MUCOSAL IMMUNOLOGY DAYS

July 10–12, 2025

Symposium 241
OXFORD, UNITED KINGDOM

APPLICATION FOR CME CREDITS SUBMITTED

An application has been made to the UEMS EACCME® for CME accreditation of this event. The number of credits awarded will be printed in the final program.

PREFACE

We are pleased to welcome you to this unique symposium, where we bring together scientists and clinician scientist to collaboratively explore the mucosal immunology of inflammatory bowel disease (IBD) through the structured framework of the Montreal Classification. This classification, based on age at diagnosis, disease location, and disease behaviour (inflammatory, stricturing, or fistulating), has long served as the foundational system for characterizing IBD in both research and clinical practice.

Throughout this meeting, we aim to delve deeply into the biological and clinical relevance of each component of the Montreal Classification. Special emphasis will be placed on understanding the immunological underpinnings that give rise to the different phenotypes of IBD seen in patients. By integrating perspectives from basic and translational science as well as clinical medicine, we hope to advance our collective understanding of IBD heterogeneity.

The symposium will culminate in a forward-looking discussion on the future of IBD classification. With emerging insights in mucosal immunology, large data sets, and disease courses, we will consider how the next iteration of disease classification might evolve to better reflect underlying disease biology and improve patient care.

We thank all participants for contributing to this important dialogue and look forward to a productive and inspiring meeting.

Oliver Brain, Ailsa Hart, James Lee, Britta Siegmund

MUCOSAL IMMUNOLOGY DAYS

July 10-12, 2025

Scientific Organization:
Oliver Brain, Oxford (UK)
Ailsa Hart, London (UK)
James Lee, London (UK)
Britta Siegmund, Berlin (DE)

Congress Venue:
Examination Schools
81 High street
Oxford, OX1 4AS
United Kingdom

For admission to scientific events your name badge should be clearly visible.

Accompanying persons are not permitted during the conference at any time.

Start of Registration:
Thursday, July 10, 2025
12:30 h
at the congress office

Start of ePoster Session:
Thursday, July 10, 2025
12:30 h

THURSDAY, JULY 10, 2025

13:00	Networking Lunch
13:45	Welcome
14:00	Setting the scene: What scientists, clinicians and patients want to know about mucosal immunology *Ailsa Hart, London; Britta Siegmund, Berlin*

SESSION I

Are we closer to a biological classification of IBD?
In the first session, we will explore the potential for a biological classification for inflammatory bowel disease. We will consider the contribution of animal models and other model systems, such as organoids, to inform us about disease pathogenesis with relevance to human disease and classification.

Chairs	*Ailsa Hart, London; Britta Siegmund, Berlin*
14:15	Keynote lecture: The 2030 (and beyond) vision for IBD: Basic science perspective *Fiona Powrie, Oxford*
14:45	Are we aiming for a biological classification for IBD? *Matthieu Allez, Montreal*
15:05	How do animal models reflect disease phenotype and IBD classification? *Christoph Becker, Erlangen*
15:25	How do other model systems (e.g. organoids, assembloids) contribute? *Laween Meran, London*
15:45	**Panel discussion**
16:00	**Coffee break with ePoster session**

SESSION II

Age at diagnosis

In this session, we will explore the relevance of age in mucosal immunology and microbiology, and its role in disease classification. We will learn about the very early onset IBD patients and how they inform us about disease pathogenesis, and how disease later in life changes with regards to its presentation and management strategies (benefits and risks of therapies) underpinned by changes in mucosal immunology.

Chairs	*Oliver Brain, Oxford; Carl Weidinger, Berlin*
16:30	Monogenic IBD in children and adults *Holm Uhlig, Oxford*
16:50	How does our immune system change with aging? *Eoin McKinney, Cambridge*
17:10	What is the impact of age on IBD presentation and management? *Sree Subramanian, Cambridge*

SESSION III

Poster pitches

Chairs	*Hannah Gordon, Oxford; James Lee, London*
17:30	10 poster pitches (each 3' pitch plus 2' discussion)
18:30	**Welcome dinner with light refreshments**

FRIDAY, JULY 11, 2025

SESSION IV

Disease Location
In this session, we will explore the contribution of mucosal immunology and microbiology to explaining how disease affects different locations e.g. rectum, colon, small bowel, oral disease etc.

Chairs	*Ailsa Hart, London; Eoin McKinney, Cambridge*
09:00	Why does disease affect different parts of the GI tract? A historical perspective. *Derek Jewell, Oxford*
	Potential major culprits:
09:30	Microbiome *Dirk Haller, Freising*
09:40	Vasculature and lymphatics *Gwendalyn J. Randolph, Saint Louis*
09:50	Immunology *Christopher Lamb, Newcastle upon Tyne*
10:00	Innervation *Fränze Progatzky, Oxford*
10:10	Mesentery *Calvin Coffey, Limerick*
10:20	**Panel discussion**
10:50	**Coffee break with ePoster session**

SESSION V

Disease Behaviour

In this session, we will explore the contribution of mucosal immunology and microbiology to explaining how disease processes occur e.g. inflammatory versus stricturing versus fistulating phenotypes of disease. We will examine whether different processes need different therapeutic targets.

Chairs	*Raja Atreya, Erlangen; Simon Travis, Oxford*
11:20	Inflammatory disease: Role of diet *Timon Adolph, Innsbruck*
11:40	Stricturing disease: A different phenotype or a consequence of inflammation? *Florian Rieder, Cleveland*
12:00	Fistulising disease: A different phenotype? *Nicolas Powell, London*
12:20	**Panel discussion**
12:40	**Lunch break with ePoster session**

FRIDAY, JULY 11, 2025

SESSION VI

Extreme phenotype/ refractory disease
In this session, we will explore the immunologic drivers of refractory disease and consider therapeutic strategies for this group of patients.

Chairs	*Dermot McGovern, Los Angeles; Holm Uhlig, Oxford*
14:00	Keynote lecture: The approach to extreme phenotype of IBD *Carl Weidinger, Berlin*
14:30	Molecular biomarkers as a potential tool for identifying patients with refractory IBD? *Aamir Saifuddin, London*
14:45	Characterization of the immunophenotype of refractory IBD *Raja Atreya, Erlangen*
15:00	Histo-molecular stratification of patients with extreme IBD phenotypes *Matthias Friedrich, Oxford*
15:15	**Panel discussion**
15:35	**Coffee break with ePoster session**

SESSION VII

Poster pitches

Chairs	*Lea-Maxie Haag, Berlin; Dirk Haller, Freising*
16:10	*10 poster pitches (each 3' pitch plus 2' discussion)*

SESSION VIII

Extraintestinal manifestations (EIM)
In this session, we will explore the immunologic and microbiologic drivers of extra-intestinal manifestations of IBD

Chairs	*Florian Rieder, Cleveland; Aamir Saifuddin, London*
17:15	Comprehensive association analyses of EIM: Consequences *Hannah Gordon, Oxford*
17:35	Urgency: Role of inflammation and other mechanisms *Noa Krugliak Cleveland, Chicago*
17:55	Fatigue: Role of inflammation and other pathways *Calum Moulton, London*
18:15	Smarter ways to consider gut and joint inflammation in IBD *Christopher Buckley, Oxford*
18:35	**Presentation of Poster Awards**
18:50	**Scientific networking with flying buffet**

SATURDAY, JULY 12, 2025

SESSION IX

Inflammation to cancer pathway in IBD
In this session, we will explore the inflammation to cancer pathway in IBD – What are the similarities and differences in developing cancer in IBD patients? How can we harness this in prompt diagnosis and improved therapies?

Chairs	*Oliver Brain, Oxford; James Lee, London*
09:00	What are the molecules involved in inflammation and cancer? *Ahmed Hegazy, Berlin*
09:25	Wnt mutation selection in colitis versus sporadic neoplasia: What, When and Why? *Simon Leedham, Oxford*
09:50	Colonic inflammation and dysplasia in PSC: Chicken or egg? *Emma Culver, Oxford*
10:15	Clinical translation: Prediction of colorectal cancer in IBD *Ibrahim Al Bakir, London*
10:40	**Panel discussion**
11:00	**Coffee break with ePoster session**

SESSION X

Future Challenges

Chairs	*Ailsa Hart, London; Britta Siegmund, Berlin*
11:30	Genetics *James Lee, London*
11:50	Epigenetics *Jack Satsangi, Oxford*
12:10	A new classification *Dermot McGovern, Los Angeles*
12:30	Closing remarks
12:45	Closing discussion with lunch

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 241	EUR 300
Students (copy of student ID required)	EUR 150

The congress fees include:
- Refreshments during coffee breaks
- Lunch on Thursday, July 10, Friday, July 11 & Saturday, July 12, 2025
- Welcome dinner on Thursday, July 10, 2025
- Snacks during networking on Friday, July 11, 2025
- A copy of the final program

CONGRESS OFFICE AND REGISTRATION

Opening Hours:

Thursday, July 10, 2025	12.30 – 18:30 h
Friday, July 11, 2025	8:00 – 18:30 h
Saturday, July 12, 2025	8:00 – 12:45 h

The Falk Foundation will take pictures during the meeting. Additionally, parts of the meeting might be recorded. By participating all attendees consent and agree with the recording and the photo shoots.

ARRIVAL

Examination Schools
81 High street
Oxford, OX1 4AS
United Kingdom

By car
There is no car parking on site, alternatively car parks are available across the city. The nearest one is St Clements.

By plane
Please take London Heathrow as arrival airport as it's the closest one to Oxford. From there the bus to Oxford takes 1 hour and runs every 20 minutes daily. For further information see www.theairlineoxford.co.uk/timetables/

By bus
The nearest bus stop and airport bus stops are on High Street just outside the Examination Schools (Queen's Lane stop).

By train
Oxford railway station is approximately a 20 minutes walk away or 10 minutes by taxi.

CONFLICTS OF INTEREST

The members of the scientific committe declare the following potential conflicts of interest:
Oliver Brain: Takeda, Abbvie, Bres, Alfasigma, Galapagos, Pfizer
Ailsa Hart: Abbvie, Johnson & Johnson, Takeda, Pfizer, Alfasigma, Roche, Celltrion
James Lee: Pasithea, GSK, MSD, Johnson & Johnson, C4X Discovery, AGplus diagnostics, PredictImmune, Abbvie
Britta Siegmund: Abbvie, Abivax, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Endpoint Health, Galapagos, Gilead, Janssen, Landos, Materia Prima, PredictImmune, Pfizer, Takeda, AlfaSigma, CED Service GmbH, MSD, Ferring

POSTER ABSTRACTS

1. Multiomic profiling reveals clinically distinct subtypes of perianal fistulizing Crohn's disease, including a novel psoriasis-like keratinizing phenotype amenable to repair
   S. Abdurahiman, J. Sabino, S. Verstockt, M. Ferrante, M. Lenfant, J. Raes, A. D'Hoore, S. Vermeire, G. Bislenghi, B. Verstockt (Leuven, BE)

2. Serum anti-TNF levels correlate with tissue levels in perianal fistulising Crohn's disease
   S. Anandabaskaran, Z. Liu, L. Hanna, A. Hart, P. Tozer (Sydney, AU; London, GB)

3. Epithelial OPA1 links mitochondrial fusion to inflammatory bowel disease
   L. Bao (Erlangen, DE)

4. Pro-inflammatory secretome from intestinal epithelium recruits regulatory T cells for barrier defence
   L. Barleben, B. Uyar, E. Kabrani, T. Vasilakis, A. Bruneau, A. Arnold, P. Gebert, S. Sai, M. Sander, L. Hammerich, T. Conrad, A. Gerard, C. Jochum, A. Akalin, F. Tacke, M. Di Virgilio, M. Kolesnichenko (Berlin, DE; Oxford, GB)

5. Assessment of macrophage types in the intestinal tissue of treatment naïve inflammatory bowel disease patients in relation to their disease and activation of the CCL2/CCR2 pathway
   J. Begum, A. Fatima, P. Rimmer, T. Iqbal, N. Sharma, V. Stoica, M. Owusu, I. Lelios, H. McGettrick, A. Iqbal, R. Welford (Birmingham, GB; Basel, CH)

6. Elderly onset inflammatory bowel disease in Singapore: Increased risk of steroid exposure
   T. Chin Kimg, Y. Tan, T. Tey, Z. Yan, Z. Koh, J. Ong, T. Ang, M. Tan, S. Ennaliza, C. Lim, S. Tay, W. Chan (Singapore, SG)

7. TIFA renders intestinal epithelial cells responsive to microbial ADP-heptose and drives colonic inflammation in mice
   L. Erkert (Erlangen, DE)

8. AIEC-dependent pathogenic Th17 cell transdifferentiation in Crohn's disease is suppressed by rfaP and ybaT deletion
   F. Facciotti, G. Leccese, M. Chiara, I. Dusetti, D. Noviello, E. Billard, F. Caprioli, M. Paroni (Milan, IT; Clermont-Ferrand, FR)

9. Voclosporin and colitis: A novel approach for inflammatory bowel disease therapy?
   M. Gabel, A. Knauss, B. Weigmann (Erlangen, DE)

10. Influence of anatomical location, genetic susceptibility, and microbiota on T-cell-mediated intestinal inflammation
    R. Gamez Belmonte (Erlangen, DE)

11. NFATc3: A driver of Treg mediated suppression of colitis
    K. Gerlach, B. Weigmann (Erlangen, DE)

12. Insults to barrier function accelerates disease progression in a novel mouse model of spontaneous colitis
    R. Giri, A. Amiss, S. Hasnain, T. Florin, M. Gala, J. Begun (Brisbane, Boston, AU)

13. Integrated multi-model analysis of intestinal inflammation exposes key molecular features of preclinical and clinical IBD
    M. Gonzalez Acera, J. Patankar, L. Erkert, R. Cineus, R. Gamez-Belmonte, T. Leupold, M. Bubeck, L. Bao, M. Dinkel, R. Wang, L. Schickendanz, H. Limberger, I. Stolzer, K. Gerlach, L. Diemand, F. Mascia, P. Gupta, E. Naschberger, K. Koop, C. Plattner, G. Sturm, B. Weigmann, C. Guenther, S. Wirtz, M. Stuerzl, K. Hildner, A. Kuehl, B. Siegmund, A. Giessl, R. Atreya, A. Hegazy, Z. Trajanoski, M. Neurath, C. Becker (Erlangen, Berlin, DE; Innsbruck, AT)

