

Methods: C57BL/6 mice were randomly distributed in two experimental groups: a standard diet (SD) and a high-fat diet (HFD)-fed group. Then, both experimental groups were submitted to a CAC induction by the administration of a dose of azoxymethane (10 mg/kg) followed by three cycles of dextran sulfate sodium (2%) in drinking water. To study the impact of obesity-associated dysbiosis on CAC development, a second assay was performed. Here the feces from lean and obese mice were collected and inoculated on ceftriaxone-treated (400 mg/kg/day during 5 days) germ-free mice submitted to CAC induction. Tumor burden was characterized through colonoscopy and colonic mucosa inflammation was evaluated by the disease activity index (DAI) and molecularly by Western-Blot, ELISA, RT-qPCR and histology studies.

Results: HFD administration resulted in an aggravation of the severity of the CAC characterized by an increase of tumor burden in comparison with SD-fed mice. This effect was associated with higher levels of DAI and an increase of the pro-inflammatory markers (COX2 and iNOS) in the colon. Additionally, fecal microbiome sequencing used in FMT showed an intestinal dysbiosis in those mice fed a HFD in comparison with SD that resulted in higher tumor burden, as well as colonic inflammation (COX2) and cell proliferation (β-catenin and AKT) in recipient CAC mice.

Discussion/Conclusion: Obesity-associated dysbiosis is involved in the alteration of the signaling pathways that obesity and CRC share, promoting colonic inflammation and tumor development observed in CAC.

9. Fibrostenosing Crohn's disease histological changes quantified by computational pathology image analysis using QuPath

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Introduction: Inflammatory Bowel Diseases (IBDs) such as Crohn's disease are estimated to affect up to 1% of the European population over the next 5 years and that number is expected to increase. Although well-established single nucleotide polymorphisms (SNPs) influence risk, the effects of Crohn's disease are mostly due to increased and prolonged inflammation involving immune-response cells in the intestinal wall, leading to progressive fibrosis, which may lead to wall thickening with partial luminal obstruction. Although immune cell populations present in these fibrostenosing lesions have been largely identified, accurate quantification of such cell populations within each intestinal wall layer has not yet been reported.

Methods: Archival formalin-fixed, paraffin-embedded terminal ileal resections from 30 control and 30 fibrostenosing Crohn's disease patients were stained using immunohistochemistry (IHC) to identify specific cell types. Collagen deposits were visualised using Picro-Sirius Red (PSR) staining. The sections were captured digitally and analysed with QuPath, an open-source whole-slide imaging and quantification software, to quantify the fibrosis and cell populations within each ileal wall layer. Specific tissue regions were annotated and labelled. The physical changes in collagen deposits were quantified using a pre-trained machine-learning classifier, while the DAB-positive IHC-detected cells were counted using the built-in positive-cell detection function.

Results: Changes in size of each intestinal wall layer were identified, revealing degradation of the mucosa by ulceration and erosion and expansion of the muscularis mucosae and serosa. The collagen deposits were shown to be present throughout all layers of the wall, especially increased in submucosa and serosa layers (4.5-fold and 5.6-fold increase, respectively). Elevated cell numbers were measured in Crohn's Disease patient samples compared with the controls for lymphocytes stained for CD3, CD4, and CD8; in addition, smooth muscle actin (SM-actin)-positive cells were increased in all layers except mucosa. Increased cell numbers were detected in muscularis mucosae (avg. 4.5-fold increase), submucosa (avg. 3-fold increase, most prominent in CD3+ stain), muscularis propria (avg. 3.6-fold increase) and serosa (avg. 4.3-fold increase) for all positive cell stains. CD3+ cells were elevated throughout the whole tissue, CD4+ cells were predominantly present in muscularis mucosae, CD8+ cells had elevated numbers in inner layers of the ileum, whilst SM-actin+ cells were mostly elevated in muscularis mucosae and serosa.

Discussion/Conclusion: The combination of IHC and QuPath enabled accurate identification and quantification of changes in tissue areas, fibrosis and specific cell populations. The software's capabilities enabled the determination of cell type localization in each of the layers. Accurate quantification could allow for better understanding of immune cell involvement in these disease processes and targeted treatment of the disease. The next steps involve expansion to more cell types such as CD20+ (B-cells), CD31 (endothelial cells), CD68 (macrophages) and fibroblasts, and incorporation of single-cell RNA-seq data for further insights in cell type and subtype composition, altered states and mechanistic involvement in inflammation and fibrosis.

10. SEPIA: A web service and database for comparative tran-scriptomic analysis of gut inflammation in mouse

Miguel Gonzalez Acera (Erlangen, DE), Christoph Becker (Erlangen, DE), Jay Patankar (Erlangen, DE)

Abstract: Inflammatory bowel diseases (IBD) are a group of intestinal disorders that affect millions of people worldwide. The main characteristics of these disorders are inflammatory episodes and/or ulcers within the intestine. Research on IBD is frequently conducted through experiments in mouse inflammation models, which simulate one or more conditions observed in human IBD. Some models mimic symptoms of human IBD more closely than others, and most employ different approaches to achieve the inflammatory response.

The variety of approaches for IBD modeling might raise ethical concerns due to the number of experiments conducted over and over again. Animal ethics committees recommend to follow the principles of 3Rs in animal research: Replace, Reduce and Refine. With the principles in mind, we have constructed a database comprising a selection of mouse intestinal inflammation models in order to perform comprehensive comparative transcriptomic analyses. The RNAseq data obtained for the models was then processed using an in-house tool and stored in a database in a structured fashion. Finally, we developed a web service that provides reliable transcriptomic information and enables simple comparative analysis to be performed on the data with ease.

Our work has already proven useful in IBD research. We have been able to observe a response by the ENS in the event of inflammation, or study the marker genes associated with type 2 immune response. By using gene markers for epithelial cells, it has been possible to observe the dynamics of the tissue in the event of an intestinal wound, as well as the changes of the paracaspase Malt1 during inflammation and resolution. The database and tool can also be used to generate new hypotheses by comparative transcriptomics without the need of cost and time consuming experiments.

11. Role of the intestinal microbiota in the antihypertensive effect of a calcium channel blocker in spontaneously hypertensive rats

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Introduction: The aim of this study was to determine the effects of amlodipine, a calcium channel blocker, on gut dysbiosis and analyze the relevance of bacterial changes in its antihypertensive properties

Methods: Male spontaneously hypertensive rats (SHR) and Wistar Kyoto rats were used. SHR rats were divided into an untreated group and a group treated with amlodipine (10 mg/kg/day) for 5 weeks. Faeces 16S rRNA, lymphocyte populations in mesenteric lymph nodes (MLNs) and aorta, intestinal integrity, intestinal sympathetic tone and inflammation in paraventricular nodes (PVN) of the hypo-thalamus were analyzed. Fecal microbiota transplantation to SHR was performed.

Results: Faeces from SHR showed gut dysbiosis, characterized by lower acetate- and higher lactate-producing bacteria, and lower strict anaerobic bacteria. Amlodipine increased anaer-

obic bacteria proportion and restored the proportion of acetate-producing bacteria populations to WKY levels. The amelioration of gut dysbiosis induced by amlodipine was associated with a decrease in gut pathology and permeability and an attenuated sympathetic drive in the gut. FMT from SHR-amlodipine to SHR decreased BP and ameliorated aortic endothelium-dependent relaxation to Ach. These changes were accompanied by a decreased proportion of Th17 in mesenteric lymph nodes and lower aortic Th17 infiltration.

Discussion/Conclusion: Amlodipine reduced gut sympathetic tone, ameliorated intestinal integrity and caused changes in the intestinal microbiota that contributed to its antihypertensive effect through immunomodulation.

12. The expression of CD69 in inflammatory bowel diseases

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Introduction: Recent reports indicate that CD69 plays an important role in the regulation of inflammatory processes. Important information is the fact that Cd69 has been identified as an indicator of lymphocyte activation. Expression was observed in lymphocytes residing in the mucosa of the large intestine. The influence of microflora and food antigens plays an important role in the correlation with Cd69 expression.

Therefore, the purpose of the research was to evaluate the expression of CD69 in inflammatory bowel diseases.

Methods: The study included a group of 10 patients diagnosed with Crohn's disease and 31 patients with ulcerative colitis. The expression of CD69 in tissue material was evaluated and determined by the immunohistochemistry. The staining reaction was observed in details in the surface epithelium. The score of immunohistochemistry Cd69 expression was evaluated as: absent, weak, medium and strong.

Results: In patients with ulcerative colitis it was observed: the weak and the medium expression of Cd69 in the surface epithelium (30.7% and 36.7%), the absence and the weak expression in normal glands (15.9% and 18.3%), predominant weak and medium reactions in dysplastic glands (33.3% and 50%), and weak in the inflammatory cells (58%). In turn, the patients diagnosed with Crohn's disease had a strong expression of Cd69 located in the surface epithelium in 90% of cases. Moreover, in the normal glands the expression defined as weak, medium and strong (10%, 30% and 20%, respectively) was noted. Only one patient was found with a dysplastic glands where the strong expression of CD69 was observed. The strong reaction of inflammatory cells to CD69 was observed in up to 90% of patients with Crohn's. Statistical analysis showed a correlation between the increase Cd69 expression in the in inflammatory cells ($p = 0.033$).

Discussion/Conclusion: CD69 in patients with ulcerative colitis and Crohn's disease is highly expressed in lymphocytes in the mucosa separated by a single layer of intestinal epithelial cells from the intestinal lumen. Whereas, in our opinion, the increased expression of Cd69 in inflammatory cells in Crohn's disease may be associated with the increase in the number of lymph nodules as a response to chronic inflammation.