14. IL-36 signaling as a drug target in Crohn's disease patients with IL36RN mutations
    J. Hecker, C. Plattner, C. Cancino, B. Loescher, J. Saurenbach, M. Letizia, D. Rieder, I. Freise, K. Koop, C. Neufert, D. Kunkel, A. Schuetz, C. Becker, R. Atreya, Z. Trajanoski, A. Franke, E. Sonnenberg, A. Hegazy, B. Siegmund, C. Weidinger (Berlin, Kiel, Erlangen, DE; Innsbruck, AT)

15. Age-dependent decline of the UPR in the colonic epithelium: Implications for mucosal integrity and chronic inflammation
T. Illankoon, K. Wong, A. Mueller, A. Amiss, J. Begun, L. Burr, S. Hasnain (Brisbane, AU)

16. TIM3 as a crucial regulator of immune and metabolic homeostasis in IBD: Potential for galectin 9 therapy?
A. Knauss, M. Gabel, B. Weigmann (Erlangen, DE)

17. Gene-environment interactions: The potential of altered diets to promote intestinal inflammation by dysregulating intestinal γδ T cells
V. Kohlhaas, Y. Nerdinger, C. Brown, P. Vantourout, A. Hayday (London, GB)

18. Linking genetic susceptibility to environmental risk – The role of the aryl hydrocarbon receptor in IBD
A. Kunkel, N. Diny, C. Stankey, C. Bourges, B. Stockinger, J. Lee (London, GB; Bonn, DE)

19. Investigating the mechanical properties of immune cells to gain deeper insights into colitis progression
I. Larafa, N. Strohlein, O. Thoma, C. Schweitzer, H. Grapp, K. Koop, M. Neurath, J. Guck, M. Waldner (Erlangen, DE)

20. Modelling barrier dysfunction in inflammatory bowel disease using a novel immunocompetent in vitro epithelial monolayer system
I. Larafa, O. Thoma, C. Gunther, S. Wirtz, M. Neurath, M. Waldner (Erlangen, DE)

21. GPR15L counteracts chronic colitis by shaping the intestinal microbiota
M. Leggio, S. Schramm, B. Ocon, S. Wirtz, F. Puertolas Balint, L. Dietz, B. Schroeder, E. Butcher, T. Mueller, M. Neurath, S. Zundler (Erlangen, DE; Stanford, US; Umeå, SE)

22. The role of SOX10 in adult enteric glial cells and intestinal inflammation
H. Limberger (Erlangen, DE)

23. The role of Fosl2 in intestinal epithelial inflammation and homeostasis
J. Lin (Erlangen, DE)

24. An autoimmune gut pathobiont translocates silently across the intestinal epithelial barrier
U. Loeschberger, J. Moleon Moya, H. Fuhrmann, M. Santos Pereira, S. Redanz, M. Kriegel, V. Plaza Álvarez (Muenster, DE)

25. SLP-76 as a potential inflammatory driver in IBD and a target of the calcineurin inhibitor voclosporin
L. Loges (Erlangen, DE)

26. Mevalonate pathway, a novel player for intestinal epithelial barrier function
R. Lopez Posadas, R. Pradhan, P. Schreier, P. Ngo, L. Becker, M. Dedden, S. Zundler, R. Atreya, A. Waisman, M. Neurath, I. Atreya; The IBDdome Consortium (Erlangen, Mainz, DE)

27. Aryl hydrocarbon receptor signalling in intestinal T cell residency
J. McGuire, J. Lindsay, A. Stagg (London, GB)

28. Paneth cells regulate intestinal lymphangiogenesis and lipid metabolism in metabolic dysfunction-associated steatotic liver disease
S. Moghadamrad (Bellinzona, CH)

29. A humanized murine model to identify translocating microbiota from autoimmune patients
J. Moleon-Moya, S. Redanz, C. Brune, U. Loeschberger, M. Pereira, H. Fuhrmann, A. Brinkhege, C. Diemer, N. Becker, A. Bredeck, M. Kriegel (Muenster, DE)

30. A unique case series on collagenous gastritis in young adults: From symptom onset to treatment outcome
S. Nario, R. Aghajani, K. De Silva, A. Malcolm (St. Leonards, AU)

31. The Impact of disrupting the BTNL-γδ T cell axis, with implications for Crohn's disease
A. Natalini, R. Dart, N. Nishan, G. Adams, D. Freydina, R. Andres Ejarque, D. Berger, C. Brown, A. Hayday (London, GB)

32. Piezo1 regulates intestinal epithelial cell physiology but is dispensable for tissue homeostasis
P. Ngo, D. Boehringer, R. Pradhan, L. Becker, B. Dietel-Schor, B. Fabry, M. Neurath, R. Lopez Posadas (Erlangen, DE)

33. Delineating molecular and microbial signatures across disease severity in treatment naïve inflammatory bowel disease through single-cell transcriptomic and microbiome profiling
R. Peter, M. Leipner, A. Paun, J. Cheesbrough, S. Danilin, A. Klein, P. Scepanovic, N. Sharma, P. Trenkle, S. Tull, A. Iqbal, T. Iqbal, D. Regan-Komito (Birmingham, GB; Basel, CH)

34. A rare case of juvenile polyposis in a patient with ulcerative colitis
M. Prokopic, M. Schnierer, P. Lietava, M. Kalman, P. Banovcin (Martin, SK)

35. TNS3 protein expression in ulcerative colitis
A. Pryczynicz, W. Romanczyk, J. Lotowska, J. Dorf, K. Guzinska-Ustymowicz (Bialystok, PL)

36. Development of a high-throughput inflammation assay
I. Roegiers, L. Weidert, J. Thomas, S. Koigi, D. Dixit, T. Korcsmaros, D. Papp (London, GB; Esch-sur-Alzette, LU)

37. The local intestinal interstitial cytokine profile provides an insight into inflamed bionaive patients with ulcerative colitis
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38. More than just an antibody: How secretory IgA could revolutionize IBD treatment
C. Sachs, S. Schmitt, B. Weigmann (Erlangen, DE)

39. Comprehensive risk assessment and prognostic factors in celiac disease: Impact of persistent villous atrophy on disease complications and survival outcomes
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40. A rare case of CVID-like disease based on haploinsufficiency of NF-κB1, with associated enteropathy
M. Schnierer, M. Prokopic, P. Lietava, M. Jesenak, P. Banovcin (Martin, SK)

41. Cell signalling in colitis-associated colon cancer
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42. Dependence of interleukin 17 and 23 expression in patients with inflammatory bowel disease on nosology and severity
M. Stoikevych, T. Tarasova, O. Tatarchuk (Dnipro, UA)

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1. Multiomic profiling reveals clinically distinct subtypes of perianal fistulizing Crohn's disease, including a novel psoriasis-like keratinizing phenotype amenable to repair

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Introduction: Perianal fistulizing Crohn's disease (pCD) affects 20–30% of patients with Crohn's disease (CD), presenting substantial clinical challenges that necessitate integrated medical and surgical approaches. Despite advancements in treating luminal CD, pCD remains challenging to manage, highlighting the need for improved understanding of its molecular pathogenesis to identify novel therapeutic avenues.

Methods: Paired fistula tract and adjacent rectal mucosa biopsies were collected from 101 patients (83 pCD, 18 cryptoglandular) and underwent 16S rRNA and RNA sequencing. Multiomics Factor Analysis (MOFA) was used to integrate the datasets, followed by unsupervised hierarchical clustering for patient stratification. Findings were validated using publicly available single-cell RNA sequencing datasets. Identified signatures were further assessed in publicly available single-cell RNA sequencing (scRNA-seq) datasets.

Results: MOFA analysis indicated transcriptomics as the dominant factor, explaining more than 80% of the variance, whereas microbial influences were minimal. Unsupervised clustering revealed three distinct patient clusters (C1, C2, C3), independent of concurrent proctitis or diagnosis (CD vs cryptoglandular fistula). Cluster C3 exhibited strong keratinization signatures in fistula tracts with epithelial-mesenchymal transition (EMT) pathway being suppressed, contrasting with clusters C1 and C2, characterized by prominent EMT signatures in the fistula and devoid of fistula keratinization. Notably, rectal keratinization differentiated C2 (keratinization present) from C1 (absent). Notably, cluster C3 patients aligned significantly with the TOPCLASS 2a classification, indicating favorable candidacy for surgical and medical repair. The mutual exclusivity between keratinization and EMT signatures suggests distinct underlying mechanisms in fistula pathology. Comparative analyses using publicly available scRNA-seq data from psoriasis patients demonstrated striking similarity between pCD keratinization signatures and psoriatic lesions, indicating a psoriasis-like keratinization process in a subset of pCD patients. Microbial profiling showed no significant bacterial associations with any patient cluster (adjusted $p > 0.05$).

Discussion/Conclusion: Our findings delineate three molecularly distinct pCD subtypes, defined largely by psoriasis-like keratinization or EMT-driven pathways in fistula and rectal tissues. Notably, the keratinized subtype appears more amenable to surgical and medical repair, underscoring the clinical relevance of this molecular phenotype. Collectively, this stratification may guide precision medicine in pCD and provides novel insights to the underlying biological pathways, potentially shaping the development of novel therapies.

2. Serum anti-TNF levels correlate with tissue levels in perianal fistulising Crohn's disease

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Introduction: Perianal fistulising Crohn's Disease (PFCD) affects up to 25% of patients with CD and remains a difficult entity to manage despite medical and surgical advancements.1 Perianal fistulas have unique immunopathogenic features lead to an aggressive phenotype of CD with studies showing the need for higher drug levels for fistula healing in pCD.2-4 Unfortunately, no medical therapy has been

shown to be more than 40% effective in maintaining sustained remission with a suggestion of a therapeutic ceiling in PFCD management.5 This calls for a better understanding of the role tissue drug penetrance plays in PFCD patients on biologic therapy. Yarur et al.6 previously showed positive correlation between serum and tissue anti-TNF level in colonic samples using homogenous mobility shift assay (HMSA). However, Adegbola et al.4 failed to identify tissue levels in PFCD patients using Liquid chromatography-mass spectrometry (LC-MS) assay. Enzyme-linked immunosorbent assay (ELISA) is well validated and used in the standard clinical practice for anti-TNF drug level measurement in blood samples. Therefore, in this novel experiment we attempted to better understand tissue biologic drug penetrance in PFCD by quantifying rectal and fistula biologic levels in patients on established anti-TNF therapy using ELISA.

Methods: Paired blood along with paired rectal and fistula tract biopsies were collected from 15 patients undergoing examination under anaesthesia surgery for active pCD on established anti-TNF therapy (greater than 14 weeks since induction). Blood was spun down on a centrifuge within 12 hours of collection to serum and stored at -80°C. Tissue biopsies were immediately deposited in cryovials and snap-frozen with liquid nitrogen and transferred on dry ice then stored at −80°C until extraction. An ELISA extraction buffer was used based on tissue weight and the supernatants were extracted for anti-TNF measurement. Preliminary analysis identified serum anti-TNF levels via standard ELISA assay however failed to identify tissue anti-TNF levels across all samples. Therefore, a secondary high sensitivity analysis was performed using IDK monitor Infliximab and Adalimumab ELISA Drug Level kits (BIOHIT Healthcare Ltd). The majority of variables were measured on a continuous scale. Associations between these variables were examined using correlation methods. Where variables were found to be approximately normally distributed, Pearsons correlation was used for the analysis. For variables with outlying values, Spearman's correlation was preferred. Comparisons of the continuous variables between genders were made. Where variables were found to be approximately normally distributed, the unpaired t-test was used for the analysis. For variables with outlying values, the Mann-Whitney test was preferred.

Results: Patient demographics are displayed in table 1. Infliximab patients (n = 8 patients) The results suggested a statistically significant association between serum level and fistula level. The correlation was positive, suggesting that higher serum levels were associated with higher fistula levels. There was also slight evidence of an association between rectal level and age, and between fistula level and age. However, neither of these results quite reached statistical significance. The correlations were positive in direction suggested that both rectal and fistula levels increased with age. Adalimumab patients (n = 7 patients)

The analysis results suggested no statistically significant associations between any pair of variables. There were some reasonably large correlations, such as those between PDAI and each of serum level, fistula level and age. However, no results achieved, or were close to, statistical significance. Analysis showing there was a trend towards correlation of high symptom burden (PDAI score) with low serum, rectum, and fistula anti-TNF levels across both Infliximab and Adalimumab patients.

Discussion/Conclusion: This is a first-of-a-kind experiment to detect anti-TNF levels in PFCD patients on established biologic therapy. In this novel study, we were able to firstly show that patients with highly symptomatic disease tend to have lower tissue drug penetrance in rectum and fistula tract and secondly that serum anti-TNF levels correlate positively with tissue levels. There are limitations to this study including the small number of patients recruited and it is unclear how well a single biopsy represents the anti-TNF drug distribution across the entire rectum and fistula tract. However, this study further shows the importance of aiming for high anti-TNF levels in serum to ensure adequate tissue penetrance. Through our work here, we have also showed the potential significance of alternative treatment targets such as tissue anti-TNF levels especially in refractory inflammatory bowel disease phenotypes such as PFCD especially as we embark on an era of personalised, precision medicine.

3. Epithelial OPA1 links mitochondrial fusion to inflammatory bowel disease

Lili Bao (Erlangen, DE)

Introduction: Intestinal immune homeostasis relies on intestinal epithelial cells (IECs) to provide a dynamic gut barrier, but also to negotiate tolerance between the microbiome in the gut lumen and the mucosal immune system in the bowel wall. Dysregulation at the intestinal epithelial barrier is a driver of inflammatory bowel disease (IBD). However, the molecular mechanisms of barrier failure are not well understood.

Methods: A mouse model was generated and further characterised by crossing loxP-flanked Opa1 alleles (Opa1fl/fl) with B6.Cg-Tg(Vil1-cre/ERT2)23Syr/J (Villin-CreERT2) transgenic mice to study the effects of impaired mitochondrial fusion and reduced OPA1 expression in the intestinal epithelium and the association with intestinal barrier function.

Results: We demonstrate dysregulated mitochondrial fusion in IECs of patients with IBD and show that impaired fusion is sufficient to drive chronic intestinal inflammation. We found reduced expression of mitochondrial fusion-related genes, such as the dynamin-related GTPase Optic atrophy 1 (OPA1), and fragmented mitochondrial networks in crypt IECs of patients with IBD. Mice with Opa1 deficiency in the gut epithelium (Opa1idIEC) spontaneously developed chronic intestinal inflammation with mucosal ulcerations and immune cell infiltration. Intestinal inflammation in Opa1idIEC mice was driven by microbial translocation and associated with epithelial progenitor cell death and gut barrier dysfunction.

Opa1-deficient epithelial cells and human organoids exposed to a pharmacological OPA1 inhibitor showed disruption of the mitochondrial network with mitochondrial fragmentation and changes in mitochondrial size, ultrastructure, and function, resembling changes observed in patient samples. Pharmacological inhibition of the GTPase dynamin-1-like protein in organoids derived from Opa1idIEC mice partially reverted this phenotype.

Discussion/Conclusion: In summary, our data demonstrate a role for epithelial OPA1 in regulating intestinal immune homeostasis and epithelial barrier function. These results provide a mechanistic explanation for the observed mitochondrial dysfunction in IBD, and identify mitochondrial fusion as a novel pathway and a potential therapeutic target.

4. Pro-inflammatory secretome from intestinal epithelium recruits regulatory T cells for barrier defence

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Introduction: Resolution of inflammation, including of colitis, requires carefully coordinated communication between different tissues. While the role of immune cells in colitis is well established, less is known about epithelial communication to its microenvironment. Most secreted factors that comprise cellular communication are directly regulated by the transcription factor NF-κB. However, which transcriptomes NF-κB regulates in epithelium during colitis progression and whether these transcriptomes exacerbate or protect from colitis remains controversial.

Methods: Here we use colonic biopsies from patients with ulcerative colitis (UC) and novel mouse models that permit specific visualisation of NF-κB in all tissues. Single-cell RNA sequencing and secretome analysis were combined to define epithelial communication at different stages of murine colitis and UC.

Results: We demonstrated that paradoxically, the NF-κB-directed pro-inflammatory secretome from the intestinal epithelial cells (IEC) is essential for recovery and for deterrence of unrestrained inflammation. Mechanistically, IEC NF-κB recruits and reprograms tolerogenic regulatory T cells that mediate protection from colitis. In ulcerative colitis patients, IEC NF-κB is not uniformly activated, as previously believed, but rather switches on transcription of select pro-inflammatory genes with concomitant repression of targets regulating T cell recruitment.

Conclusion: Our findings map the dynamic changes of epithelial communication to mucosal leukocytes and identify a crucial protective mechanism initiated by IEC essential for resolution and recovery.

5. Assessment of macrophage types in the intestinal tissue of treatment naïve Inflammatory bowel disease patients in relation to their disease and activation of the CCL2/CCR2 pathway

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Introduction: Resident intestinal macrophages maintain gut homeostasis and exhibit a hypoactive tolerogenic phenotype. Recently, subsets of intestinal macrophages have been identified based on CD11c expression, differing in their inflammatory profiles. Pro-inflammatory CD11c+ monocyte-like macrophages are elevated in inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), and are recruited via the CCR2/CCL2 chemokine pathway. This study examines CCL2-driven blood monocyte migration and its role in shaping intestinal macrophage subsets in newly diagnosed patients.

Methods: Patients with suspected IBD were seen in an inception clinic. Intestinal biopsies and matched blood samples were collected from pre-treatment UC and CD patients during index colonoscopy. Those without inflammation formed a 'non-IBD' control group. Biopsies were cultured for conditioned media and digested for flow cytometry. CCL2 levels in intestinal secretome were measured via ELISA and Olink proteomics. Monocyte chemotaxis toward CCL2 was assessed with or without CCL2/CCR2 antagonists, and whole blood monocyte subsets were analysed using flow cytometry.

Results: We identified distinct CD11c+ and CD11c− macrophage populations in IBD tissue, with expansion of CD11c+ cells in inflamed regions expressing higher CCR2 and CX3CR1. The increase in tissue inflammatory macrophages correlated with increased circulating blood monocytes. Chemotaxis assays revealed enhanced CCL2-driven monocyte migration in IBD patients compared to controls, which could be blocked by antagonizing CCR2 or CCL2.

Discussion/Conclusion: Our data highlight the CCL2/CCR2 axis as a key driver of monocyte recruitment and differentiation into pro-inflammatory intestinal macrophages in IBD. Overall this underscores the significance of targeting the CCL2/CCR2 pathway and that it might be an important driver in the development IBD.

6. Elderly onset inflammatory bowel disease in Singapore: Increased risk of steroid exposure

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Introduction: Elderly onset inflammatory bowel disease (EOIBD) has variable characteristics in the published literature. This study aims to compare the treatment and clinical outcomes of between EOIBD and adult onset IBD (AOIBD).

Methods: This is a retrospective study involving IBD patients seen at three hospitals in Singapore from 2020 to 2023. Patients were identified from the Singapore National IBD registry. Those with missing data on age at IBD diagnosis were excluded. EOIBD is defined as age of diagnosis ≥ 60 years old and AOIBD as age of diagnosis from 18 to 59 years old. We performed 2:1 nearest neighbor propensity score matching (by gender, year of IBD diagnosis and type of IBD) of participants with AOIBD to EOIBD. The matched samples were analyzed using modified poisson regression with robust standard errors, linear regression, and Cox proportional hazards regression.

Results: A total of 1195 participants were identified after excluding those with missing date of IBD diagnosis, of which 10.8% were EOIBD (n = 130). 164 AOIBD patients were identified as suitable matches, and 128 with EOIBD patients had at least one suitable match. The median age at IBD diagnosis among adult-onset and elderly-onset participants were 41 (interquartile range [IQR], 33–51) and 67 years (IQR, 63–72.5), respectively. There was no evidence of an imbalance between groups for any of the matched

variables following propensity score matching. After accounting for differential follow-up time between the two groups, modified poisson regression with robust standard errors showed a higher risk of steroid exposure (risk ratio [RR] = 1.38, 95% CI: 1.07–1.80) and malignancy (RR = 2.39, 95% CI: 1.24–4.60) among EOIBD compared to AOIBD. There was higher rate of mortality among EOIBD compared to AOIBD (hazard ratio = 5.43, 95% CI: 1.74–16.93). There were no significant differences in terms of immunomodulator and biologics use between the two groups. there was a trend of higher rates of IBD-related hospitalization among EOIBD (RR = 1.34, 95% CI: 0.97–1.85).

Discussion/Conclusion: EOIBD is associated with increased risk of steroid exposure and malignancy. Judicious use of steroids and malignancy screening should be performed for EOIBD.

7. TIFA renders intestinal epithelial cells responsive to microbial ADP-heptose and drives colonic inflammation in mice

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Introduction: Intestinal immune homeostasis relies on intestinal epithelial cells (IECs), which provide an efficient barrier and maintain a state of tolerance between the microbiome and the mucosal immune system. Proper epithelial microbial sensing and handling are crucial to prevent excessive immunity, as seen in patients with inflammatory bowel disease (IBD). However, the molecular mechanisms underlying these processes remain incompletely understood.

Methods: TIFA expression was analyzed in crypt epithelial cells of both the large and small intestine, as well as in the inflamed intestines of mice and IBD patients. Additionally, the role of IL-22 signaling in regulating TIFA expression in IECs was investigated. Functional experiments assessed IEC responsiveness to the bacterial metabolite ADP-heptose and downstream inflammatory signaling pathways, including NF-κB and inflammasome activation, and chemokine production. A mouse model of experimental colitis was used to evaluate the impact of TIFA deficiency on intestinal inflammation.

Results: TIFA was constitutively expressed in crypt epithelial cells of both the large and small intestine and was highly induced in the inflamed intestine of mice and IBD patients. IL-22 signaling via STAT3 was identified as a key mechanism driving TIFA expression in IECs. Functionally, TIFA was essential for IEC responsiveness to ADP-heptose. ADP-heptose-induced TIFA signaling triggered an inflammatory response in the epithelium, characterized by NF-κB and inflammasome activation, as well as increased chemokine production. Mice lacking TIFA were protected from intestinal inflammation in an experimental colitis model.

Discussion/Conclusion: This study provides evidence that TIFA plays a critical role in intestinal inflammation and mediates epithelial inflammatory responses to bacterial metabolites. Targeting TIFA signaling may be a potential therapeutic strategy for the treatment of IBD.

8. AIEC-dependent pathogenic Th17 cell transdifferentiation in Crohn's disease is suppressed by rfaP and ybaT deletion

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Introduction: Mucosal enrichment of the adherent-invasive E. coli (AIEC) pathotype and the expansion of pathogenic IFNγ-producing Th17 (pTh17) cells have been linked to Crohn's disease (CD) pathogenesis. However, the molecular pathways underlying the AIEC-dependent pTh17 cell transdifferentiation in CD patients remain elusive.

Methods: We created and functionally screened a transposon AIEC mutant library of 10.058 mutants to identify the virulence determinants directly implicated in triggering IL-23 production and pTh17 cell generation. pTh17 cell transdifferentiation was assessed in functional assays by co-culturing AIEC-infected human dendritic cells (DCs) with autologous conventional Th17 (cTh17) cells isolated from blood of healthy donors (HD) or CD patients.

Results: AIEC triggered IL-23 hypersecretion and transdifferentiation of cTh17 into pTh17 cells selectively through the interaction with CD-derived DCs. Moreover, the chronic release of IL-23 by AIEC-colonized DCs required a continuous IL-23 neutralization to significantly reduce the AIEC- dependent pTh17 cell differentiation. The multi-step screenings of the AIEC mutant's library revealed that deletion of ybaT or rfaP efficiently hinder the IL-23 hypersecretion and hampered the AIEC-dependent skewing of protective cTh17 into pathogenic IFNγ-producing pTh17 cells.

Discussion/Conclusion: Overall, our findings indicate that ybaT (inner membrane transport protein) and rfaP (LPS-core heptose kinase) represent novel and attractive candidate targets to prevent chronic intestinal inflammation in CD.

9. Voclosporin and colitis: A novel approach for inflammatory bowel disease therapy?

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Introduction: The treatment of inflammatory bowel disease (IBD) remains a challenge. Voclosporin, a novel calcineurin inhibitor originally developed for lupus nephritis, has recently shown potential as a therapeutic option for IBD in preliminary studies. This study aims to investigate the therapeutic effects of voclosporin in experimental colitis models and analyze its intracellular signaling pathways. Given the structural similarity between voclosporin and cyclosporine A we seek to further explore the efficacy, advantages, and molecular mechanisms of voclosporin in the context of IBD.

Methods: We conducted in vivo analyses to assess hapten-induced oxazolone colitis using mini-endoscopy, histology, multiphoton endomicroscopy (MPEM), flow cytometry, and immunofluorescence staining. Additionally, in a second approach, we investigated the in vitro effects of voclosporin on ITK activation at the molecular level in human PBMCs.

Results: Voclosporin treatment effectively suppressed established colitis in mice and reduced the activation of IL-2-inducible tyrosine kinase (ITK), a key driver of inflammation in IBD identified in previous studies. Additionally, in vitro stimulation of human PBMCs demonstrated decreased protein expression of the kinases ITK, LCK, and ZAP70 following treatment with both voclosporin and cyclosporine A. Notably, voclosporin exhibited superior efficacy in reducing T cell activity compared to cyclosporine A. These findings support voclosporin as a promising novel therapeutic approach for acute intestinal inflammation.

Summary: As an further development of cyclosporine A, voclosporin exhibits a protective effect in oxazolone-induced colitis, with a mechanism of action similar to that of cyclosporine A. Given its remarkable efficacy and improved tolerability in diseases such as lupus nephritis, repurposing voclosporin for conditions like inflammatory bowel disease appears highly promising.

10. Influence of anatomical location, genetic susceptibility, and microbiota on T-cell-mediated intestinal inflammation

Reyes Gamez Belmonte (Erlangen, DE)

Introduction: Inflammatory bowel disease (IBD) is a chronic intestinal disorder traditionally classified into two subtypes: Crohn's disease (CD) and ulcerative colitis (UC). Although its pathophysiology remains incompletely understood, the prevailing paradigm is that it results from a complex interplay of genetic, environmental, microbial and immune factors. Notably, the analysis of these factors highlights critical differences not only between UC and CD, but also between ileal and colonic CD, beyond their anatomical location. Given the central role of T-cells in IBD, we aim to investigate how intestinal location, Caspase 8-mediated genetic susceptibility, and microbiota composition shape the inflammatory responses following in vivo T-cell activation.

Methods: Systemic and intestinal inflammation was assessed in wild-type (WT) mice, germ-free mice, mice with antibiotic-induced microbiota depletion and Casp8ΔIEC mice after administration of anti-CD3 to induce systemic T-cell activation.

Results: Our findings demonstrate that the intestinal tract is a primary target of systemic T-cell activation, with the severity of inflammation strongly influenced by anatomical location, revealing a distinct immune profile in the small versus large intestine. Consistent with the link between Caspase 8 deficiency and very early-onset of IBD, we observed exacerbated severity in animals with a deletion of Caspase 8 in intestinal epithelial cells. Furthermore, germ-free mice showed protection against T-cell-mediated inflammation, underscoring the contribution of microbiota to T-cell mediated responses.

Discussion/Conclusion: Our data support the notion that intestinal inflammation is shaped by a number of factors, including genetics, microbiota and anatomical location. The differential susceptibility of small versus large intestine to T-cell-mediated inflammations suggests the need for tailored therapeutic strategies.