13. Intestinal mesenchymal cells modulate inflammation and gut microbiota composition in a mouse model of inflammation-induced colorectal cancer

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Introduction: Inflammatory bowel disease (IBD) is a chronic autoimmune disease that increases the risk of developing ulcerative colitis-associated colorectal cancer (CAC), usually associated with a worse prognosis than non-inflammatory driven colorectal cancer. Injection of other mesenchymal stromal cells has shown promising efficacy in reducing intestinal inflammation, both at preclinical and clinical level. However, little is known about the effect that human intestinal mesenchymal stromal cells (iMSCs) exert on CAC and its associated microbiota, known to be a promising therapeutic target.

Methods: CAC was induced in female C57BL/6J mice (n = 12/group) by intra-peritoneal administration of azoxymethane (10 mg/kg) followed by three cycles of 2% (w/v) of DSS (sulfate dextran sodium) in drinking water. The disease activity index (DAI) was monitored daily in every DSS cycle. During the last two disease peaks, intraperitoneal administration of 0.5 x 106 iMSCs/mouse was carried out. The effect of the iMSCs administration was evaluated at both macroscopic and molecular level (RT-qPCR, western blot and FACs) by assessing different markers involved in the disease development. In addition, the fecal microbiota was analyzed by Illumina MiSeq 16s V4-V5 sequencing.

Results: iMSCs administration significantly reduced both weight loss and DAI as well as tumor number and size. In addition, iMSCs reduced the colonic expression of several inflammatory mediators that promote CAC development (e.g. IL-6, TNF-α, IL-17/IL-23 or COX-2), and the activation of Akt and STAT-3 signaling. On the other hand, iMSC administration modulated the composition of immune cell populations and increased bacterial species diversity, the number of OTUs and re-established the abundance of some key phyla, such as Verrucomicrobia, Proteobacteria and Actinobacteria, ameliorating the observed gut dysbiois.

Discussion/Conclusion: In summary, the data obtained show that iMSCs protect against the development of CAC, thanks to both their powerful immunomodulatory effects and their ability to modulate the associated intestinal microbiota.

14. Dysmotility associated by colonic inflammation is attributed to preferential neurogenesis of nitrergic neurons in the myenteric plexus of DSS colitis mouse colon

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Introduction: The enteric nervous system (ENS) continues to undergo various invasions throughout life (intestinal inflammation, intestinal infection, dysbiosis etc.), which causes neurodegeneration in the ENS. Thus, it is assumed that neurogenesis is induced to compensate for these neuronal deaths and maintain the neuronal network in the fully developed adult ENS as well as the embryonic and early postnatal ENS. However, these underlying

mechanisms in adulthood are largely unknown. Therefore, we aimed to investigate neurogenesis in the ENS of DSS colitis mouse colon.

Methods: Male C57BL/6N mice (12-weeks old) were administered 2% DSS for 8–11 days. After DSS treatment, the longitudinal muscle-myenteric plexus preparations and frozen sections from the distal colon were used for immunohistochemistry. The segments of distal colons were mounted in organ baths and then exposed to a neuroactivator veratridine.

Results: Veratridine-induced TTX-sensitive contractions were significantly sup-pressed in DSS colitis mouse colons s, which were reversed by a NOS inhibitor. Immunohistochemical analyses revealed that Sox2-expressing newly born neurons were observed within the myenteric ganglion of the colon, but not the ileum. Furthermore, there were no significant differences in neuronal density in the colon between normal mice and DSS colitis mice (n=7), whereas the proportion of nitrergic neurons per ganglion was significantly increased in DSS colitis mouse colon ($n = 8$, $p < 0.01$). Moreover, the proportion of Sox2-expressing nitrergic neurons to Sox2-expressing neurons per ganglion was significantly increased in DSS colitis mouse colon ($n = 4$, $p < 0.01$).

Discussion/Conclusion: These findings suggested that the colitis caused an imbalance in the enteric neural circuit composed of excitatory motor neurons and inhibitory motor neurons in the myenteric plexus of the colon, which resulted in the colonic dysmotility. Furthermore, Sox2-expressing newly born neurons within the myenteric ganglion imply that neurogenesis constantly occurs to maintain the gut homeostasis against various injuries in the colon.

15. Development of 3D immunocompetent epithelial model combining colon epithelium monolayer with CD4+ T cells to study mucosal inflammation

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Introduction: In vitro colon epithelial models are a powerful tool to study the morphology, as well as the interaction between pathogens and epithelial cells. However, classical cell line models have limited biological relevance and functional representation of the interaction between immune cells and intestinal epithelial barrier. Specifically, CD4+ T cells are an important mediator of intestinal inflam-mation, but their crosstalk with epithelial cells is not fully understood.

Methods: To better mimic the in vivo structure of the epithelial barrier, we have developed an immunocompetent 3D murine colon epithelial model combining a fully differentiated epithelial monolayer with CD4+ T cells to evaluate mechanisms of epithelial-immune crosstalk. Briefly, murine colon crypts were isolated and digested into single cells, and were grown onto a transwell system. Once fully differentiated, in vitro stimulated CD4+ T cells were co-cultured with the epithelial monolayer.

Results: The model displayed the expression of markers representative of different types of epithelial cells. These included intestinal epithelial cells (E-cadherin), goblet cells (Mucin 2), enteroendocrine cells (Chromogranin A), paneth cells (Lysozyme) and stem cells (Lgr5+). Furthermore, we observed that the epithelial monolayer formed tight junctions evaluated by transepithelial electrical resistance (TEER) and expressed tight junction markers mainly ZO-1, Occludin and Claudin 1. Besides, these monolayers are metabolically active since they produced various types of cytokines such as IFN-γ, IL-1β, TNF-α, IL-6 and IL-8. To induce inflammation, dextran sulfate sodium (DSS) was applied on the epithelial monolayer resulting in an increase of IFN- γ and IL-1β secretion and a decrease in the expression of MUC2 and Chga.

Addition of CD4+ T cells to the epithelial monolayer followed by DSS treatment induced an even higher expression of IFN-γ and TNF-α compared to the epithelial monolayer alone, along with a decrease of IL-8 secretion.

Discussion/Conclusion: Overall, our data indicate that the presented model might be a helpful tool to study epithelial-immune crosstalk in vitro and supplement in vivo studies of mucosal inflammation.

16. Evaluation of the Lavandula stoechas L. extract in the experimental model of irritable bowel syndrome

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Introduction: Irritable bowel syndrome (IBS) is a very common disease, which does not have optimal treatment. For this reason, prebiotics with immunomodulatory properties can be of great interest. The aim of this study was to evaluate the effects of Lavandula stoechas L. extract in an experimental model of IBS in rats induced by intracolonic instillation of acetic acid.

Methods: Female Wistar rats were administered 2% acetic acid, 3 days after they were divided into three different treated experimental group (n = 10), which received orally the extract at 1, 10 and 25 mg/kg; a non-IBS and an untreated control IBS group were included. The effect of the treatment was evaluated by determinations of intestinal hyperalgesia and hypersensitivity, inflammatory state and intestinal barrier integrity, as well as the composition of the intestinal microbiota.

Results: The IBS control group showed higher values in comparison with non-IBS group. The treated rats with 25 mg/kg of Lavandula stoechas extract showed reduced colorectal distension (CRD) score values and the referred pain compared to IBS control group. When the rats were sacrificed, the expression of different markers was evaluated in colonic tissue by qPCR. The results revealed that the extract was able to alter the expression of COX-2 and toll like receptors. Moreover, the extract was also able to restore the reduce expression of the mucins. Lavandula stoechas extract reduced the visceral hypersensitivity as well as the referred pain clearly involved in IBS. Additionally, the extract treatment was able to improve the gut dysbiosis associated with experimental IBS.

Discussion/Conclusion: Lavandula stoechas extract could be a potential novel treatment for IBS since it ameliorates visceral hypersensitivity and hyperalgesia as well as the intestinal inflammation and gut dysbiosis.

17. Comparison expression of Bcl-xl in ulcerative colitis and Crohn's disease

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Introduction: Ulcerative colitis and Crohn's disease are a risk factors for colon cancer. Patients with colorectal Crohn's disease have a less risk of colorectal cancer than that of patients with ulcerative colitis. Literature describes significant role of apoptosis in the evolution of pathogenesis of ulcerative colitis and Crohn's disease. Apoptosis or programmed cell

death is the major genetically regulated process of cell self-destruction. Apoptosis in physiological condition plays an essential role by controlling and allowing elimination of damaged or cancerous transformed cells. Over expression of one of the proteins regulating apoptosis: Bcl-xL, causing increased survival of cancer cells, results in tumor progression and metastasis formation. The anti-apoptotic protein Bcl-xL is located on the surface of the mitochondrial membrane and in the endoplasmic reticulum membrane. Bcl-xL built up of four domains (BH1-BH4) plays an important role in the inhibition of cytochrome c release through binding to Bax and Bak proteins. It is also involved in the neoplastic process. According to numerous studies, Bcl-xL over-expression contributes to carcinogenesis by protecting tumor cells from death.

Our study objective was the immunohistochemical assessment of the expressions of the apoptosis-regulating protein Bcl-xL in ulcerative colitis and Crohn's disease.

Methods: The 55 patients with ulcerative colitis, 21 patients with Crohn's disease, and 15 patients without any inflammatory pathology were analyzed in this study.

Immunohistochemical examination was performed according to the following protocol. Formalin-fixed, paraffin-embedded tissue specimens were cut on a microtome into 4 Qm sections, which were then deparaffinited in xylene mid hydrated in alcohol. To expose the antigen, the slides were heated in a microwave oven for 15 min in citric buffer (pH = 6.0). The activity of endogenous peroxidase was blocked by incubating the sections in 0.5% hydrogen peroxide in methanol. Next, the samples were incubated with anti-human Bcl-xL antibody (Bcl-xL, clone N-19, Santa Cruz Biotechnology). Reaction was performed in immunoperoxidase technique using Novocastra Peroxidase Detection System. Color reaction for peroxidase was done with DAB chromogen.

At least six files in each tissue were counted for each specimen at a magnification of x400.

Results: Cytoplasmic reaction in every case was observed. Expression of Bcl-xL in unchanged epithelium (in control group) was the lowest, greater in Crohn's disease and the strongest was observed in ulcerative colitis, particularly in altered dysplastic crypts.

Discussion/Conclusion: These investigations suggest that expression of anti-apoptotic Bcl-xL is associated in formation of dysplastic changes in colorectal glands. Elevated expression of Bcl-xL protein in ulcerative colitis, by protecting damaged cells from apoptosis, may lead to malignant transformation and tumor formation greater than in Crohn's disease.

18. Bioelectrical impedance analysis and hematological scales – A brand new combination for the evaluation of IBD patients?

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Introduction: In the light of the current knowledge, body composition assessed with bioelectrical impedance analysis (BIA) was not evaluated together with hematological indices in the single study on inflammatory bowel disease (IBD) patients, so far.

Methods: Thus, we enrolled 93 participants to the survey: 54 patients with Crohn's diseases (CD) and 39 – with ulcerative colitis (UC). They were treated with one of biologics: infliximab (n = 48) or vedolizumab (n = 45). We tried to look for the significant associations between BIA measurements, clinical scales (CDAI, SES-CD, MAYO) and hematological markers (red blood cell distribution width to platelet ratio – RPR, red blood cell distribution width to lymphocyte ratio – RLR, neutrophil to lymphocyte ratio – NLR and mean platelet volume to platelet ratio – MPR) together with CRP.

Results: Significant dependences were noted between BIA results, clinical IBD scales, hematological indices and CRP. We did not notice any notable differences according to the type of administered biological agent. In CD group body cell mass (BCM) correlated positively with SES-CD ($p < 0.05$). On the other hand, there was a positive correlation between reactance (Xc) and total MAYO score among UC patients ($p < 0.05$). Furthermore, Xc correlated negatively with MPR in the course of UC ($p < 0.05$). Other two more significant relationships were observed in UC group: a positive one between BCM and RPR ($p < 0.05$) and a negative one between extracellular water (ECW) and NLR ($p < 0.05$); finally, phase angle (PhA) correlated notably in the positive manner with CRP ($p < 0.005$).

Discussion/Conclusion: Achieved results suggest that changes in body composition in IBD patients can be reflected by deviations in hematological scales. Perhaps, further investigations could show some kind of certain relationships between the pattern of response on biological agents and character of results in BIA analysis and hematological indices.

19. Effects of hydrochlorothiazide on intestinal dysbiosis in spontaneously hypertensive rats

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Introduction: The objective of the study was to investigate the effects of hydrochlorothiazide (HCTZ) on neuroinflammation and hypertensive intestinal dysbiosis, as well as to analyze the significance of bacterial changes on the antihypertensive effect.

Methods: Male Wistar Kyoto rats (WKY) and spontaneously hypertensive rats (SHR) were used. The SHR rats were divided in three groups: one group was treated with vehicle (1% methylcellulose), SHR treated with captopril (85 mg/kg/day p.o.), and SHR with HCTZ (90 mg/kg/day p.o.) for five weeks. Faeces 16S rRNA, lymphocyte populations in mesenteric lymph nodes and aorta, intestinal integrity, intestinal sympathetic tone and inflammation in paraventricular nodes (PVN) of the hypothalamus were analyzed. A faecal microbiota transplantation (FMT) of faecal content from donor SHR-HCTZ to SHR recipient was performed.

Results: Faeces from SHR showed gut dysbiosis, characterised by lower acetate- and higher lactate-producing bacteria, and lower strict anaerobic bacteria. Both drugs increased anaerobic bacteria proportion, while hydrochlorothiazide decreased butyrate-producing bacteria. The amelioration of gut dysbiosis induced by captopril was associated with a decrease in gut pathology and permeability and an attenuated sympathetic drive in the gut and neuroinflammation and oxidative stress in PVN. By contrast, HCTZ was unable to reduce neuroinflammation, gut sympathetic tone and gut integrity in SHR. In addition, this drug normalized vascular NADPH oxidase activity, aortic relaxation induced by acetylcholine and blood pressure. However, FMT from SHR-HCTZ to SHR had no effects on vascular function.

Discussion/Conclusion: HCTZ was unable to modify the gut-brain axis, although it caused changes in the microbiota that did not contribute to its antihypertensive effect.

20. Dietary fibers: Prebiotics to prevent the development of cardiovascular complications linked to systemic lupus erythematosus

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Introduction: Gut microbiota has been shown to control the development of renal and vascular complications associated with systemic lupus erythematosus (SLE). This study is to investigate whether dietary fiber intake prevents these complications in a genetic mouse model of lupus.

Methods: Female NZBWF1 (SLE) mice were treated with resistant-starch (RS) or inulin-type frutans (ITF). In addition, inoculation of faecal microbiota from these experimental groups to recipient normotensive female C57Bl/6J germ-free (GF) mice was performed.

Results: Both fiber treatments, especially RS, prevented the development of hypertension, renal injury, improved the aortic relaxation induced by acetylcholine, and the vascular oxidative stress. RS and ITF treatments increased the proportion of acetate-, and butyrate-producing bacteria, respectively, improved colonic inflammation and integrity, endotoxemia, and decreased helper T (Th)17 proportion in mesenteric lymph nodes (MLNs), blood, and aorta in SLE mice. However, disease activity (splenomegaly and anti-ds-DNA) was unaffected by both fibers. T cell priming and Th17 differentiation in MLNs and increased Th17 infiltration was linked to aortic endothelial dysfunction and hypertension after inoculation of faecal microbiota from SLE mice to GF mice, without changes in proteinuria and autoimmunity. All these effects were lower in GF mice after faecal inoculation from fiber treated SLE mice.

Discussion/Conclusion: These findings support that fiber consumption prevented the development of hypertension by rebalancing of dysfunctional gut-immune system-vascular wall axis in SLE.

21. Limosilactobacillus fermentum modulates the gut microbiota and produces anti-cancer metabolites to protect against inflammation-associated colorectal tumorigenesis

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Introduction: Intestinal inflammation contributes to the development of colorectal cancer (CRC), through activation of oncogenes and inhibition of apoptosis. This study evaluates the effect of the immunomodulatory probiotic Limosilactobacillus fermentum CECT5716 in an experimental model of colitis-associated CRC (CAC), focusing on its impact on the microbiome.

Methods: CAC was induced in C57Bl/6 mice by administration of azoxymethane followed by three cycles of dextran sulfate in drinking water (2%). A group of CAC mice was treated with L. fermentum (5 x 108 CFU/mouse/day). Tumor damage was assessed using the disease activity index (DAI) and colonoscopy. Additionally, different inflammatory markers and immune populations in colon samples were analyzed by gene expression, WB and FACS. Intestinal contents were analyzed for microbial composition (Illumina MiSeq).

Results: L. fermentum reduced the number and size of the tumors observed, accompanied by a decrease in the expression of markers involved in tumor generation such as Ccnd1 and Angpt2, while increasing pro-apoptotic markers. In addition, a reduction in myeloid immune cell infiltration, including macrophages, neutrophils and mast cells, was observed, as well as a decrease in the expression of different pro-inflammatory cytokines (IL-1β, IL-6, IL-12 and IL-23). Finally, L. fermentum modulated microbiota composition, which is altered due to the tumor process, by recovering microbial biodiversity.

Discussion/Conclusion: L. fermentum CECT5716 decreases experimental tumor development, thus revealing an anti-proliferative and pro-apoptotic effect in vivo. This beneficial effect is associated with its immunomodulatory properties, and is ability to modulate intestinal microbiome. Thus, the probiotic L. fermentum could be considered as a complementary approach in the management of CRC in humans.

22. Impact of processing of wheat flours on their ATI-induced TLR4 stimulating bioactivity

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Introduction: Amylase Trypsin Inhibitors (ATIs), a family of 17 non-gluten wheat proteins are triggers of non- celiac wheat sensitivity. ATIs are resistant to gastric acid, digestive proteases and heat, and interact with Toll-Like Receptor 4 (TLR4) on intestinal myeloid cells and thus promote intestinal and extra-intestinal inflammation. We tested several wheat samples that were harvested/processed vs. respective controls during different growth stages (n = 2), separated grain parts (n = 5), germination (n = 5), fertilization (n = 7), fermentation (n = 16) and peeled grains (Einkorn [n = 3], spelt [n = 2], common wheat [n = 3] and Durum [n = 3]) for their in vitro TLR4 stimulation potential using our proprietary Hela TLR4 dual reporter cells.

Methods: All wheat samples were quantitatively extracted for ATIs and tested for TLR4 stimulating bioactivity, normalized to dry wheat flour weight, using our Hela TLR4 dual reporter cell line that measures both cell viability and TLR4 activity. LPS contamination was ruled out using PMB Sepharose. Resultant bioactivities were analysed for their correlation with total ATIs and ATI subspecies as determined by concatamer-based quantitative mass spectrometry.

Results: All grain fractions showed comparable TLR4 stimulating bioactivities, while wheats harvested at late growth stage showed overall decrease in bioactivity. Yeast or acid fermentation decreased bioactivities time-dependently up to 50% after 24 hrs, while seed peeling resulted in a loss of up to 40–50% activity when compared to non-peeled pure grain samples. Germination showed no impact on bioactivity. In all samples there were no significant changes in gluten content and composition when tested using the G12 and R5 ELISA. Fertilisation with increased nitrogen levels increased bioactivities.

Discussion/Conclusion: MS analysis and quantification of all ATI subspecies in the wheat samples, either processed or unprocessed, usually does not correlate well with their bioactivities. Long-term, fermentation only mildly affects bioactivities. Our recent findings indicate that ATI bioactivity is the result of complex interactions.