11. NFATc3: A driver of Treg mediated suppression of colitis

Katharina Gerlach (Erlangen, DE), Benno Weigmann (Erlangen, DE)

Introduction: NFATc3, a member of the nuclear factor of activated T cells family, has been implicated in immune responses and inflammation. It is a transcription factor essential for activation and function of T cells regulating cytokine expression and cell proliferation. Elevated numbers of NFATc3+ cells in the lamina propria of patients with inflammatory bowel disease (IBD) suggest a regulatory role for this transcription factor in mucosal inflammation, prompting us to investigate its function in colitis.

Methods: NFATc3 expression was analyzed in IBD patient tissues using qPCR and immunofluorescence. To study its function, NFATc3 knockout (KO) mice were treated with oxazolone to induce colitis. Furthermore, transfer colitis experiments were performed in RAG1 knockout mice to study the effects of NFATc3-deficient T cells. Colonic inflammation was monitored by mini-endoscopy and lamina propria mononuclear cells (LPMCs) were isolated for FACS analysis.

Results: In the T cell compartment we found higher numbers of NFATc3+ cells in the lamina propria of IBD patients providing strong evidence for the regulation of NFATc3 in colitis. Functionally, NFATc3 KO mice exhibited minimal inflammation during experimental oxazolone-induced colitis, supporting the pro-inflammatory effect of this transcription factor. Furthermore, the expression of FoxP3, a marker of Tregs, was significantly increased in NFATc3 KO mice, suggesting that NFATc3 negatively regulates Tregs. Adoptive transfer of NFATc3-deficient T cells into RAG1 knockout mice resulted in delayed onset of inflammation and increased Treg numbers compared to wild-type T cells.

Discussion/Conclusion: NFATc3 emerges as a key regulator of colonic inflammation by modulating Treg activity and immune cell infiltration. These findings highlight the potential of targeting NFATc3 as a therapeutic approach for inflammatory bowel diseases, offering a novel avenue for treatment development.

12. Insults to barrier function accelerates disease progression in a novel mouse model of spontaneous colitis

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Introduction: Genome-wide association studies have discovered multiple variants with small effect-sizes however, their contribution to the overall heritability of ulcerative colitis (UC) remains modest. Identifying “private” familial mutations with larger effect sizes can provide insight into novel IBD pathways. We identified a family with multiple members affected by severe UC necessitating colectomy across three generations. We identified a likely causative missense mutation in a conserved residue of the OTUD3 gene through exome sequencing. Mutations in OTUD3 are common in the South Asian population (0.1%) but are not associated with severe disease, suggesting an environmental modifier involved in the severe phenotype of this Australian family.

Methods: OTUD3 global knock out and epithelial specific knockout mice were challenged with DSS (1.5%) as well as challenged with high fat diet and high fructose diet. Disease severity as well as molecular changes in the colon were assessed, along with intestinal permeability.

Results: Global and intestinal epithelial cell specific OTUD3 disruption develop spontaneous colitis by 12 weeks of age that is accelerated by DSS exposure, with impaired recovery and dietary exposure. High fat diet (HFD) and high fructose diet (HFrD) accelerated the spontaneous colitis phenotype as early as 6 weeks of age, with impaired barrier integrity in OTUD3-/- mice as measured by FITC dextran permeability and penetration of luminal bacteria deep into the colonic crypts and liver.

Discussion/Conclusion: Our investigation identified a novel role of OTUD3 in intestinal epithelial homeostasis. The progressive spontaneous colitis was accelerated and augmented after disruption of barrier function with DSS or dietary changes, provided mechanistic insight into the impact of diet in genetically susceptible individuals, and supporting the environmental modification of genetic risk underlying the increasing incidence of IBD.

13. Integrated multi-model analysis of intestinal inflammation exposes key molecular features of preclinical and clinical IBD

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Introduction: Inflammatory bowel disease (IBD) is a chronic condition characterized by the appearance of inflammation in the gut tract. It is driven by complex epithelial, immune and genetic interactions, but its aspects are not fully recapitulated in preclinical models. To improve the translational relevance and identify conserved molecular mechanisms, a comparison between commonly used IBD models is essential.

Methods: We selected 13 widely used IBD mouse models, and performed a multi-model comparative transcriptomic analysis between them to identify conserved and model-specific cellular, sub-cellular and molecular signatures. With a similar approach, we employed curated and a priori statistical correlative methods to compare the transcriptomes of IBD patients and mouse intestinal inflammation models at bulk and single cell levels.

Results: These analyses revealed cellular compositions, IBD-related pathways and ontologies that are translatable between patient cohorts and mouse models. Furthermore, we identified a conserved core inflammatory gene signature related to innate immunity, T-cell homing and epithelial barrier homeostasis that translates into the new mouse gut molecular inflammation score (mMIS). Moreover, statistical deconvolution revealed distinct signatures for T-cell, B-cell and enteric neurons in specific mouse IBD models. The model compendium database is available for researchers as a web explorer (http://trr241.hosting.rrze.uni-erlangen.de/SEPIA/).

Discussion/Conclusion: Through this integrated multi-model approach, we provide a framework to assess systematically the molecular landscape of intestinal inflammation. The findings in this study reveal conserved inflammatory circuits, and offer a tool for model exploration and selection, a valuable resource for the IBD research community.

14. IL-36 signaling as a drug target in Crohn's disease patients with IL36RN mutations

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Introduction: The IL-36 signaling pathway has recently been identified as a key regulator of intestinal homeostasis and inflammation. However, the role of mutations in the IL-36R signaling pathway in the pathogenesis of inflammatory bowel disease remains unclear.

Methods: Mutations in the IL-36 receptor antagonist (IL-36RA, IL36RN) were identified in a cohort of 86 ulcerative colitis patients, 244 Crohn's disease patients and 45 non-inflamed controls by whole exome sequencing followed by targeted Sanger sequencing. In-depth immune cell profiling of one IL36RN-mutated patient was performed using mass cytometry and multiplexed immunoassays. Overexpression experiments and functional assays characterized identified IL36RN mutations. Clinical and molecular responses of one IL36RN-mutated patient to a combined treatment with the IL-36R-blocking antibody spesolimab and the TNF-blocker certolizumab-pegol were assessed by fecal calprotectin, endoscopy, multiplexed immunoassays and mass cytometry.

Results: We identified four Crohn's disease patients with heterozygous missense mutations in IL36RN. Experimental overexpression and functional assays demonstrated that two identified mutations resulted in a reduced protein expression of IL-36RA. In-depth immune profiling of one IL36RN-mutated patient revealed an increased response of PBMCs to IL-36 stimulation and elevated serum levels of IL-36-regulated cytokines. Administration of the IL-36R-blocking antibody spesolimab to this patient resulted in a reduction of intestinal inflammation and a decrease in pro-inflammatory immune cells in both PBMCs and lamina propria mononuclear cells (LPMCs) during therapy.

Discussion/Conclusion: Our findings indicate that pathogenic IL36RN mutations may contribute to the pathogenesis of Crohn's disease in a subset of patients and that inhibiting IL-36 signaling in combination with TNF-blockade could offer a personalized therapeutic approach for these patients.

15. Age-dependent decline of the UPR in the colonic epithelium: Implications for mucosal integrity and chronic inflammation

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Introduction: Misfolded protein accumulation in the endoplasmic reticulum (ER) causes ER stress, a hallmark of various pathological conditions. Eukaryotic cells counteract this stress via the unfolded protein response (UPR), a regulatory network that promotes correct protein folding. Age-related increases in protein misfolding has been observed independent of disease, suggesting that the decline in the UPR's function is a natural consequence of ageing. Although the relationship between the UPR and ageing has been explored in the context of neurodegenerative disease, its impact on mucosal epithelial cells (EC) in the intestines remains largely unexplored. We hypothesise that age-related senescence of the UPR contributes to a heightened susceptibility and severity of inflammation in aged individuals.

Methods: To address this, we utilised both human samples and mouse models. Human colon biopsies were accessed from the Mater Research IBD biobank which includes a wide range of patient samples, both with and without inflammatory bowel disease (IBD). The samples were sorted into three age groups: young (< 25 years), middle-aged (30–50 years), and aged (> 65 years). C57BL/6 mice aged between 4- and 96-weeks were used as a control model of ageing. Winnie mice (Muc2 gene mutation), a model of intestinal inflammation, were investigated at various ages between 4- and 45-weeks. Intestinal ECs were isolated and qRT-PCR was utilised to assess changes in the gene expression of UPR components throughout ageing and inflammation. Additionally, histological analysis of intestinal proteins in relation to the UPR was conducted using immunohistochemistry, immunofluorescence, and histochemical staining.

Results: qPCR analysis of colonic ECs in aged C57BL/6 (control) mice revealed a significant decline of various components of the UPR throughout ageing from 4- to 96-weeks, with a peak in expression at 8-weeks. Winnie mice (model of intestinal inflammation), when compared to age-matched controls,

exhibited a significant reduction in the expression of downstream UPR markers, particularly in older age. Analysis of human colon biopsies similarly revealed an age-dependent increase in markers of ER stress, despite trends of decline in UPR components. Analysis of mucin production, which is indirectly mediated by the UPR, via qRT-PCR and tissue staining revealed an age-related decline in C57BL/6 mice, and a more pronounced decrease observed in Winnie mice throughout ageing.

Discussion/Conclusion: Our results indicate that there is a decline in the UPR with age in intestinal ECs, meaning that it becomes less effective at stress management in older age. This is observed by the increase in ER stress alongside a decrease in downstream UPR pathways in both the human and murine context. Additionally, we see chronic intestinal inflammation in the murine context accelerates and enhances the downregulation of the UPR in ageing. This indicates that older aged individuals with chronic intestinal inflammation may experience exacerbated symptoms as a result of a compromised UPR.

16. TIM3 as a crucial regulator of immune and metabolic homeostasis in IBD: Potential for galectin 9 therapy?

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Introduction: Inflammatory bowel disease (IBD) is characterized by chronic gastrointestinal inflammation driven by dysregulated T cell activity and cytokine secretion. TIM3, a T cell immunoglobulin and mucin domain receptor with co-inhibitory effects on T cells, plays a key role not only in context with cancer but also IBD. However, the intracellular mechanisms by which TIM3 influences IBD remain poorly understood.

Methods: We investigated TIM3 deficiency using an experimental colitis model. Through mini-endoscopy, histology, immunofluorescence staining, flow cytometry, ELISA, and untargeted metabolomic analysis of lamina propria mononuclear cells (LPMCs), we evaluated TIM3's role in colitis and its metabolic implications. Additionally, we tested recombinant galectin 9, a TIM3 ligand, as a potential therapeutic intervention.

Results: TIM3-deficient mice displayed aggravated colitis with increased T cell activity and an associated metabolic shift. Furthermore, a galectin 9 administration in vitro induced T cell apoptosis, reducing T cell activity, in a dose-dependent manner. Importantly, galectin 9 levels were diminished in chronic experimental colitis, underscoring its therapeutic potential

Discussion/Conclusion: Our findings suggest that a TIM3 deficiency disrupts metabolic homeostasis and increases oxidative stress, highlighting TIM3's dual role as a regulator of immune activation and metabolic balance. Galectin 9 emerges as a promising therapeutic target in IBD.

17. Gene-environment interactions: The potential of altered diets to promote intestinal inflammation by dysregulating intestinal γδ T cells

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Introduction: γδ T cell enrichment in the intestinal epithelium is well documented in mice and humans. The cells' development and steady-state phenotypes are regulated by poorly understood, B7-like, butyrophilin-like (BTNL) proteins [human BTNL3+8; mouse Btnl1+6] expressed specifically by gut epithelial cells. Thus, mice lacking the Btnl1-4-6 locus have greatly reduced numbers of Vγ7+ intraepithelial lymphocytes (IELs), while persons homozygous for a hypomorphic allele (BTNL8*3) carry fewer Vγ4+ IELs and are at increased risk of severe Crohn's disease, a form of inflammatory bowel disease (IBD) (PMID: 37708268). Consistent with this, rodent Vγ7+ IELs and human Vγ4+ IELs have been implicated in maintaining tissue integrity via a TCR-dependent process known as "normality sensing" (PMID: 35165446).

Methods: Several environmental risk factors for IBD are also known, including high fat diet (HFD). Given that γδ T cells regulate dietary adaptation (PMID: 33737460), we hypothesised that HFD might act in part by dysregulating the BTNL-γδ IEL axis, limiting the maintenance of the epithelial barrier, and contributing to epithelial erosion a pathognomonic feature of IBD.

To test this hypothesis, we established a series of dietary stresses, including HFD, high-carb, and high-protein diets, and examined their impact on γδ IEL in wild-type and Btnl deficient mice.

Results: Our results provide evidence of genetic environmental interactions in that HFD dysregulates the intestinal γδ IEL compartment, with reduced availability of mature Vγ7+ IELs that are partly replaced by immature cells, phenocopying a major trait of Btnl-deficient mice. The replacement by immature cells are caused by both, increased proliferation and tissue homing. Furthermore, the remaining γδ IELs show diet-dependent differences in their immunophenotypic characteristics, including DNAM1, TIGIT and TCR signalling strength, which collectively indicate altered activity and function.

Discussion/Conclusion: Our data suggest that HFD dysregulates the intestinal γδ IEL compartment, particularly Vγ7+ IELs, both in terms of availability and function. The pathological implications of this, and whether dietary regulation affects γδ IEL by acting directly through the Btnl axis are now being examined, with a view to identify actionable targets.

18. Linking genetic susceptibility to environmental risk – The role of the aryl hydrocarbon receptor in IBD

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Introduction: The importance of environmental triggers and genetics in IBD is well established, however, underlying biological mechanisms remain poorly understood. The aryl hydrocarbon receptor (AHR) is a ligand-dependent transcription factor acting as an environmental sensor for compounds derived from dietary and microbial metabolites as well as external pollutants. Well-known for its role in promoting barrier integrity in the gut, AHR has recently been identified as a risk factor for ulcerative colitis (UC) through genome-wide association studies. Notably, the site of association hints at a macrophage-specific regulatory element. We sought to understand what role AHR plays in macrophages.