23. The TLR4-activating potential of dietary wheat amylase trypsin inhibitors (ATIs) depends on their interaction with other wheat proteins

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Introduction: Amylase Trypsin Inhibitors (ATIs) are a family of 17 non-gluten wheat proteins which accounts to 3–4% of total protein. They can interact with Toll-like receptor 4 (TLR4) on myeloid cells, are resistant against heat, gastric acid and digestive enzymes, and their nutritional intake with wheat products promotes intestinal and extraintestinal inflammation, especially worsening of autoimmune diseases, a facet of non-celiac wheat sensitivity (NCWS). ATI subspecies form monomers, dimers, or tetramers. However, how far the oligomeric state of ATI affects their TLR4 stimulating potential has not been clear. Therefore, we aimed to study major ATI species for their capacity to activate TLR4 on our Hela dual TLR4 reporter cell line that measures TLR4 activating potential.

Methods: ATIs were precipitated from extracts of wheat flour and further purified using HPLC with gradient systems of acetonitrile and trifluoroacetic acid or ammonium formate. Resultant fractions were assessed via gel electrophoresis, ATI-subtype specific western blots, mass spectrometry (MS) and bioactivities were determined.

Results: High TLR4 stimulating bioactivity was only detected in high and low Mw ATI fractions. Other activities were lost in precipitates that formed during purification. MS analysis showed that bioactivity was dependent on partially pepsin-digested 1–2 ATI subspecies, largely monomers, and their interaction with other specified molecules.

Discussion/Conclusion: 1. A complex interaction of only certain partially pepsin-digested ATI subspecies with other wheat proteins appears to determine their interaction with TLR4 and thus their bioactivity. 2. This may explain the high variation in ATI bioactivities in different wheats and under variant cultivation conditions, which often does not correlate well with ATI (subspecies) content as determined by MS. 3. A better characterization of these interactions during wheat growing and food processing will be important for growing wheat and preparing wheat products with low immune stimulatory potential.

24. TLR4 stimulating bioactivity of wheat ATIs depends on the location of cultivation

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Introduction: Wheat amylase-trypsin inhibitors (ATIs) are strong innate immune system activators with a variant primary but a largely conserved secondary structure. They are resistant to gastric acid, digestive enzymes and heat, and stimulate toll-like receptor 4 (TLR4) on intestinal monocytes, macrophages, and dendritic cells, promoting intestinal and extraintestinal inflammation. We determined the biological activity of ATIs in different wheat genotypes and species cultivated in different locations.

Methods: Diploid, tetraploid and hexaploid (modern) wheats (n = 180), including species such as einkorn (n = 3), emmer (n = 3), durum (n = 4), sSpelt (n = 4), and common hexaploid wheat (n = 2), were grown at 2–4 different locations in Germany. ATIs were quantitatively

extracted. TLR4 stimulating bioactivity was determined using our Hela TLR4 dual reporter cells. LPS contamination was excluded using PMB-Sepharose. Mass spectrometry analyses were performed with ATI target peptide concatamers as standard that permitted exact quantification of 8 major ATIs (CM1, CM2, CM3, CM16, CM 17, 0,19, 0,28, 0,53).

Results: ATI bioactivity showed a high variability (from 4- to 6-fold difference), even among modern hexaploid wheats as well as in tetraploid Durum wheats. Both genotype and location were determinants of bioactivity. Proteomic analysis reflected this variability of ATI bioactivity showing an up to 2-fold variation among the tetrameric ATIs CM1,2,3,16,17, and an up to 4-fold variation among the dimeric ATI 0.19, 0.28, 0.53. There was no good correlation between bioactivity and the quantity of a certain ATI-subtype.

Discussion/Conclusion: 1) ATI can be quantitatively extracted from wheat genotypes and species; 2) a dual reporter TLR4 transfected HeLa cell line was established that permitted sensitive and reproducible measurement of ATI bioactivity; 3) There is a high variability of ATI bioactivity and subspecies content depending on wheat genotype/species and site of cultivation; 4) ATI bioactivity depends on molecular factors beyond genotype, location, cultivation and mere ATI subspecies content.

25. The oral tissue transglutaminase inhibitor ZED1227 prevents gluten-induced enteropathy in the humanized NOD-DQ8 mouse model of celiac disease

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Introduction: Celiac disease (CeD) is triggered by gluten peptides that escape intestinal digestion and are bound to HLA-DQ2 or -DQ8 in the small intestinal lamina propria. The CeD autoantigen tissue transglutaminase (TG2) deamidates certain glutamine residues in these peptides, which improves their binding to both HLAs, enhancing the gluten-specific T cell response, resulting in small intestinal inflammation, including villous atrophy and increased intraepithelial lymphocytes (IELs) as CeD-specific hallmarks. We developed and tested ZED1227, an oral inhibitor of TG2, in a mouse model of small intestinal inflammation induced by poly-IC and in a humanized transgenic CeD mouse model (NOD-DQ8 mice) that develops mild features of human CeD after gluten sensitization and on a gluten containing diet. Villous atrophy, IELs and the pattern and expression of relevant immune cell subsets were studied in gluten challenged NOD-DQ8 mice treated with placebo or ZED1227-treted NOD-DQ8 mice.

Methods: B6 Mice received intraperitoneal poly-IC together with 50 or 150 mg oral ZED1227/kg vs. vehicle to induce small intestinal inflammation 2 h before sacrifice, and intestinal TG2 activity versus secreted and deposited TG2 was measured by incorporation of biotinyl-pentylamine. Gluten-sensitized NOD-human DQ8 transgenic mice fed a gluten-containing or gluten-free diet for 3 weeks received daily oral gavages of ZED1227 (25 or 50 mg/kg) vs. vehicle for the last week.

Results: ZED1227 completely blocked intestinal TG2 activity in the poly:IC model. In NOD-DQ8 mice, ZED1227 prevented gluten-induced villous atrophy, increases in IEL, CD45, CD3, CD8, CD68 and Ki67 positive cells, and decreased proinflammatory transcripts and serum levels of CeD specific antibodies.

Discussion/Conclusion: 1. Oral ZED1227 effectively blocked TG2 activity in vivo and attenuated CeD in our transgenic NOD-DQ8 mouse model. 2. The NOD-DQ8 model predicted therapeutic efficacy of ZED1227 that was later demonstrated in a phase 2a clinical trial of 160 CeD patients in remission who were challenged with gluten (Schuppan et al., NEJM 2021), qualifying as preclinical toll to assess novel pharmacological therapies.

26. SEFA-1024, a structurally engineered EPA derivative reduces intestinal inflammation in mice by restoring intestinal mucosal barrier function

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Introduction: Inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC), are characterized by chronic inflammation of the gastrointestinal tract of only partly known etiology. Environmental factors such as diet seem to play an important role in initiation and maintenance of IBD. Although omega-3 fatty acids, such as eicosapentaenoic acid (EPA), and their endogenously generated metabolites have shown promise in pre-clinical models of IBD clinical translation has not been realized. We tested SEFA-1024 that has been designed to remain in the gut, which is not subject to beta-oxidation, while displaying high activity in signaling via G-protein coupled receptors, in the murine colitis model induced by dextran sodium sulfate (DSS).

Methods: Colitis was induced in C57BL/6J mice with dextran sulfate sodium (DSS) in the drinking water. With the start of the DSS challenge, mice were treated once daily with corn oil (vehicle) or SEFA-1024 by oral gavage. Body weight was measured daily. Morphological, histological, and biochemical analyses in the colon were performed.

Results: SEFA-1024 treatment dose-dependently almost prevented colitis in morphological and histological analyses. SEFA1024 significantly suppressed the expression of colonic pro-inflammatory cytokines TNF-α, IL-1β, IL-6 and S100A8 compared to the vehicle treated controls. Flow cytometry revealed decreased infiltration of inflammatory myeloid immune cells. Moreover, SEFA1024 treatment enhanced the quantity of goblet cells and induced the expression of protective factors and mucins by goblet cells, as exemplified by upregulated mucin 2 (MUC2), trefoil factor 3 (TFF3) and staining of PAS-positive cells.

Discussion/Conclusion: 1) SEFA-1024 ameliorates DSS induced colitis in mice dose-dependently 2) SEFA-1024 administration enhanced the quantity of goblet cells and induced protective mucins in goblet cells 3) The key mechanisms of SEFA-1024 action that promoted mucus barrier integrity and anti-inflammatory effects in DSS colitis are currently under investigation 4) SEFA-1024 should be further explored as therapy of IBD.

27. The inflammatory role of IL-4Rα signaling in IBD is limited to monocytes at the onset of colitis

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Introduction: Animal models suggested that IL-4 receptor alpha (IL-4Rα) signaling promotes inflammatory bowel disease (IBD). However, blocking IL-13 signaling in colitis patients failed to produce clinical benefit. Here, we clarified the function of IL-4/IL-13 signaling during IBD and how far targeting IL-4Rα signaling provides a therapeutic benefit.

Methods: Different time points were chosen to study IL4Rα kinetics in intestinal inflammation due to DSS or TNBS treatment, using wildtype mice compared to mice with general IL-4/IL-13 double knockout, and with general, myeloid and epithelial cell specific deletion of IL-4Rα. An antisense oligonucleotide targeting IL-4Rα was applied in DSS-induced colitis. IL4Rα mRNA expression was measured in colonic biopsies of patients with inflammatory bowel disease (IBD).

Results: Genetic deletion of IL-4/IL-13 and IL-4Rα protected from experimental DSS colitis. Knockdown of IL-4Rα in intestinal epithelial cells was ineffective, while IL-4Rα ablation in myeloid cells protected mice against colitis. Intestinal IL-4Rα expression was upregulated at colitis onset and declined with disease progression. This initial peak was caused by gut-invading inflammatory monocytes and IL-4Rα function in these cells was required for colitis induction. Therapeutic targeting of IL-4Rα with a specific ASO before colitis induction was protective, but failed to inhibit disease progression. Analysis of IBD patient biopsies confirmed downregulation of IL-4Rα expression as a general feature of established IBD.

Discussion/Conclusion: IL-4Rα signaling by myeloid cells has an impact on intestinal inflammation and regulates experimental colitis development in a time and stage dependent manner. Since IL-4Ra is only upregulated early in colitis, therapies targeting IL-4Rα will likely be more effective in mild IBD and IBD prevention compared to highly active colitis.

28. Epithelial c-MET expression is associated with active inflammatory bowel disease and IBD-associated colorectal cancers

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Introduction: Inflammatory bowel disease (IBD) is a chronic relapsing-remitting condition where the chronic inflammatory burden increases the risk of clinical complications including IBD-associated colorectal cancer (IBD-CRC). There remains a clinical need to identify novel targets to treat active inflammation and prevent IBD-CRC. c-MET is a receptor tyrosine kinase upregulated in sporadic CRC and associated with poor outcomes. However, recent data suggest that c-MET may also play an important role in wound healing. This preliminary study investigated the expression of c-MET in both IBD and IBD-CRC.

Methods: Expression of c-MET was assessed by immunohistochemistry in formalin-fixed paraffin-embedded biopsies of normal colonic mucosa from non-IBD patients (n = 30), quiescent (n = 16) and actively inflamed (n = 11) IBD mucosa, dysplastic IBD mucosa (n = 18), and a tissue microarray of IBD-CRC cases (n = 101). Stained sections were semi-quantitively scored as ‘absent’, ‘weak’, ‘moderate’, or ‘strong’ c-MET intensity by two expert observers.

Results: Positive epithelial cytoplasmic and membranous c-MET expression was observed in all tissue specimens, indicating ubiquitous expression in the colorectum. There was no difference in c-MET expression intensity between patients with quiescent IBD mucosa (chronic background inflammation) compared to colorectal mucosa from non-IBD patients ($p = 0.404$). Patients with actively inflamed IBD mucosa had increased expression intensity of c-MET compared to patients with quiescent disease ($p < 0.001$). Foci of IBD-dysplasia ($p < 0.001$) and IBD-CRC ($p < 0.001$) had stronger expression of c-MET compared to patients with quiescent disease. There was no difference between patients with actively inflamed IBD mucosa and IBD-dysplasia ($p = 0.512$) or IBD-CRC ($p = 0.0.290$). In IBD-CRC, c-MET expression was not associated with available clinico-pathological data or overall survival.

Discussion/Conclusion: c-MET is upregulated in actively inflamed IBD mucosa and in IBD-CRC. Mechanistic studies are now needed to determine whether this is protective (e.g. promotion of wound healing during active inflammation) or pathogenic (e.g. driving chronic inflammation and carcinogenesis).

29. Increased epithelial HMGB1 expression is associated with inflammatory bowel disease and associated colorectal can-cers

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Introduction: Patients with inflammatory bowel disease (IBD) have increased risk of colorectal cancer (CRC), with poorer survival. Chronic mucosal inflammation is the greatest risk factor for IBD-CRC. There is need to improve understanding of IBD-CRC pathogenesis and identify new treatment targets. HMGB1 protein is ubiquitously expressed in the nucleus and shuttles to the cytoplasm under cellular stress. HMGB1 impacts cellular responses, acting as a cytokine when secreted. This study investigated expression of HMGB1 in IBD and IBD-CRC and explored biological effects of HMGB1 in human colon.

Methods: HMGB1 expression was assessed immunohistochemically in formalin-fixed paraffin-embedded biopsies from patients with ulcerative colitis (UC, n = 36) and colonic Crohn's disease (CD, n = 41). Tissue microarrays of IBD-CRC (n = 14) and sporadic CRC (n = 650) with matched normal epithelium (n = 50) were also immunostained. Wound healing and proliferation assays were performed on Caco2 cells (ATCC®HTB-37TM). qRT-PCR for epithelial barrier permeability and cytokine genes, and exploratory RNA-Sequencing, was performed on HMGB1-stimulated human colonic organoids (n = 4).

Results: Normal colonic epithelium express strong nuclear and absent cytoplasmic HMGB1. In sporadic CRC there is reduction in nuclear and emergence of cytoplasmic HMGB1 ($p < 0.001$). Patients with UC ($p < 0.001$) and CD ($p < 0.001$) have increased cytoplasmic HMGB1 compared with normal epithelium. Further, IBD-CRC patients had stronger cytoplasmic HMGB1 compared to UC ($p < 0.001$) and CD ($p = 0.004$). HMGB1 did not impact wound healing or proliferation. HMGB1 was not associated with differential expression of epithelial barrier permeability or cytokine genes in human colon organoids. However, RNA-Sequencing identified altered expression of key genes associated with IBD and CRC (increased MUC5AC, CLCA1, IFI6, IL-33, SERPINB2, GSTM5, CDC25C and PPBP, and decreased PLA2G2A, CPA6, ECM1, SLC46A1, CD177, Bcl-2, DMBT1, ICAM-1,LSAMP and SERPINA1).

Discussion/Conclusion: Epithelial cytoplasmic HMGB1 expression is increased in IBD, IBD-CRC and sporadic CRC. The biological effects of HMGB1 in IBD and associated colonic malignancy warrants further investigation.

30. Characterization of gut microbiota in the colonic mucosa in Crohn's disease patients as a tool for developing new therapeutic approaches

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Introduction: Crohn's disease (CD) patients suffer from chronic intestinal inflammation that has been clearly associated with gut dysbiosis. However, studies comparing mucosal and

stool microbiota in these patients are still lacking. Therefore, the aim of this study was to investigate the differences in faecal and mucosal-associated microbiota in CD patients, which can determine disease evolution and treatment response.

Methods: Prospective study was conducted in CD patients. At the baseline visit, colonic mucosal biopsies, from damaged and healthy areas, and stool samples were collected for microbiome characterization. All samples were submitted to DNA extraction and then, sequenced using MiSeq Illumina platform. The microbiome analysis was performed by using bioinformatic tools.

Results: Beta diversity analysis revealed differences in the microbiome profile depending on the source of the sample (damaged or healthy biopsies and stool samples). This was confirmed at genus level since an enrichment of Prevotella was observed in the microbiota from faeces, whereas both Shigella and Lachnocostridium appeared increased in the colonic mucosa. Although microbiota in both damaged and healthy mucosa were quite similar, a higher presence of Lachnospiraceae, and more specifically Citrobacter europaeus, was observed in the damaged mucosa. Moreover, when the relationship between microbiota composition in the stools and the clinical status in CD patients was performed, no significant correlation was observed. However, when Shigella or Citrobacter were found in the damaged mucosa, a positive correlation was observed with duration time in disease evolution and its extension.

Discussion/Conclusion: CD patients showed a specific profile in mucosa-associated microbiota, characterized by the increased presence of Shigella sp. and Citrobacter europaeus, which could be considered as future targets in the development of new therapies or to evaluate disease evolution.

31. Beneficial effect of organosulfur compound from Allium spp. on mucosal immunology in a mouse model of colitis-associated colorectal cancer

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Introduction: Colorectal cancer (CRC) is the third most commonly diagnosed and deadly cancer worldwide. An important factor is an exacerbated inflammatory response in the gut mucosa and it is associated with increased risk for CRC. The aim of study was to evaluate the impact of the organosulfur compound Propyl-Propane-Thiosulfonate (PTSO) from Allium spp., with reported anti-inflammatory properties, in the tumoral progression in a model of colitis-associated CRC (CAC).

Methods: C57Bl/6 female was pretreated with micro-encapsulated PTSO (1 mg/kg) for 2 weeks and then, CAC was induced by administration of azoxymethane followed by three cycles of dextran sulfate in drinking water (2%). PTSO treatment was maintained during all assay and a group treated with 5-fluorouracil (15 mg/kg) was used as control. Tumoral process was assessed using the disease activity index (DAI) and by colonoscopy. Moreover, inflammatory markers and immune populations in colon and mesenteric lymph nodes (MLNs) samples were analyzed by flow cytometry. Additionally, the immunomodulatory and antiproliferative/antitumoral properties of PTSO have been analyzed in vitro by using human colon cells lines (HCT-116, CACO-2, NCM-356) and co-culture models combining these cells lines with human immunity-cells (HMC-1.2).

Results: PTSO pretreatment reduced the macroscopic colonic inflammation, thus resulting in an amneliotarion of tumor development in CAC model. This was associated with a reduction of myeloid immune cell infiltration in the colonic mucosa, including macrophages (CD45+CD-11b+Ly6G-MHCII-Ly6C-) and neutrophils (CD45+CD11b+Ly6G+). Moreover, PTSO increased lymphoid cells (CD3+), specifically Th cell (CD3+CD4+) population in MLNs. This effect was associated to an antiproliferative effect evidenced by a reduction of pSTAT3/STAT3 ratio in colon. In vitro studies revealed that PTSO supplementation reduced tumor cell proliferation and migration.

Discussion/Conclusion: PTSO pretreatment decreases experimental tumor development, thus revealing an immunomodulation and anti-proliferative effect in the tumoral process. Therefore, PTSO could be considered as a novel complementary therapeutic strategy in the management of CRC in humans.

32. Tigecycline in the treatment of obesity-associated colorectal cancer: Impact on colon inflammation and gut dysbiosis

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Introduction: Obesity is associated with altered colonic epithelial permeability that impairs mucosal immune response and constitutes a risk factor for colorectal cancer (CRC). Both obesity and CRC share altered cellular pathways and gut dysbiosis, resulting in the release of metabolites that promote tumorigenesis. In the present study the effects of tigecycline, an antibiotic with immunomodulatory properties, were evaluated in an experimental model of colitis-associated CRC (CAC) in obese mice, with special attention on the altered immune function.