Methods: AHR was disrupted in primary human monocyte-derived macrophages through CRISPR/Cas9 editing. AHR-dependent changes were then assessed through RNA-sequencing and functional assays. Multiple mouse models of AHR interference were used for analysis of bone marrow-derived macrophages (BMDM) and primary intestinal macrophages in naïve and inflammatory conditions. Further, the effects of AHR-targeted dietary intervention on experimental colitis were analysed.

Results: Successful AHR disruption in human macrophages was confirmed through loss of ligand-dependent expression of canonical AHR target genes. AHR-deficient macrophages displayed a higher inflammatory profile with distinct changes in phenotype, metabolism and function. We showed an upregulation of AHR in murine macrophages during intestinal adaptation and identified AHR-upregulating factors in BMDM. Further, we demonstrated the effect of nutrition based AHR induction in experimental colitis and revealed changes in the inflammatory landscape through RNA-sequencing of intestinal macrophages in naïve and inflammatory conditions.

Discussion/Conclusion: These results are a first step towards understanding the putative anti-inflammatory function of AHR in intestinal macrophages. Through ongoing research, we aim to uncover the mechanism behind AHR-facilitated regulation of inflammatory responses.

19. Investigating the mechanical properties of immune cells to gain deeper insights into colitis progression

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Introduction: Inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis, are characterized by chronic and recurrent inflammation of the gastrointestinal tract. Immune cell trafficking, including neutrophils, is a critical process in IBD progression, as these cells are key mediators of the immune response. We hypothesize that changes in the mechanical properties of immune cells,

particularly neutrophils, play a central role in IBD pathogenesis and progression by influencing their migration and function. To investigate this, we use real-time deformability cytometry (RT-DC), a novel, high-throughput technique capable of rapidly assessing the size, shape, and deformation of single cells. This method allows us to systematically characterize the mechanical properties of immune cells, identify distinct cell populations in human and mouse blood samples, and evaluate their functional relevance in the context of ulcerative colitis.

Methods: Blood samples from IBD patients were analysed using RT-DC to identify cell populations and further investigate their mechanical properties. To replicate the phenotype in vitro, neutrophils isolated from healthy donors were stimulated with serum from healthy or UC patients as well as pro-inflammatory cytokines (TNF-α, GM-CSF, LPS), followed by RT-DC and bulk RNA sequencing to examine transcriptional changes. 3D gel matrix migration assays were performed to study neutrophils motility. Blood samples from an acute DSS mouse model were also processed for RT-DC analyses. Also, colon samples were collected an digested using Tissue Grinder and neutrophil subsets, including their maturation states, were characterized using RT-DC and flow cytometry (FACS).

Results: Our preliminary findings demonstrate that neutrophils in blood from UC patients exhibit increased size and reduced stiffness compared to healthy individuals as inflammation progresses. Similar to this, in vitro stimulation of neutrophils with serum from UC patients resulted in increased size and upregulation of activation markers, including CD11b, CD63, CD64, and CD66. This was also observed when stimulating the neutrophils with GM-CSF and TNF-α. Interestingly, our bulk RNA-seq analysis revealed a significant upregulation of pathways associated with cytoskeleton organization, as well as increased expression of key cytoskeletal genes, including ACTB, TPM1, TPM2, TPM3, and TPM4, upon stimulation with UC serum compared to healthy serum. These findings highlight the pronounced impact of UC serum on cytoskeletal dynamics. Additionally, our observations demonstrate an increase in the motile fraction during migration within a 3D gel, both when stimulated with UC serum and when treated with GM-CSF. Furthermore, in colitis mouse models, blood neutrophils also showed an increase in size during the course of colitis. Besides, colon-infiltrating neutrophils exhibited not only an increase in number but also an increase in area. Notably, we were able to identify two colon infiltrating populations based on the size of cells, that will be further characterized.

Discussion/Conclusion: Collectively, our findings suggest that the mechanical properties of neutrophils, including their stiffness, activation, and migratory behavior, play a critical role in influencing disease pathogenesis and progression. Understanding these mechanical changes could provide valuable insights for developing new therapies targeting neutrophil mechanics.

20. Modelling barrier dysfunction in inflammatory bowel disease using a novel immunocompetent in vitro epithelial monolayer system

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Introduction: Inflammatory bowel diseases (IBDs), such as Crohn's disease and ulcerative colitis, are chronic conditions marked by persistent inflammation and disruption of the intestinal epithelial barrier. The incidence of IBD has increased in recent decades, driven by factors like immune dysregulation and pathogen exposure. In vitro epithelial models have become essential for studying intestinal morphology, epithelial-pathogen interactions, and barrier function under inflammatory conditions. In this study, we developed a fully differentiated murine colon epithelial monolayer system that incorporates both innate and adaptive immune cells, including polarized macrophages and T cells. We further explored the impact of pathogens, specifically Salmonella Typhimurium (S. Typhimurium), on bacterial-induced barrier disruption, epithelial cell death, and bacterial translocation across the epithelium, highlighting the critical role of immune cells in these processes.

Methods: Murine colon crypts were isolated, treated, and cultured on transwell inserts to form differentiated epithelial monolayers. CD4+ T cells were isolated from the spleens of C57BL/6 mice and polarized into Th0, Th1, and Th17 subsets. Macrophages were generated from bone marrow cells and polarized into naïve M0, pro-inflammatory M1, and anti-inflammatory M2 phenotypes. These cells were then cocultured with the epithelial monolayers, and the system was further characterized. The monolayers were stimulated with proinflammatory cytokines and infected with luminescent strain of S. Typhimurium.

Barrier integrity was assessed using fluorescence staining, permeability assays, and transepithelial electrical resistance (TEER) measurements.

Results: The epithelial monolayer models expressed lineage-specific markers, including EpCAM for epithelial cells, Mucin 2 for goblet cells, and Chromogranin A for enteroendocrine cells. Tight junction integrity was assessed by measuring transepithelial electrical resistance (TEER) and confirming the expression of tight junction proteins including ZO-1, Occludin, Claudin 1 and Claudin 2. Stimulation with IFN-γ alone or in combination with TNF-α, led to significant increases in cell death and permeability, indicating barrier disruption. To better understand the interplay between the immune system and the epithelial layer, coculture models were established with innate and adaptive immune cells. Interestingly, Th0, Th1, and Th17 cells were found to disrupt epithelial integrity, with Th1 and Th17 cells having the most pronounced effect, as evidenced by elevated IFN-γ and IL-17 production. In contrast, macrophages, particularly M0 and M1, reinforced the epithelial barrier. Furthermore, infection with S. Typhimurium led to a marked decrease in TEER, further highlighting the impact of bacterial invasion on barrier integrity. Also, 3D imaging demonstrated bacterial translocation from the apical to basolateral surface of the monolayer, accompanied by barrier damage and a decrease in ZO-1 protein expression. Interestingly, coculture with M1 macrophages enhanced barrier integrity, resulting in increased TEER compared to monolayers exposed to bacteria alone. Besides, M0 and M2 macrophages exhibited an even stronger protective effect against the bacterial infection, leading to a further increase in TEER, highlighting their anti-inflammatory role as evidenced by the elevated production of IL-10.

Discussion/Conclusion: This study demonstrates the efficiency of our immunocompetent murine colon epithelial monolayer model for investigating epithelial barrier integrity and host-pathogen interactions together with the immune cell compartment. The model will be also used for studying potential therapeutic treatments that could be relevant in the pathophysiology of IBD.

21. GPR15L counteracts chronic colitis by shaping the intestinal microbiota

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Introduction: The G protein-coupled receptor 15 (GPR15) is expressed on gut-homing T cells and its interaction with GPR15 ligand has been shown to crucially control integrin-dependent adhesion to the endothelium. However, the impact of GPR15L on experimental colitis and inflammatory bowel disease (IBD) is currently not clear.

Methods: We studied GPR15L in experimental colitis with Gpr15l-deficient and -overexpressing mice as well as with rectal application of recombinant GPR15L. We performed phenotypical and molecular disease characterization using endoscopy, IVIS, histology, immunofluorescence, FISH, qPCR. We also performed bulk RNA and metagenomic sequencing. We analyzed the expression of GPR15L in samples from IBD patients and non-IBD controls and correlated it with clinical information. We explored the function of GPR15L in vitro using radial diffusion assays and antimicrobial assays.

Results: Acute DSS colitis was aggravated in Gpr15l-deficient mice compared to Gpr15l-proficient mice, while it was attenuated in Gpr15l-transgenic mice. This was T cell-independent, since the phenotype was conserved in Rag-/-Gpr15l-/- mice. RNA sequencing of colon tissue from Gpr15l-/- and Gpr15l+/+ mice with DSS colitis showed differential regulation in genes related to mucosal barrier function and host-microbiota crosstalk. Accordingly, 16S rRNA sequencing revealed a substantial difference in the intestinal microbial diversity of Gpr15l-/- and Gpr15l+/+ mice. Shotgun metagenomics and radial diffusion assays revealed that GPR15L acts as a selective anti-microbial peptide. Rectal supplementation of recombinant GPR15L in Gpr15l-/- mice rescued increased disease severity in acute DSS colitis. Patients with IBD showed reduced expression of GPR15L compared to controls. Furthermore, the expression of GPR15L was lower in patients with high disease severity compared to those with low severity.

Discussion/Conclusion: GPR15L counteracts experimental colitis and seems beneficial in human IBD. Mechanically, it acts as an anti-microbial peptide to promote the homeostasis of the intestinal microbiota. Thus, GPR15L emerges as a potential future therapeutic approach for IBD.

22. The role of SOX10 in adult enteric glial cells and intestinal inflammation

Heidi Limberger (Erlangen, DE)

Introduction: Enteric glial cells (EGCs) contribute to intestinal homeostasis by regulating various processes including the epithelial barrier, neuronal function and motility. Moreover, EGCs have immunomodulatory properties and thus play an active role during intestinal inflammation.

Mature EGCs are characterized by the expression of SOX10, a transcription factor essential for the development and differentiation of the enteric nervous system (ENS). While the function of SOX10 during ENS development is well understood, its role in adult EGCs and thereby in intestinal homeostasis remains elusive.

Methods: By utilizing Plp1-CreERT2 mice crossed to Sox10fl/fl-IRES-EGFP animals, we created a Sox10 reporter mouse with inducible, glial-specific Sox10 ablation (Sox10iΔEGC) enabling the investigation of SOX10 function in the ENS of adult mice. For this purpose, Sox10iΔEGC mice were studied under steady-state conditions and during DSS-induced colitis to examine the importance of SOX10 in health and disease. In vitro studies using sorted EGCs isolated from Sox10fl/fl and Sox10iΔEGC mice complemented our in vivo data.

Results: Sox10iΔEGC mice showed weight loss and constipation three weeks following tamoxifen induction as well as impaired small intestinal motility. The observed dysmotility phenotype in Sox10iΔEGC mice was caused by a significant reduction of EGCs in the small and large intestine following Sox10 deletion and accompanied by slight alterations in the microbiota composition. Moreover, preliminary data indicated an elevated susceptibility to DSS-induced colitis in Sox10iΔEGC mice.

Consistent with our observations in vivo, FACS sorted Sox10iΔEGC EGCs lost their typical morphology and key EGC transcriptional markers in vitro. RNA sequencing results confirmed the loss of glial identity in these Sox10iΔEGC EGCs indicative of a shift towards the neuronal lineage.

Discussion/Conclusion: Our results support the role of SOX10 as a regulator of glial identity in mature adult EGCs and highlight the importance of proper EGC function for intestinal homeostasis.

23. The role of Fosl2 in intestinal epithelial inflammation and homeostasis

Jingran Lin (Erlangen, DE)

Introduction: Fos-related antigen-2 (Fra-2), a member of the activator protein 1 (AP-1) family of transcriptional activators, is involved in a variety of cellular processes, including proliferation and differentiation. While it is highly expressed in intestinal epithelial cells, its role in intestinal homeostasis and inflammation remains unknown, however, several genome-wide association studies (GWASs) also reported associations of single-nucleotide polymorphisms (SNPs) within the promoter of Fosl2 with risk for Crohn's disease, ulcerative colitis.

Methods: Fosl2 IEC (Fosl2 intestinal-epithelial-cells specific knockout) mice were established, small intestine organoids which isolated from Fosl2 IEC mice. RNA-sequencing and CUT&RUN were performed in the steady state. We investigated whether Fosl2 affected the degranulation process and subsequent replenished responses of Paneth cells through some disease models, like LPS, Citrobacter, Eimeria induced inflammation and infection in the gut. Injecting TNF in Fosl2 IEC mice leads to the study of influence from Fosl2 in paneth cell activity. Microbiota analysis were tested from stool in mice small intestine. Isolated organoids were stimulated with some pro-inflammatory cytokines like IL-22, IFNγ and TNF-α to investigate the PC antimicrobial function. Stimulation of carbachol to organoids were used to show the secretion of lysozyme.

Results: Paneth cell deficiency is found in steady state mice in PCR and immunofluorescence staining results, significant down-regulation of paneth cell markers showed in RNAseq data. Fosl2 plays a protective role in LPS, Citrobacter or Eimeria induced infectious disease models with the decreasing in the expression of some paneth cell markers, like MMP7 and ANG4. After 20 h of TNF injection, paneth cell decreasing significantly in Fosl2 IEC mice compared with wt mice showed in PCR, HE staining and immunofluorescence staining. Stimulation of IL-22 and TNFa in wt organoids causes significant down-regulation of Fosl2, and in Fosl2 IEC organoids can cause the decreasing of the expression of some paneth cell markers like MMP7 and ANG4, while lysozyme secretion is significantly decreased with stimulation of carbachol.

Discussion/Conclusion: We show that Fosl2 plays an important role in Paneth cell differentiation and function, influences paneth cell degranulation and lysozyme secretion, regulates the homeostasis and inflammation of the gut, might be a potential therapeutic targets for IBD.

24. An autoimmune gut pathobiont translocates silently across the intestinal epithelial barrier

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Introduction: The gut microbiota promotes inflammation at the gut barrier in IBD and beyond the barrier in extraintestinal autoimmune diseases such as lupus and autoimmune liver diseases. In mice, the gut pathobiont Enterococcus gallinarum (EG) was shown to translocate to lymphoid tissues and the liver, instigating lupus, autoimmune hepatitis and primary sclerosing cholangitis (Manfredo Vieira et al, Science. 2018; Nakamoto et al, Nat Microbiol. 2019; Gronke et al, Sci Transl Med. 2025). Moreover, EG was found to evolve within the host into distinct lineages with different translocation dynamics (Yang et al, Nature 2022). However, the mechanisms behind the bacterial translocation remain unclear, which we aim to decipher here.

Methods: Co-cultures of bacteria with the Caco-2 cell line in a transwell system were used to test epithelial integrity with FITC-dextran and transepithelial electrical resistance, respectively. Translocation dynamics of bacterial strains (ancestral and within-host evolved) were examined by culturing medium from the lower chamber at different time points. For imaging, cells were infected with CFSE-stained or native bacteria and visualized using confocal microscopy and electron microscopy, respectively.

Results: Ancestral and evolved EG rapidly translocate within 30 min but show quantitative differences ($n = 3$; $p = 0.019$). Unexpectedly, the epithelial integrity remained intact even 14 hours post-infection in contrast to a pathogenic Salmonella strain that rapidly broke down barrier integrity ($n = 4$; $p = 0.0109$). Confocal and EM imaging revealed EG transcytosis through epithelial cells without evidence for a paracellular route or ultrastructural changes suggestive of barrier disruption.

Discussion/Conclusion: EG rapidly translocates across epithelia via transcytosis similarly to gut pathogens, however, without epithelial disruption during the early stages tested thus far. This process may facilitate silent spread in vivo, which subsequently triggers extraintestinal autoimmunity in liver and lymphoid organs. Dissecting the exact mechanisms may aid in understanding the development of systemic autoimmune diseases as well as extraintestinal complications in IBD.

25. SLP-76 as a potential inflammatory driver in IBD and a target of the calcineurin inhibitor voclosporin

Laura Loges (Erlangen, DE)

Introduction: While calcineurin inhibitors like cyclosporine and voclosporin offer hope for steroid-refractory ulcerative colitis and lupus nephritis, the intricate details of how they tame T-cell activation in inflammatory bowel disease (IBD) have remained elusive. Our study dives deep into this crucial area, focusing on the adaptor protein SLP-76 to reveal its critical role in IBD pathogenesis and its surprising sensitivity to calcineurin inhibition.

Methods: We meticulously analyzed human intestinal biopsies from IBD patients using qPCR and immunofluorescence, and then stimulated peripheral blood mononuclear cells (PBMCs) with anti-CD3/CD28 in the presence or absence of cyclosporine or voclosporin, followed by rigorous qPCR and flow cytometry analysis.

Results: SLP-76 was significantly upregulated in samples from intestinal tissue originating from ulcerative colitis (UC) and Crohn's disease (CD) patients and correlated with histopathological disease severity. In contrast, no differences in SLP-76 expression were observed in PBMCs at baseline or after stimulation. Treatment with calcineurin inhibitors resulted in marked dephosphorylation within the T cell

signalling pathway in CD4+ and CD8+ T cells, with stronger effects observed for voclosporin. Notably, only voclosporin led to a reduction in total SLP-76 protein levels, almost complete inhibition of the activation marker CD69 and suppression of the Ras-MAPK pathway (as shown by reduced MAPK1, pERK1/2 and phospho-c-Jun).

Discussion/Conclusion: Our new findings align perfectly with previously reported SLP-76 deficiencies in Jurkat cells and gene deficient murine models. Taken together, the data support a regulatory role for SLP-76 in IBD pathogenesis and suggest that voclosporin may exert part of its immunosuppressive effect through direct modulation of this signalling hub.

26. Mevalonate pathway, a novel player for intestinal epithelial barrier function

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Introduction: Attachment of isoprenoids during prenylation results in an increased hydrophobicity of target proteins, which facilitates their membrane binding and protein-protein interactions. Therefore, the synthesis of isoprenoids occurs via the mevalonate pathway, which is also responsible for the de novo synthesis of cholesterol. Interestingly, prenylation of Rho GTPases within intestinal epithelial cells (IECs) maintains epithelial integrity in the gut and contributes to intestinal homeostasis (López-Posadas, 2016; Martín-ez-Sánchez, 2023). As a regulator of prenylation, the mevalonate pathway (MVP) has been associated to inflammation and cancer. We then wondered how this metabolic route can impact on intestinal epithelial barrier function, and thereby, contribute to Inflammatory Bowel Disease (IBD) pathogenesis.

Methods: We have utilized experimental colitis models, gut tissue from IBD patients and intestinal organoids to investigate the functional interplay between the MVP within IECs and intestinal inflammation.

Results: Interfering with the MVP resulted in epithelial alterations and intestinal inflammation. Thus, inhibition of the HMGCR-catalyzed rate-limiting step by statins lead to epithelial leakage (downregula-tion of E-cadherin and claudin-1 expression) and worsening of DSS-induced colitis in mice. On the other hand, the exposure of intestinal organoids to statins resulted in impaired survival and decreased cell proliferation. Accordingly, deletion of Hmgcr within IECs in transgenic mouse models (HMGCRiΔIEC mice) caused severe intestinal pathology, characterized by increased intestinal permeability (transmu-cosal passage of FITC Dextran), decreased epithelial cell proliferation and loss of stem cells, alterations on intercellular junction proteins, elevated expression of proinflammatory cytokines and tissue infiltra-tion of immune cells. Bulk RNA-sequencing experiments from gut tissue from HMGCRiΔIEC mice and statin-treated intestinal organoids suggested the blockade of the MVP within IECs caused defects in cell division, as well as alterations on lipid metabolism, ultimately resulting in intestinal inflammation. Mechanistically, our data demonstrated that defective mitochondrial function contributes to epithelial damage upon MVP blockade. Thus, decreased mitotracker staining, diminished TOM20 expression and increased p62 expression can be detected in gut tissue from HMGCRiΔIEC mice and simvastatin-treated organoids. Strikingly, a dysfunction of MVP can also be observed in gut tissue samples from IBD patients and experimental colitis models. Last, modulation of the MVP using the FDFT1 inhibitor zaragozic acid was able to rescue the survival of intestinal organoids exposed to pro-inflammatory cytokines.

Discussion/Conclusion: Our data demonstrated that MVP is a novel player in epithelial barrier function in the gut, and can thereby contribute IBD pathogenesis. Thus, MVP emerges as a new target in the diagnosis and therapy of epithelial injury and mucosal inflammation in IBD patients.

27. Aryl hydrocarbon receptor signalling in intestinal T cell residency

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Introduction: Environmental exposures are integral to mucosal inflammation in inflammatory bowel disease (IBD), but mechanistic understanding is lacking. The aryl hydrocarbon receptor (AHR), an environmental sensor responsive to dietary components and microbial metabolites, has been implicated

in IBD pathogenesis. Tissue resident memory T cells (TRM) derived from circulating gut-tropic memory T cells express AHR and play a pivotal role in the intestinal inflammation of IBD. This work tested the hypothesis that AHR signalling influences the development of human intestinal TRM.

Methods: Blood CD45RA+ ('naïve'), and both β7+ ('gut-tropic') and β7- CD45RA- memory T cells were isolated by FACS from healthy, human donors. Expression of AHR, and its target CYP1A1, were measured by qRT-PCR. Cells were cultured sequentially in IL-15 and TGFβ, with AHR agonist (FICZ), antagonist (CH223191) or vehicle alone. TRM-like cells (CD69+CD103+) were identified by flow cytometry and expression of TRM-associated genes (ZNF683 (Hobit), PRDM1 (Blimp-1), S1PR1, KLF2) measured by qRT-PCR.

Results: Memory T cell populations expressed high levels of AHR and generated significantly more CD103+CD69+ TRM-like cells upon culture in IL-15/TGFβ. These cells had the transcriptional profile of TRM with increased expression of ZNF683 and PRDM1, but reduced expression of genes encoding the tissue egress molecule S1PR1 and its regulator KLF2. In the presence of AHR antagonist the generation of TRM-like cells was reduced and expression of S1PR1 and KLF2 maintained. Gut-tropic memory cells (when compared to β7- CD45RA- cells) expressed more CYP1A1 ex vivo, indicative of AHR signalling, and gave rise to significantly more TRM-like cells. Reflecting active AHR signalling prior to culture, generation of TRM-like cells from gut-tropic cells was relatively resistant to AHR antagonism.

Discussion/Conclusion: AHR signalling enhances the generation of TRM-like cells and the increased residency potential of gut-homing T cells may reflect higher intrinsic AHR activity. Determining how AHR ligands shape the development and function of intestinal TRM will inform our understanding of immune-environment interactions in health and IBD.

28. Paneth cells regulate intestinal lymphangiogenesis and lipid metabolism in metabolic dysfunction-associated steatotic liver disease

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Introduction: Paneth cells (PC) are involved in the regulation of intestinal microbiota, and their function in intestinal lymph- and angiogenesis has been recently described. Uptake of dietary lipids is largely dependent on intestinal lymphatic vessels, and impairments in their density or function may result in significant depletion of lipids in the liver. In this study, we assessed the effects of PC deficiency in a model of metabolic dysfunction associated steatotic liver disease (MASLD).

Methods: We induced functional inactivation of PC in male and female mice (Sox9lox/loxVilCreERT2) by intraperitoneal injection of 1mg/day of tamoxifen for three consecutive days. One week later, all mice, PC-deficient, and control littermates were randomly subjected to a high sucrose/fructose – high fat (60% lard) (HFD) or standard (SD) diet for 16 weeks. Intraepithelial leakage of FITC-albumin was measured in vivo using laser-probe endomicroscopy. Several tissues were harvested for histological examination, molecular biology analyses, and imaging mass cytometry (IMC). Fecal samples were collected at both the start and end of the experiment to assess intestinal dysbiosis and fat content.

Results: All mice fed HFD gained weight compared to SD, but the weight gain in PC-deficient-HFD was significantly lower than in HFD-controls. Consistent with these findings, the severity of hepatic steatosis was significantly lower in PC-deficient-HFD compared to HFD-control mice. IMC of liver tissue revealed lower levels of collagen deposition and steatosis associated with fewer macrophages and neutrophils activation/infiltration in PC-deficient-HFD than in control-HFD mice. In vivo, microscopy showed a lower disruption of intestinal vascular barriers in PC-deficient-HFD than in HFD-control mice. The intestinal expression of distinct lymphangiogenic genes (VEGFC, VEGFR3, Prox1) was reduced in the PC-deficient HFD or SD. Consistent with these data, we detected a higher fecal fat content in PC-deficient-HFD mice compared to their counterparts. The alpha diversity of the fecal microbiota showed no significant differences based on gender or PC deficiency in the SD groups. Nevertheless, the beta diversity showed significant differences in PC-deficient fed SD after 16 weeks. Furthermore, we found significant alpha- and -beta diversity associated with decreased Bacteroidota and increased Firmicutes in HFD and PC-deficient mice.

Discussion/Conclusion: PC deficiency attenuated the severity of steatosis and fibrosis in mice, suggesting their regulatory role on intestinal lymphatics contributing to the pathogenesis of MASLD. Thus, Paneth cells may represent a novel target for intervention in MASLD.

29. A humanized murine model to identify translocating microbiota from autoimmune patients

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Introduction and Objective: Under certain conditions, commensal microbiota can cross the gut barrier into the liver and secondary lymphoid organs, where they trigger autoimmune responses. These translocating bacteria, known as pathobionts, thereby contribute to immune-mediated diseases like primary sclerosing cholangitis and systemic lupus erythematosus (SLE) in mice1,2. However, identifying human translocating pathobionts remains challenging given that extraintestinal tissues are difficult to study in patients. Objective: To identify gut barrier translocating bacterial species of human origin in humanized antibiotic (Abx)-pretreated and germ-free mice.

Methods: Stool samples from patients with SLE and control subjects were stored under anaerobic conditions. SPF mice were treated with broad-spectrum Abx to reduce murine microbiota before colonization. Germ-free and Abx-pretreated SPF mice were colonized with fecal human microbiota and treated with imiquimod to induce a TLR7-driven immune response, which mediates an SLE-like phenotype3. After euthanasia, organs like Peyer`s patches, mesenteric lymph nodes (MLN), liver, spleen, and kidney were homogenized and cultivated under selected conditions to maximize species detection.

Results: We identified several tissue-translocated bacteria including previously identified murine autoimmune pathobionts (Enterococcus gallinarum and Limosilactobacillus reuteri). Translocation was detected not only in gut-associated organs (MLN and liver), but also in systemic sites like spleen and kidney. Tissue isolates of human origin included a human cross-reactive lupus pathobiont, Bacteroides thetaiotaomicron, indicating stable colonization. Pathogenic T-cell and autoantibody responses were detectable in association with translocated microbiota.

Conclusion: Humanized gnotobiotic culture-based model allows the systematic identification of translocating gut microbiota, including pathobionts previously linked to autoimmune pathogenesis1,4,5. Importantly, tissue culture of strains allows further host-microbiota studies in vivo and vitro such as within-host evolution and microbial pathogenesis.

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30. A unique case series on collagenous gastritis in young adults: From symptom onset to treatment outcome

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Introduction: Collagenous gastritis is a rare condition diagnosed histologically as collagen band deposition > 10 µm within gastric lamina propria. A bimodal age distribution is suggested by previous small case series, with most reports in the paediatric population and those over 50 years old. Paediatric patients are reported to present more with anaemia and isolated gastric involvement, whereas patients over 50 years old are more likely to present with diarrhoea and concurrent collagenous colitis. We report a series of six young adult patients, fitting outside the typical age distribution, and describe their clinical phenotype, treatments and outcomes.

Methods: Six young adult patients with a diagnosis of collagenous gastritis within metropolitan Sydney were identified. Individual patient consent was obtained for all patients. The following patient data were recorded retrospectively: demographics, symptoms, medications, blood tests, endoscopy and histology

reports and patient outcome. The characteristics of the six patients with collagenous gastritis are summarised in Table 1.