Methods: CAC was induced in obese C57BL/6 mice fed a high-fat diet (HFD), by azoxymethane administration, followed by three cycles of dextran sodium sulfate in drinking water. The experimental groups, depending on the diet and treatment, were: standard diet (SD), HFD and HFD+tigecycline (25 mg/kg/day during the last 7 weeks). Disease activity index (DAI) was evaluated, and colonoscopy images were taken. After sacrifice, tumor burden was analyzed, and colon and fat samples were taken for cytometry, RT-qPCR, histology and Western-Blot analyses. Stool samples were collected for microbiota composition analysis by Illumina MiSeq sequencing.

Results: CRC induction was aggravated in obese mice fed HFD in comparison with those receiving SD, as evidenced by higher DAI values and tumor burden. Conversely, tigecycline reduced the tumor number and size. Moreover, tigecycline administration reduced the infiltration of immune cells in colonic tissue of HFD-fed mice, which was associated with a downregulation of proinflammatory cytokines expression. Histologically, tigecycline ameliorated the carcinoma-like lesions with invasive capacity. Similarly, the levels of proliferation markers (ki67, Stat3, Akt, β-catenin) were downregulated in colonic mucosa from tigecycline treated groups. Finally, CRC induction in obese mice resulted in colonic dysbiosis and altered bile acid profile, which was ameliorated after tigecycline administration.

Discussion/Conclusion: Tigecycline reduces the aggravation of the colonic tumorigenesis process induced in obese mice through the restoration of the altered immune response and modulation of microbiota composition.

33. Inter-organ crosstalk in the context of intestinal inflammation

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Introduction: Patients suffering from inflammatory bowel dieses (IBD) develop extra-intestinal manifestations (EIM), which can affect almost every organ system including the hepato-pancreato-biliary and musculoskeletal system. Various factors such as the microbiota or tryptophan metabolism are suggested to promote such extra-intestinal diseases, but underlying molecular mechanisms for the different gut-organ axes remain poorly understood. Hence, suitable in vivo and in vitro models are required to investigate inter-organ crosstalk.

Methods: The gut-liver as well as the gut-bone axis was evaluated in Casp8ΔIEC mice, a preclinical mouse model of Crohn's disease (CD) ileitis and colitis, mimicking several human features and enabling research to investigate EIM. Additionally, human and murine organoids were used to characterize the impact of tryptophan metabolisms and bacterial outer membrane vesicle (OMVs) to promote EIM.

Results: Besides a microbiota-dependent disease localization, Casp8ΔIEC mice displayed osteoporosis as seen in patients but also features of liver fibrosis and inflammation. Mechanistically, we could show that intestinal inflammation was linked to an altered tryptophan metabolism and AHR-signalling, which are assumed to be mediators of EIM. Moreover, mechanistic and functional analysis of intestinal- and liver-derived organoids as well as in vitro osteoclast differentiation enables us to decipher the complex mechanisms and pathways connecting IBD and PSC (gut-liver axis), but also IBD and osteoporosis (gut-bone axis).

Discussion/Conclusion: Accordingly, the impact of intestinal inflammation to promote extra-intestinal manifestations could be addressed with the Casp8ΔIEC mouse model, but also ex vivo by taking advantage of organoid in order to investigate the different underlying gut-organ-axes and to increase current knowledge.

34. Colonic resistance, opportunistic infections, and mesenteric vessels endothelial dysfunction in IBD may have possible mutual genetic background

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Introduction: Inflammatory bowel disease (IBD) patients are a high-risk population for opportunistic infections. IBD pathogenesis is commonly realized through metabolic and immune mechanisms involving vascular and digestive systems injury. Immune system has strong influence on both colonic mucosa and endothelium and may have strong molecular-genetic background. Opportunistic infections refer to microorganisms with limited or no pathogenic capacity in healthy human bodies but cause diseases or induce infections when the immune system is compromised by other diseases. However, there is lack of data connecting genetics, vascular-endothelial changes and colonic changes including dysbiosis and inflammation. The aim of this study is to find possible connections of the endothelial function and mesenteric vessels remodelling depending on A1166C polymorphism of angiotensin II type 1 receptor (AGTR1) gene in IBD patients with colonic dysbiosis as a background for opportunistic infection and vascular-endothelial injury as well.

Methods: Observational study includes 104 IBD patients with colonic dysbiosis (CD) in stable remission. Standard aerobic and anaerobic microbiology techniques with nosology identification and quantity composition of microbiota were used. Intimae-media thickness (IMT) of abdominal aorta (AO) and other flow mediated parameters of mesenteric vessels evaluated sonographically. NO (nitrite/nitrate) plasma concentration, vascular adhesive molecule (sVCAM-1) level was defined by IEA. AGTR1 (A1166C) genes polymorphisms assessed in PCR.

Results: The microbial overgrowth syndrome of II–IV degree detected in 95.1–95.9% of cases. CC- genotype carriers of AGTR1 gene had heavier dysbiosis of III-IV grades. Patients with A-allele, had lower frequency of dysbiosis ($p = 0.004$) and moderate severity ($p = 0.037$). CC genotype of AGTR1 gene characterized by elimination of obligate colonic indigenous constant microorganisms and contamina-tion by pathogenic (E. coli Hly+) and opportunistic (Proteus), Enterobacteriaceae, Peptococci, Clostridium and Candida fungi. In patients with CC genotype of the AGTR1 gene a significant reduction of Bifidobacteria (35.7%, $p < 0.001$), Lactobacilli (24.1%, $p < 0.01$) and enterococci (1.5%) was found. On this background, significant increase of enterotopathogenic Escherichiae (8.94 3 0.08 lg CFU/g), opportunistic Enterobacteriaceae (8.78 3 0.11 lg CFU/g), Hafniae (8.69 3 0.09 lg CFU/g), Proteus – by 55.2%, Staphylococci (5.92 3 0.14 lg CFU/g), Candida fungi (5.60 3 0.10 lg CFU/g) was observed.

Discussion/Conclusion: The CC genotype of AGTR1 gene is generally characterized by elimination of normal colonic autochthonous obligate microflora and contamination by pathogenic, opportunistic and conditionally pathogenic micro-organisms. The mechanism possibly involves changes of mesenteric arteries and endothelial function and may predict failures of both standard and faecal transplant therapies.

35. Different E. coli variants play an important role in modelling of both colonic resistance and immune response in healthy and inflammatory conditions

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Introduction: It is generally accepted that mucosal microbiota plays an important role in pathogenetic cascade leading to colonic inflammation and development of IBD. It is also known that IBD causes significant changes in colonic resistance, for instance acting as an independent risk factor for C. difficile infection as well. However, therapeutic outcome in relation to microbiota is comparatively poor.

Existing studies point on possible peculiarities of microbiota as an integral part of colonic inflammation involving the linkages of genomic, microbiomic, proteomic, and metabolomic factors acting both synergically and opportunistically.

E. coli is often considered as a primary target for research, currently focusing on microbiome and potential influence on metabolomics. E. coli is one of the most diverse bacterial species with only 20% of the genes in a typical E. coli genome shared. The idea of this study is based on current data regarding microbiota's role in pathogenesis of IBD and is aimed on studying various variants of E. coli at inflamed colon as an important component of colonic resistance and its failure.

Methods: Ninety-five (mean 38.66 3 3.11 yrs) individuals with different forms of chronic colonic inflammation (37 [38.95%] clinically proven IBD) and 58 healthy donors participate in the study. Colonic resistance studied in mucosal bioptates. Standard aerobic and anaerobic microbiology techniques with nosology identification and quantity composition of microbiota were used. Immunotyping (0, K, H antigens) and PCR (genomic study) were used for identification of E. coli variants.

Results: In 95 patients, 100 variants of E. coli of were found (1.05 per case). E. coli 055:K59 was found in 29.82%, E. coli 044:K74 in 12.28% and E.coli 026:K60/075:K95 – only in few cases. In IBD patients E. coli 0124:K72, 025:K1 and 028ac:K66 were observed in 75.68%. E. coli 0124:K72, 025:K1, 028ac:K66, 0144:K, 0124:K72, and 0144:K – in rest of samples. In addition to bifibacteria deficit by 46.65% and lactobacteria by 46.39%, microbiota included C. diversus, E. aerogenes, Proteus spp., Hafnia alvei, Candidae, with Bacteroides growth by 69.09%, and conditionally pathogenic Peptococci by 59.24%. Surprisingly, genomic study of hlyA and K1 genes showed insufficient correlation emphasizing IBD and colitis.

Discussion/Conclusion: E. coli plays an important role in modelling both colonic resistance and immune response in both healthy and inflammatory conditions. This study confirms the role of microbiota in development of IBD. However, selected genes cannot explain E. coli influence on the mucosal barrier and wider range of genomics must undergo further research.

36. The interplay between microbiota, immune response, and intestinal permeability in an enteral dysfunction syndrome

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Introduction: Failure of normal intestinal functioning is often characterized as an enteral dysfunction syndrome (EDS) which is the leading course of hospital-associated mortality in Europe and is characterized by increased intestinal permeability, hepatic dysfunction, and different systemic complications of acute and chronic character. It has multiple clinical presentations as well as different causes and outcomes. Pathogenesis of EDS is complex and to some extent, unclear. It is hypothesized that microbiota may participate in this malicious condition both s a trigger and important component of the vicious circle which includes changes of gut microbiocenosis with endotoxin release and following physiologic effect including immune response and nitric oxide (NO) changes. The objective of the study is to find whether changes of gut microbiota, Antiendotoxin Core Antibodies (EndoCAb) and NO levels are related in pathogenesis of EDS and what are these relationships.

Methods: Study included 87 patients with clinically proven EDS, mean age – 49.06 3 8.34 yrs. Control – 30 practically healthy individuals of respective age and gender. EndoCAb and NO (nitrite/nitrate) assessed by ELISA. Colonic lumen and mucosal microflora studied microbiologically employing standard aerobic and anaerobic techniques with taxonomic class identification and population levels calculation.

Results: We observe significant changes of the colonic microbiota in EDS: reliable decrease ($p < 0.05$) or elimination of autochthonic anaerobic microorganisms and hyperproliferation of conditionally pathogenic Enterobacteriacea: E. coli, including Hly+ – 9.31 3 0.62 lg CFU/g against 7.39 3 0.56 lg CFU/g in control; Klebsiellae – 5.17 3 0.40 lg CFU/g against 3.48 3 0.49 lg CFU/g in control, Proteus – 6.23 3 0.35 lg CFU/g, and Serratia – 5.49 3 0.74 lg CFU/g (not found in control). EndoCAb changes were not uniform. Moreover, in patients with severe (complicated by liver failure or acute lethal) clinical course of disease EndoCAb IgM (1.05 3 0.02 MMU/ml) and IgG (2.51 3 0.11 GMU/ml) were significantly lower than in control ($p < 0.01$). However, positive current of the syndrome, even accompanied by MODS, gives higher figures of IgM (2.98 3 0.23 MMU/ml) and IgG (9.57 3 0.84 GMU/ml). In most cases (83–95.4%) significant ($p < 0.05$) EndoCAb growth was observed only week of disease. In four (4.6%) cases only IgM increased, while IgG level remained low. NO levels rose reliably ($p < 0.05$) in all observed patients with EDS (42.96 3 2.75 mmol/l vs. 34.61 3 3.07 mmol/l in healthy subjects).

Strong negative correlation ($r = -0.79$, $p < 0.05$) between EndoCAb and NO levels was found only in negative course cases.

Discussion/Conclusion: Excessive growth of conditionally pathogenic Enterobacteriacea and endotoxin release is associated with insufficient production of antinuclear anti-endotoxin antibodies (EndoCAb). NO adds to EDS severity by means of decreased motility and increased intestinal permeability. This intestinal leakage plays role as pathophysiologic vicious circle forming conditions for microbiome changes and refractory changes of associated chains of pathogenesis.

37. Aging phenotypes of CD8+ T cells correlate with course of the disease in patients with Crohn's disease

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Introduction: Aging is described as the loss of function at a molecular and cellular level over time, which affects the organism as a whole. The prevalence of disorders such as cancer or cardiac diseases increase with age. Aging however, has little effect on the incidence of inflammatory bowel diseases (IBD), which are considered diseases of the young. IBD pathophysiology is influenced by various factors, with T cells playing a key role. This study aims to understand age-related changes occurring within T cell compartment in Crohn's disease (CD) patients.

Methods: We collected blood and tissue samples from patients with CD, age 19–80 years. Disease activity was assessed using Harvey-Bradshaw-Index (HBI < 5 was considered remission; HBI ≥ 5, active disease). Peripheral blood mononuclear cells (PBMCs) were evaluated for markers for T cell maturation and co-stimulatory molecules.

Results: Our results on PBMCs revealed age-related changes in CD4+ and CD8+ T cell maturation in patients with CD, while T cell numbers were comparable among young and elderly patients. More specifically, naïve T cells were significantly decreased in the elderly population (> 50 years old), mirrored by a significant increase in effector memory CD4+ T cells and terminally differentiated TEMRA CD8+ T cells. CD8+ T cells from patients with CD were especially affected by age, where accumulation of CD27-CD28- T cells was predominant in both blood and tissue biopsies. Interestingly, increased TEMRA and CD27-CD28-CD8+ T cells were specific to elderly patients (≥ 50 years old) with CD in remission compared to young ones. Furthermore, CD27-CD28-CD8+ T cells, but not CD4+ T cells, could be used describe major adverse outcomes in CD patients with disease in remission over a period of 18 months.

Discussion/Conclusion: Overall, CD8+CD28- T cells might be relevant during disease progression in aged patients with CD. Understanding the functional role of these cells might help for development of targeted therapies for CD.

38. Protective effect of microbiota-derived short-chain fatty acids on vascular dysfunction in mice with systemic lupus erythematosus induced by Toll-like receptor 7 activation: Role of Th17 lymphocytes

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Introduction: Toll-like receptors (TLRs) are involved on the onset and progression of human and spontaneous mouse models of systemic lupus erythematosus (SLE). TLR7 activation causes vascular dysfunction in non-autoimmune controls mice and accelerates cardiovascular pathology in lupus-prone mice. Considering that short-chain fatty acids (SCFAs) inhibit immune and inflammatory pathways we aimed to determine if SCFAs, acetate and butyrate, prevent vascular dysfunction and blood pressure (BP) elevation in mice with SLE induced by TLR7 activation with imiquimod (IMQ).

Methods: Female BALB/c seven- to nine-week-old mice were randomly divided into 4 experimental groups: 1) an untreated control; 2) a group treated with IMQ; 3) an IMQ-treated group supplemented with magnesium acetate (68 mM); or 4) IMQ-treated with sodium butyrate (40 mM) in the drinking water. IMQ cream (1.25 mg of 5%) was administered through topical application for 8 weeks.

Results: Both SCFAs treatments prevented the development of hypertension and cardiac hypertrophy, improved the aortic relaxation induced by acetylcholine and the vascular oxidative stress. Acetate and butyrate treatments improved colonic integrity, endotoxemia, and decreased helper T (Th)17 proportion in mesenteric lymph nodes (MLNs), blood, and aorta in mice with SLE induced by IMQ. The changes in MLNs were associated with increased mRNA levels of GPR43 in acetate-treated mice and with increased GPR41/43 and lower histone deacetylase (HDAC)-3 in butyrate-treated mice. However, disease activity (splenomegaly, hepatomegaly, and anti-ds-DNA) was unaffected by both SCFAs. T cell priming and Th17 differentiation in MLNs and increased Th17 infiltration was linked to aortic endothelial dysfunction and hypertension after inoculation of faecal microbiota from IMQ-treated mice to GF mice. All these effects were abolished in GF mice by acetate or butyrate treatment.

Discussion/Conclusion: In conclusion, these findings support that SCFAs con-sumption prevented the development of hypertension by rebalancing of dysfunctional gut-immune system-vascular wall axis in SLE induced by TLR7 activation.

39. Advanced architectural changes of the intestinal epithelium are more frequent in children with UC

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Introduction: Ulcerative colitis (UC) is a chronic intestinal multifactoral disorder of large intestine. It is characterized by a widespread inflammation of the mucous membrane located in the rectum and sigmoid colon at the initial stage, then covers the whole colon. It has been observed the development of ulcers and microabscesses in the crypts that later has been replaced by connective tissue leading to stenosis of occupied segments in advanced cases.

The aim of this study was to evaluate the association of structural changes in colorectal epithelium in ulcerative colitis with the age of patients.

Methods: The study consisted of 52 patients with ulcerative colitis (33 adults and 19 children). Endoscopic materials were taken from archival paraffin-embedded tissue. Sections were stained with H&E and subjected to routine histological evaluation. According to Geboes classification, an analysis of the severity changes (architectural changes, the assessment of crypt destruction, erosions and ulcers) was performed depending on the patients' age.

Results: The location of the disease correlated negatively with age of the patients ($p < 0.04$). In children, the inflammation is most common in the whole intestine (48%), then in the rectum (28%) and sigmoid colon (24%). Conversely, adult patients with UC had the highest percentage of disease situated on the sigmoid colon (53.3%) lower in the rectum (31.1%), and the whole large intestine (15.6%) ($p = 0.040$).

Histopathological analysis demonstrated a small, moderate and severe diffuse or multifocal architectural disorders in 10, 17, 24 patients, respectively. It was observed that this parameter correlated with the patients' age ($p = 0.008$) too. The degree of structural damage of the intestinal epithelium decreased with the age of the patients.

We didn't find a correlation between age and existance of erosions and ulcers. But correlation between age and assesment of crypt destruction was on a borderline signification ($p = 0.57$) Also an advanced crypt destruction was associated with younger age.

Discussion/Conclusion: Ulcerative colitis occurs in both children and adults but it seems that the disease process involves much more advanced lesions and causes more structural destruction of the intestinal epithelium in the young patients.

40. Intestinal anti-inflammatory effects of Salvia verbenaca extract in the TNBS model of rat colitis

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Introduction: Nowadays, there is an increasing interest in complementary medicine, including herbal remedies, in the treatment of inflammatory bowel diseases. The aim of this study was to evaluate the intestinal anti-inflammatory properties of a hydroalcoholic extract of Salvia verbenaca in the trinitrobenzenesulphonic acid (TNBS) model of rat colitis, a well characterized model with some resemblance to human IBD.

Methods: Female Wistar rats were assigned to four groups: non-colitic, control colitic and colitic treated groups with S. verbenaca extract (10 and 25 mg/kg/day) or dexamethasone (1.2 mg/kg/day), starting the same day of TNBS colitis induction. Rats were sacrificed one week after. Colonic damage was assessed macroscopically and biochemically. Several markers of pro-inflammatory status and intestinal epithelial integrity were evaluated by qPCR. In vitro immunomodulatory properties of different concentrations (0.1–100 Qg/ml) of S. verbenaca extract were determined in LPS-stimulated CMT-93 cells by evaluating the production and/or expression of different cytokines involved in the intestinal inflammation.

Results: S. verbenaca showed an intestinal anti-inflammatory effect, as evidenced by reduced colonic damage and weight/length ratio. The extract also decreased colonic myeloperoxidase activity and increased glutathione content. S. verbenaca extract reduced the colonic expression of the pro-inflammatory cytokines IL-1β, IL-6, IL-12a and IL-23 and the adhesion molecule ICAM-1, as well as of the chemokine MCP-1. S. verbenaca extract was also able to significantly up-regulate the expression of the markers of intestine epithelial integrity: villin and the mucin MUC-2 and MUC-3. Moreover, it displayed immunomodulatory properties in vitro since it decreased Il-6 and TNF-a production and expression in LPS-stimulated epithelial cells.