Results: Mean age at time of diagnosis was 24.2 ± 3.5 years (range, 17–32 years; 4 males, 2 females). Mean age at time of symptom onset was 21.3 ± 4.1 years (14–29 years). Mean symptom duration prior to diagnosis was 2.8 3.0 years (0–11 years). The main presenting symptoms were abdominal pain (4/6) and fatigue related to iron or vitamin deficiency (3/6). 3/6 patients had associated immunoglobulin deficiencies. In most patients, the endoscopic appearance was abnormal affecting the fundus more than the antrum. Concurrent collagenous colitis and diarrhoea was present in only one case. Typical gastric histology included mild-moderate chronic gastritis with thickened collagen band, often with a prominence of fundus and body changes compared to other causes of gastritis. Treatment consisted of budesonide in two cases, proton pump inhibitors in three cases and no treatment in two cases. In terms of outcomes, partial or complete symptom improvement occurred in 5/6 patients, yet complete endoscopic and histological remission was rare (1/6). The endoscopic improvement in patient 3 is shown in Figure 1.

Discussion/Conclusion: Collagenous gastritis is rare and although previously thought to have a bimodal distribution in paediatric patients and over 50-year-olds, we report that it may also occur in the young adult population. Clinical presentations in this population are diverse, with a predominance of abdominal pain, and iron or B12 deficiency. The prognosis of collagenous gastritis in young adults is generally good, with most patients clinically improving, however complete endoscopic or histological remission is rare. Many aspects of aetiology and optimum management of this condition remains unclear.

31. The Impact of disrupting the BTNL-γδ T cell axis, with implications for Crohn's disease

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Introduction: The development of mouse and human intestinal TCRγδ+ intraepithelial lymphocytes depends on organ-specific butyrophilin-like (BTNL) molecules expressed by mature healthy epithelial cells. Interestingly, genetic variants of BTNL have been associated with Crohn's disease (CD) severity and post-COVID childhood MIS-C. In this context we hypothesise that common, idiopathic cases of such diseases reflect an underlying disruption of the BTNL-γδ+ IEL axis, thus impairing barrier integrity. To test this, we now define the impact of acute and constitutive BTNL deletion on healthy mouse and human gut tissues, including γδ IEL, and then ask whether such signatures are evident in CD patients.

Methods: To this end, we compare the scRNASeq phenotypes of healthy colon, including γδ IEL, from donors with or without variant alleles of BTNL3+8, cross-referencing to the impacts of constitutive and acute BTNL deletion in mice, as measured by transcriptomics and flow cytometry. The aggregate results are then compared with publicly available scRNAseq datasets of CD patients.

Results: The constitutive deletion of mouse and human BTNLs leads to reduced Vγ7+/Vγ4+ cells with atypical phenotypes phenocopying immature cells in mice (CD122lo, Thy1+, TIGIT−, Lag3−, CD8αα−, CD5+, CD24+), with likewise significant increases of CD5+ expression on Vγ4+ cells in humans: of note, this phenocopies that of Vγ4+ cells in inflamed IBD tissues. Acute Btnl1 loss in mice did not immediately deplete Vγ7+ cell numbers but did rapidly alter the cells' phenotype and transcriptomes, with acquisition of a gene signature reported for disrupted immunosurveillance in the skin, namely downregulated Tnfrsf9, Xcl1, Ptpn6, upregulated Klrk1 (encodes NKG2D), and decreased expression of CD69 and TIGIT, which is likewise decreased by IBD-associated cytokines. Concurrent transcriptomic changes in epithelial, stromal and other immune compartments after BTNL deletion will be also presented.

Discussion/Conclusion: These results are important to establish whether or not disruption of the BTNL-γδ+ IEL axis alone is sufficient to induce early biomarkers of gut inflammation, consistent with BTNL-deficiency pre-disposing toward penetrating CD. Such a result should offer actionable targets en route to new therapies.

32. Piezo1 regulates intestinal epithelial cell physiology but is dispensable for tissue homeostasis

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Introduction: Mechanosensation is essential for intestinal functions like motility and defecation (Kola, Docsa et al. 2023). Mechanical input shapes tissue architecture; while impaired mechanosensation is linked to gut diseases (Kola, Docsa et al. 2023). The outer layer of the gut mucosa, composed of continuously renewing intestinal epithelial cells (IEC), is constantly subjected to mechanical forces. Besides, a tight regulation of IECs is necessary to maintain barrier function and prevent epithelial leakage (a hallmark of inflammatory bowel disease, IBD) or the accumulation of cell masses, which could potentially lead to cancer. At a basic level, constant IEC number relies on the balance between cell division at the crypt base and cell shedding at villus tip. Interestingly, the mechanosensitive channel Piezo1 was recently identified as a key player regulating both of these processes in zebrafish (Eisenhoffer, Loftus et al. 2012, Gudipaty, Lindblom et al. 2017). We then explored the role of Piezo1 in regulating epithelial integrity in mice and humans, with a particular focus on inflammation and tumorigenesis.

Methods: Piezo1-dependent mechanosensation in IECs was explored using cell/organoid models. We took advantage of gut samples from IBD patients and animal models to assess the clinical relevance of Piezo1 in the context of IBD and colorectal cancer (CRC). Additionally, a comprehensive study on mice lacking Piezo1 in IECs under physiological and pathological conditions was conducted.

Results: In vitro, our data showed that Piezo1 channel was expressed throughout the human and mouse intestinal tract, with higher expression in colon. Its expression was increased in experimental colitis and colorectal cancer models. Of note, in human sample, PIEZO1 expression was altered in patients with ulcerative colitis, and positively correlated with the severity of inflammation in this group. In colon cancer cells, we detected changes in intracellular calcium level upon Piezo1 activation (by Yoda1), as well as altered PIEZO1 expression and localization, in response to stretching/ crowding and shear stress stimuli. Using traction force microscopy, we showed that Piezo1 activation could significantly influence the contractility and pressure exerted by intestinal organoids on the surrounding extracellular matrix (ECM). This activation also led to a reduction in cell proliferation and survival, while the abrupt deletion of Piezo1 resulted in organoid's abnormal growth. In vivo, Piezo1 deletion in the intestinal epithelium caused no major alterations at steady state, except delayed gut motility. In pathological conditions, Piezo1-deficient mice showed no increased susceptibility or resistance to DSS-induced colitis or AOM-DSS-induced tumorigenesis.

Discussion/Conclusion: Our findings indicate that while Piezo1 is important for IEC physiology, it is not critical for maintaining IEC numbers in vivo. Its influence on experimentally induced inflammation and cancer is also minimal.

33. Delineating molecular and microbial signatures across disease severity in treatment naïve inflammatory bowel disease through single-cell transcriptomic and microbiome profiling

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Introduction: Inflammatory bowel disease (IBD), including Crohn's disease (CD) and Ulcerative colitis (UC), is a chronic inflammatory condition with driven by genetic, immune, microbiome, and environmental factors. This study aims to elucidate the cellular and microbial landscape of adult treatment-naive IBD patients with varying disease severity to identify potential disease mechanisms and therapeutic targets, presenting one of the largest IBD single-cell datasets to date.

Methods: Patients with suspected IBD were referred to a rapid access IBD 'Inception' clinic. Faecal samples were obtained pre-treatment and shotgun metagenomics was undertaken. During the index

diagnostic colonoscopy, tissue biopsies were collected from inflamed and non-inflamed regions of the colon in UC and colon + ileum in CD. Single-cell RNA sequencing (scRNA-seq) was performed using 10x Genomics. Baseline clinical metadata and longitudinal therapeutic outcomes were collected over a two-year period for stratification across disease severity and response.

Results: We analysed 1.4 million cells from 68 treatment-naive IBD patients (38 CD, 30 UC) and 70 symptomatic controls without mucosal inflammation. Shotgun metagenomic sequencing was performed on 36 IBD patients with matched scRNA-seq data to explore host-microbe interactions.

Our analysis revealed distinct cellular populations and gene expression profiles between IBD patients and controls along the disease severity axis. Specific immune cell subsets were significantly expanded in IBD patients, with inflammatory monocytes particularly prominent in those with higher disease severity, exhibiting upregulated expression of pro-inflammatory cytokines and chemokines. Additionally, a shift from IgA to IgG antibody-producing cells was observed along the disease severity axis, indicating a dysregulated immune response associated with disease progression. Faecal microbial community typing based on pathway abundance revealed two clusters defined by low or high abundance of Bacteroidetes phylum taxa. Integration with clinical metadata and transcriptional profiles showed that Bacteroidetes-high UC patients displayed lower levels of inflammation and up-regulation of interferon signalling in B cells and myeloid cells.

Discussion/Conclusion: This comprehensive profiling of treatment-naive IBD patients provides valuable insights into the cellular and microbial factors contributing at disease onset. Our findings offer a deeper understanding of the underlying disease pathology along the axis of disease severity, expanding the dynamic range of IBD patient profiling and informing future therapeutic strategies that may more quickly put patients on the right treatment and better address the causes of IBD in addition to the inflammatory response alone.

34. A rare case of juvenile polyposis in a patient with ulcerative colitis

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Introduction: Juvenile polyposis syndrome (JPS) is a rare autosomal dominant disease characterized by the presence of hamartomatous polyps, most commonly in the colon, with a high risk of colorectal cancer (39%). Like JPS, ulcerative colitis is also associated with an increased risk of colorectal cancer, and both diseases often present with enterorrhagia. We present a case of a patient with concomitant occurrence of both of these diseases.

Case report: A 37-year-old man was referred to a gastroenterologist for long-term progressive enterorrhagia, abdominal pain, and weight loss. Colonoscopy revealed left-sided ulcerative colitis (eMayo 1) with dozens of inflammatory polyps (> 50) of various shapes and sizes (max. 4.5 cm). Four subpedunculated dysplastic adenomatous polyps (< 2 cm) were also found, but in the right colon (EMR performed). Given that there was a family history of colorectal cancer in the paternal grandfather and genetically unverified polyposis in the father (with colectomy and gastrectomy), we performed additional genetic testing for polyposis syndromes with confirmation of juvenile polyposis (SMAD4 in heterozygous form). We found no polyps on subsequent gastroscopic examination. Thereafter, despite treatment with mesalazine and corticosteroids, clinical and laboratory UC activity persisted (FCP 830 ug/g) with daily enterorrhagia. At follow-up colonoscopy, the bloody inflammatory polyps and erythema of the surrounding mucosa of the left colon persisted, therefore we initiated ustekinumab treatment. Given the histological description of both juvenile and inflammatory polyps, in order to minimize the risk of malignant recurrence and limit the bleeding, we performed multiple colonoscopy sessions with polypectomy of most polyps. This resulted in the normalization of clinical and laboratory activity of UC, and gradually with subsequent polypectomy sessions, complete resolution of enterorrhagia. No further dysplasia was found.

Conclusion: The concomitant occurrence of JPS and UC is very rare and only a few case reports have been published so far. In the management of both diseases, we follow the international recommendations for each disease separately, keeping in mind the patient's preferences.

35. TNS3 protein expression in ulcerative colitis

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Introduction: TNS3 (tensin 3) is a member of the tensin family of proteins that form bridges between actin filaments and β-integrins, known as focal adhesions. As such, they mediate signalling between the intracellular environment and the extracellular matrix. Tensins are responsible for maintaining the structure of the cellular cytoskeleton and are involved in many signalling pathways. They are also involved in the regulation of cell migration, proliferation and apoptosis. The importance of tensins in cell adhesion and migration has been demonstrated by the presence of these proteins in podosomes and invadopodia, which determine the phenomenon of epithelial-mesenchymal transformation (EMT). Tensin 3 can also act as a protein phosphatase and probably as a lipid phosphatase. The aim of this study was to evaluate and compare the expression of TNS3 protein in ulcerative colitis.

Methods: The study included 18 patients with ulcerative colitis (UC). Endoscopic material was obtained from archival paraffin-embedded tissue. Sections were stained with H&E and subjected to routine histological evaluation. Severity grading was performed according to the Geboes classification. The expression of TNS3 protein in tissue sections was assessed by immunohistochemical methods. The colour reaction was observed in the glandular epithelium. The staining reaction was scored as negative - no expression or expression in < 10% of glandular crypts; or positive - expression in ≥ 10% of glandular crypts.

Results: In the glandular epithelium, TNS3 expression was present in 8/18 cases (55.5%) of ulcerative colitis. Statistical analysis showed a positive correlation between TNS3 positive expression and higher grade dysplasia in ulcerative colitis ($p = 0.023$). High TNS3 protein expression also correlated with significant changes in mucosal architecture ($p = 0.045$) and crypt destruction ($p = 0.005$). Furthermore, positive TNS3 expression was more frequent in UC with moderate and severe chronic inflammatory infiltrates ($p = 0.037$).

Discussion/Conclusion: The present study suggests that higher TNS3 expression may be involved in advanced and chronic stages of ulcerative colitis.

36. Development of a high-throughput inflammation assay

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Introduction: Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract affecting over 2 million people in Europe and 6-8 million people worldwide. The multifactorial nature of the disease and current experimental limitations make IBD challenging to study, delaying the development of new therapies. Innovative approaches are therefore needed to study this highly complex disease. Organoids emerged as novel in vitro, near-physiological 3D models of the intestinal epithelium that accurately recapitulate in vivo phenotypes, including inflamed phenotypes of IBD, and are therefore highly valuable model systems to model IBD.

Methods: We developed a high-throughput inflammation assay by including patient-derived organoids in a Gut-on-Chip system. We hypothesized that a gut-on-a-chip model combined with patient-derived organoids can recapitulate key features of IBD (e.g., loss of barrier function, increased levels of cytokines). To recapitulate these hallmarks in vitro, both IBD and healthy-derived organoids were seeded on the apical side of both a Transwell model and the Mimetas OrganoPlate model. After a differentiation period, the epithelium was then basally exposed to a mix of proinflammatory stimuli (TNF-α, IL-1β) for 24 and 48 h. To assess the model, we analyzed gene expression of inflammation-related genes with RT-qPCR, cytokine secretion, cell morphology, barrier function (permeability assays), serotonin secretion and cytotoxicity.