Discussion/Conclusion: Salvia verbenaca extract showed intestinal anti-inflammatory activity in the TNBS-induced colitis. This beneficial effect can be related to its antioxidant prop-

erties and the downregulation of the immune response, which can improve the intestine epithelial barrier.

41.IBD diagnosis and geographical clustering

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Introduction: The aetiology of Inflammatory bowel disease (IBD) is not fully understood. Genetic predisposition & the role of the gut microbiome are predominant research. Geographical clustering has not been well studied & might indicate novel environmental triggers to predisposition & disease course.

We aimed to review a well-defined population of patients, with IBD, within Newcastle-upon-Tyne to determine if there was geographical clustering.

Methods: We identified a cohort of patients with IBD, who lived in NE1-NE7 since their diagnosis. Patients responded with their place of residence at birth, onset of symptoms and time of diagnosis. The study received full ethical approval. Data was collected over 3.5 years.

K-Functional analysis and disease mapping were applied to investigate the distribution of IBD. This determined whether IBD patients were clustered and whether specific areas had an elevated risk of IBD, and if particular factors influenced that risk.

Results: The regional population was 244,665. 270 cases of IBD within NE1–NE7; 107 CD, 153 UC, 10 IBD-U. There was a difference in the mean age of diagnosis between the 3 groups: CD 32 years, UC 44 years, IBD-U 40 years. There was no difference in the Index of Multiple Deprivation status between cases of CD and UC at the time of diagnosis, no clustering of cases of IBD, CD or UC, at the point of diagnosis. The risk of an individual in the population having IBD was elevated in NE7 & lowest in NE1,2 and 3. The risk for UC was similar to that for IBD as a whole, whilst for CD was similar across the 7 post codes.

Discussion/Conclusion: Clustering of cases was not found. There was a suggestion that there is spatial variation in the risk of IBD within urban and suburban postcodes in Newcastle-upon-Tyne. The risk of CD was less variable in comparison to UC.

42. First in human trial of IMU-856, an orally available regulator of barrier function and regeneration for the treatment of celiac disease

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Introduction: IMU-856 is an orally available and systemically acting small molecule modulator that targets a transcriptional regulator of intestinal barrier function and regeneration of bowel epithelium. In preclinical studies, IMU-856 has been shown to avoid suppression of immune cells. IMU-856's mechanism of action could therefore present a new approach to treat celiac disease and other intestinal barrier function associated diseases without the serious consequences associated with many immunosuppressive therapies.

The objectives of this phase 1/1b trial are to determine the safety, tolerability, and pharmacokinetics of IMU-856 in healthy volunteers and celiac disease patients, and to obtain proof of concept data.

Methods: This is a first-in-human, double-blind, randomized, placebo-controlled trial of IMU-856 in healthy volunteers and patients with celiac disease. In the phase 1 trial, healthy volunteers received single and multiple ascending doses of IMU-856 or placebo to assess safety, tolerability, and pharmacokinetics. In the phase 1b trial, two different doses of IMU-856 were tested in patients with well-controlled celiac disease during a 15-day gluten challenge to measure disease biomarkers and symptoms.

Results: IMU-856 was safe and well-tolerated with a benign adverse event profile and pharmacokinetics that allow once-daily dosing. There were no systematic clinically relevant findings relative to safety and tolerability, as assessed by physical examination, clinical laboratory tests, vital signs, and 12-lead electrocardiograms. Ongoing phase 1b provided proof of concept data for IMU-856 in patients with well-controlled celiac disease during periods of gluten-free diet and gluten challenge.

Discussion/Conclusion: IMU-856 was safe, well-tolerated and may offer extensive potential for the treatment of celiac disease as well as other diseases (intestinal and systemic) with compromised intestinal barrier function.

43. Considerations for peripheral blood transport and storage during large-scale multicentre metabolome research

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Introduction: Large-scale, multicentre, longitudinal studies are key to understanding complex relationships between the metabolome and digestive diseases, providing appropriate sample collection and processing. Stabilisation of metabolites from blood requires freezing that may be confounded by transport and storage variables. Gold standard immediate sample separation and freezing must be balanced with pragmatic research design.

Methods: We collected whole blood in lithium heparin tubes from five non-fasting adults. Ten conditions were tested to model varying storage times of whole blood and plasma at 4°C, and long-term storage of plasma at -20°C or -80°C. We performed metabolomics using reversed-phase chromatography (RPC) liquid chromatography–mass spectrometry (LC-MS) and nuclear magnetic resonance (NMR) spectroscopy. Raw data were preprocessed and quality assessed to generate global profiling datasets and targeted extraction of predefined metabolite panels. Analyses were performed in MetaboAnalyst V.5.0 and R. 'Adonis' was used to test the impact of each technical variable on multivariate metabolomic profiles using false discovery rate adjusted p-values (1000 permutations). For single metabolites, p-values are based on KruskalWallis with Fishers least significant difference post-hoc test.

Results: LC-MS profiles clustered by subject (all $p = 0.002$), irrespective of storage time/temperature. Analysis of whole blood storage time found all LC-MS metabolites were stable except for lysophosphatidylserine (18:0/0:0) and lysophosphatidic acid (22:6/0:0) (both $p < 0.001$), which were more abundant at 72 h. Interindividual differences were maintained up to 72hr at 4°C. No single LC-MS metabolite was linked to plasma storage time/temperature.

Small molecule NMR metabolite profiles clustered by subject ($p < 0.001$) but also by storage time/temperature ($p = 0.001$). Further analysis showed lactic acid was significantly higher after 24 h and 72 h at 4°C ($p < 0.001$). Following removal of lactic acid NMR signals, this association with storage time/temperature was no longer statistically significant.

Discussion/Conclusion: Our data provide reassurance regarding variations in blood sample handling and storage. These results form a basis for designing multi-centre metabolomic biomarker studies.

44. The impact of nutrition on gut-brain inflammation

Victor Zevallos (Newcastle upon Tyne, GB), Nir Yogev (Cologne, DE), Luisa Klotz (Muenster, DE), Ari Waisman (Mainz, DE), Detlef Schuppan (Mainz, DE)

Introduction: The link between consumption of dietary proteins and activation of the immune system has been clearly observed in conditions such as coeliac disease, wheat allergy and recently in non-coeliac wheat sensitivity. Gluten peptides can trigger an intestinal Th1 T cell response, leading to small intestinal villous atrophy and a wide range of associated comorbidities. Furthermore, non-gluten proteins, particularly amylase trypsin inhibitors (ATI), can stimulate the innate immune system via activation of the Toll-like receptor 4 (TLR4) on myeloid cells. Here, we explored the effects of dietary wheat proteins on gut-brain inflammation.

Methods: We conducted feeding trials using the experimental autoimmune encephalitis (EAE), a preclinical model of multiple sclerosis (MS). EAE was induced in C57BL/6J mice on standardised dietary regimes with defined content of gluten/ATI. Mice received a gluten and ATI-free diet with defined carbohydrate and protein (casein/zein) content, supplemented with gluten and/or ATI. The effect of dietary ATI on clinical EAE severity, on intestinal, mesenteric lymph node, splenic and CNS subsets of myeloid cells and lymphocytes was analysed. Furthermore, we compared the inflammatory effects of wheat proteins on peripheral blood mononuclear cells from MS patients and healthy controls, confirming transferability to patients.

Results: Dietary ATI dose-dependently caused significantly higher EAE clinical scores compared to mice on other dietary regimes, including on gluten alone. This was mediated by increased numbers and activation of proinflammatory intestinal, lymph node, splenic and CNS myeloid cells, and of CNS-infiltrating encephalitogenic T-lymphocytes. Expectedly, ATI activated peripheral blood monocytes from both MS patients and healthy controls.

Discussion/Conclusion: Dietary wheat ATI activate murine and human myeloid cells. The amount of ATI present in an average human wheat-based diet caused mild intestinal inflammation, which was propagated to extraintestinal sites, leading to exacerbation of CNS inflammation, and worsening of clinical symptoms in EAE. These results support the importance of the gut brain axis in inflammatory CNS disease.

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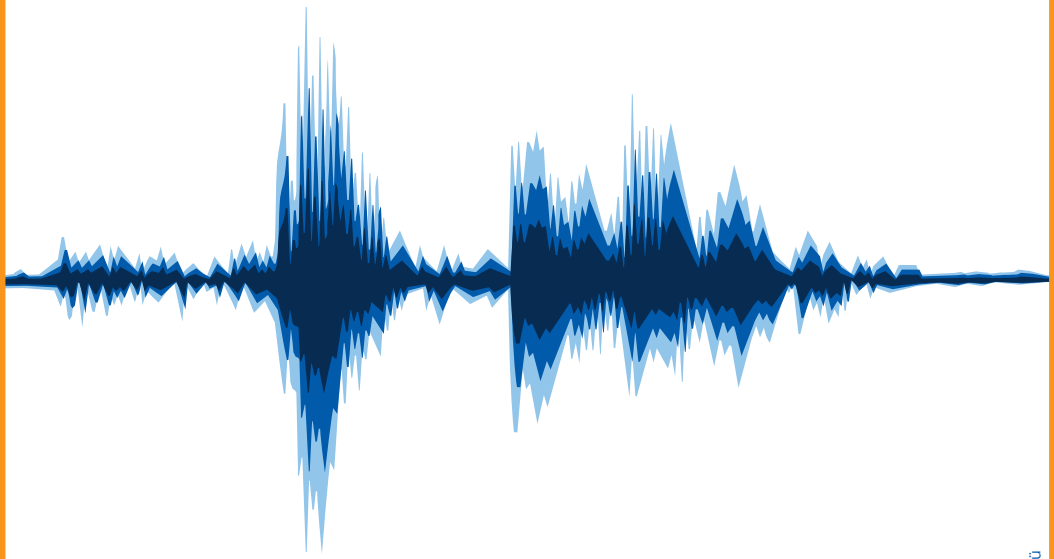

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