Results: We observed a significant increase in cytotoxicity towards the epithelium 48h after basal exposure to the pro-inflammatory cytokine mix, while no significant effect on epithelial barrier integrity was observed.

Discussion/Conclusion: In the future, the model complexity can be further increased by adding extra cell types and ultimately be used to further dissect mechanisms of clinically relevant gut metabolites on the intestinal epithelial layer in the context of IBD.

37. The local intestinal interstitial cytokine profile provides an insight into inflamed bionaive patients with ulcerative colitis

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Introduction: Proinflammatory cytokines identified in the mucosal microenvironment at the site of inflammation are involved in the pathophysiology of inflammatory bowel diseases such as ulcerative colitis (UC). We hypothesize that the local cytokine production is significantly altered in inflamed regions of the intestine and cannot be predicted by plasma measurements. Our goal is to identify personalized cytokine signatures in UC patients' interstitial space depending on their disease progression.

Methods: We isolated interstitial fluid (IF) from the intestinal mucosa using the tissue elution method in 6 bionaive inflamed UC patients, 11 patients in remission, 13 patients in deep remission (DR) (UCEIS + Mayo = 0) and 27 healthy controls as part of the InFlame study (DRKS00031203). We took biopsies from rectum, descending and ascending colon and ileum in 400 mcg NaCl for 2 h elution in 4°C. Obtained IF and plasma was used for multiplex immunoassays of 18 proinflammatory cytokines.

Results: Cytokines such as VEGF, IL-16 and IL-12p40 are present in healthy controls and UC patients in the IF. Depending on the severity of the disease, more cytokines can be detected. Cytokine concentrations increase in the more aboral localizations of the colon with the rectum showing a unique cytokine pattern. Cytokines that can be detected in plasma show much lower concentrations and the cytokine signatures found in plasma and IF are distinct. Moreover, deep remission can be distinguished from mild activity in local interstitial profiles and clusters in the PCA with healthy individuals.

Discussion/Conclusion: Isolation of IF is a valuable approach to assessing inflammation in UC patients, improving our understanding of DR, mild residual activity and more severe conditions. We can identify cytokines that drive inflammation in UC and characterize the inflammatory cytokine signature in the intestinal interstitial space associated with a healthy gut. Future targeted therapies should also consider the unique cytokine profiles of individual patients being expressed in the rectum.

38. More than just an antibody: How secretory IgA could revolutionize IBD treatment

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Introduction: Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are characterized by chronic, relapsing inflammation of the gastrointestinal tract. While systemic anti-TNFα IgG therapies are effective for some, many patients either fail to respond or develop resistance, requiring alternative treatments. Secretory immunoglobulin A (SIgA), the predominant immunoglobulin at mucosal surfaces, plays a key role in immune exclusion and gut microbiota modulation. SIgA transport is mediated by the polymeric immunoglobulin receptor (pIgR), but in IBD, reduced pIgR expression suggests impaired SIgA transport. The role of SIgA in reverse transport within the intestinal epithelium and its interaction with gut bacteria in IBD remains unclear. This study aims to elucidate the functional relevance of SIgA in IBD pathogenesis and its potential as a therapeutic target.

Methods: The bioavailability and tissue distribution of orally administered SIgA antibodies were investigated in experimental colitis models using fluorescence-based imaging and confocal microscopy. The impact of SIgA on epithelial barrier integrity was assessed via transepithelial electrical resistance (TEER). Additionally, pIgR expression was quantified in colonic biopsies from IBD patients using qPCR to explore its role in SIgA transport.

Results: Reduced pIgR expression in active IBD biopsies indicates impaired SIgA transport, potentially worsening mucosal inflammation. Orally administered SIgA showed prolonged stability and preferentially localized to the intestinal mucosa, while systemic administration led to rapid degradation. In the TNBS-induced colitis model, SIgA treatment significantly reduced inflammation compared to IgG controls. Confocal imaging revealed SIgA uptake by epithelial and dendritic cells, suggesting their role in SIgA transport and immune modulation.

Discussion/Conclusion: Our findings highlight the critical role of SIgA, against inflammatory cytokines like TNF, in modulating intestinal inflammation and maintaining mucosal homeostasis. SIgA-mediated bacterial selection and immune modulation should offer a novel therapeutic target for IBD.

39. Comprehensive risk assessment and prognostic factors in celiac disease: Impact of persistent villous atrophy on disease complications and survival outcomes

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Introduction: Celiac disease (CD) is an autoimmune disorder triggered by gluten ingestion, leading to intestinal villous atrophy. While a gluten-free diet (GFD) is the mainstay of treatment, some patients exhibit persistent villous atrophy (pVA) on follow-up biopsies. The long-term implications of pVA in CD patients adhering to GFD remain concerning, particularly regarding complications and mortality risk.

Methods: Our primary objectives were to evaluate the association between pVA and long-term outcomes in CD patients and assess the performance of a novel scoring system identifying patients at high risk of pVA. We conducted a retrospective analysis including 151 patients diagnosed with CD between 2014 and 2020 who underwent follow-up duodenal biopsies. Patients with follow-up biopsies were older at diagnosis (mean 44 ± 16 years) and more frequently presented with classical CD patterns (50.6%). The median follow-up duration was 110 months (IQR, 74–161). Patients were categorized based on the Marsh classification (≥ 3a) for pVA assessment. CD complications included refractory CD, ulcerative jejuno-ileitis, abdominal lymphomas, and small bowel carcinomas. We implemented a 5-point scoring system incorporating age at diagnosis ≥45 years, classical CD pattern, lack of clinical response to GFD, and poor GFD adherence (weighted as two points).

Results: Approximately 24.5% of patients demonstrated pVA, with these individuals showing a significantly higher risk of complications (HR = 7.61, 95% CI: 3.18–17.64, $p < 0.001$). During follow-up, 9 patients (5.96%) developed complications, including three cases of refractory CD, one B-cell lymphoma, three cases of persistent malabsorption, and two cases of ulcerative jejuno-ileitis. Notably, 7 of these 9 patients had pVA. Patients who underwent follow-up duodenal biopsy showed improved overall survival compared to those who did not ($p < 0.05$). While most patients adhered to GFD, 35.1% maintained persistent VA at follow-up. Importantly, 29.72% of patients with pVA were asymptomatic. The median follow-up duration for patients with follow-up biopsies was significantly longer at 110 months (IQR, 74–161) compared to 60 months (IQR, 24–110) for those without follow-up biopsies ($p < 0.001$). Mortality causes in patients with CD complications were predominantly related to disease progression, with a higher frequency of CD-related deaths

Discussion/Conclusion: Our study demonstrates that pVA in CD patients following GFD significantly correlates with increased complication risks and mortality. The novel 5-point scoring system proves effective in stratifying patients by pVA risk, particularly in identifying high-risk individuals, including those who are asymptomatic. This scoring system enables personalized follow-up strategies and early intervention opportunities, potentially improving long-term outcomes in CD patients. Regular follow-up biopsies appear crucial for risk assessment and prognosis evaluation, especially in patients identified as high-risk by the scoring system.

40. A rare case of CVID-like disease based on haploinsufficiency of NF-κB1, with associated enteropathy

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Introduction: Common variable immunodeficiency (CVID) is a primary immunodeficiency disorder characterized by insufficient levels of immunoglobulins, resulting in increased susceptibility to infections. In approximately 90% of CVID-affected individuals, no genetic cause of the disease has been identified. NFKB1 haploinsufficiency is a significant etiology for CVID. Monoallelic NFKB1 variants are associated with opportunistic infections, autoimmunity, non-infectious enteropathy, autoinflammation, lymphoproliferation, and cancer. Here, we present a case of a patient with CVID enteropathy treated with vedolizumab.

Case report: A 39-year-old woman with a family history of CVID (father) was diagnosed with CVID in 2001 (confirmed in 2016 as a monogenic form of CVID based on haploinsufficiency of NF-κB1, pathogenic mutation c.2265T> A, p.Tyr755*). After several immunoglobulin substitution therapies and recurrent infections, she was admitted to the Internal Clinic of Gastroenterology with severe pancytopenia, diarrhea, and weight loss for treatment and further diagnostics. After complex examination, histology confirmed duodenal enteropathy (MARSH 3A). Coeliac disease was excluded both immunohistochemically and genetically. The diagnostic conclusion was enteropathy associated with CVID. Immunoglobulin substitution was increased, and sirolimus was added to the therapy. Due to adverse effects, sirolimus was replaced by budesonide. Despite reaching the maximum doses of immunoglobulins, no significant clinical or laboratory improvement was achieved. After further consideration, biological therapy with vedolizumab (300 mg IV Q8W) in combination with immunoglobulins was initiated. After the third cycle of therapy, rapid improvement in clinical symptoms, laboratory findings, and quality of life was achieved. The patient continues therapy and follow-up with good results.

Conclusion: Vedolizumab, due to its gut-selective mechanism of action, reduces the risk of developing opportunistic infections in patients with CVID-associated enteropathy and can, in selective cases, be administered to induce and maintain remission of CVID enteropathy. In the management of CVID-like diseases associated with enteropathy, we follow international recommendations for treatment.

41. Cell signalling in colitis-associated colon cancer

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Introduction: Colitis-associated carcinoma (CAC) is a major complication arising in patients with a long-standing ulcerative colitis (UC) and Crohn's disease (CD). Albeit numerous studies report on the mutational landscape of CAC, its transcriptomic landscape is poorly understood. Thus, to interrogate the tumour ecology and mechanisms behind CAC development, we adopted a muti-modal approach utilizing FFPE tissues from human CAC patients and colon organoids. We leveraged immunology bulk gene expression and spatial gene expression to derive a robust gene signature of CAC at a single cell resolution.

Methods: To comprehensively profile the CAC immune microenvironment, we created a targeted bulk RNA dataset (Nanostring immunology v2) covering relevant clinical FFPE samples encompassing 40 patients suffering from either IBD or CAC, alongside inflammation-free healthy controls (10 patients/group). We observed a robust upregulation of the SPP1 (Secreted Phosphoprotein 1) gene encoding osteopontin (OPN) and Fibronectin-1 (FN1) in CAC. Subsequently, we extended our methodology to spatially resolved transcriptomics (Xenium) using 5 µm FFPE sections from CAC (10 patients, UC patients (4 patients) and healthy controls (HC: 4 patients). This provided insights into the spatial and single cell expression of SPP1 and its target receptors at a subcellular resolution. Furthermore, we mapped the ligand-receptor pairs onto cell types to uncover SPP1 signalling in CAC. These findings were validated at a protein level by whole FFPE section confocal microscopy.

Results: Immunology gene expression (Nanostring) dataset revealed a strong upregulation of SPP1 gene encoding OPN in CAC as compared to UC and CD. Spatially resolved transcriptomics (Xenium) unveiled the spatial heterogeneity of SPP1 expression in CAC, that is primarily arising from CD68+ CD163+

macrophages in CAC, validated through OPN/CD68 immunostainings. Ligand-receptor (LR) analysis revealed a distinct LR pairing focusing on SPP1, that is secreted by macrophages (outgoing signal) and signals to T cells (incoming signal) via upregulated CD44 and integrin receptors. Furthermore, CAC tumour cells surrounding the SPP1+ macrophages exhibited a distinct gene expression signature associated with T cell exclusion and immunosuppression in CAC.

Discussion/Conclusion: We identified a CAC specific upregulation of SPP1 at both RNA and protein levels, expressed by CD68+ CD163+ macrophages. Mutually exclusive spatial location of SPP1/OPN+ macrophages and CD8+ T cells suggests a crucial indirect role of SPP1/OPN in mediating an immunosuppressive tumour microenvironment. We further uncovered a CAC-specific, single cell gene expression signature that has the potential to identify pre-malignant stages of CAC.

42. Dependence of interleukin 17 and 23 expression in patients with inflammatory bowel disease on nosology and severity

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Introduction: Inflammatory bowel disease (IBD) is a serious medical and social problem, which leads to a significant interest in the study of etiology, pathogenesis, development of diagnostic and therapeutic complexes. There is growing evidence that IL-17 and IL-23 are potent mediators of inflammatory reactions in various tissues, including the intestine. In this regard, it is important to study the level of cytokines depending on the severity of IBD. The aim of the study was to determine the expression of interleukins 17 and 23 in patients with inflammatory bowel disease, depending on the nosology and severity.

Methods: We examined 80 patients with IBD (63 patients with ulcerative colitis [UC] and 17 patients with Crohn's disease [CD)], who were divided according to the severity of the course by the Mayo index for UC and the Best index for patients with CD. The control group consisted of 10 practically healthy individuals. Serum levels of IL-17 and IL-23 were determined by enzyme-linked immunosorbent assay using a Stat Fax 303 Plus enzyme-linked immunosorbent assay (USA). Reagent kits from TECAN IBL International GmbH (Germany) were used in the study.

Results: The concentration of IL-17 in patients with UC and CD was significantly higher by 11.4 times ($p < 0.05$) and 17.6 times ($p < 0.05$), respectively, compared with the control group. The median level of IL-23 was 1.5 times higher (p 0.05) in the group of patients with CD compared to the group of patients with UC. The median level of IL-23 in patients with UC (8.1-fold, $p < 0.05$) and CD (7.5-fold, $p < 0.05$) was significantly increased compared with controls, but did not differ significantly between nosologies. The level of IL-17 was significantly higher in patients with moderate and severe UC compared with the control group. There were no significant differences in IL-17 levels between groups of UC patients with different severity. The median level of IL-23 was significantly higher in patients with moderate UC (7.4-fold, $p < 0.05$) and in patients with severe UC (11.2-fold, $p < 0.05$) compared with controls. In patients with severe UC, the concentration of IL-23 was 1.5 times higher ($p < 0.05$) compared with its level in patients with moderate UC. Correlations of IL-23 levels with the endoscopic activity index ($r = +0.347$; $p = 0.005$) and Mayo index ($r = +0.295$; $p = 0.020$) were established. The content of IL-17 was 9.9 times ($p < 0.05$) and 9.0 times ($p < 0.05$) higher than in the control group in patients with moderate and severe severity of the course of CD, respectively, without a significant difference in severity. In the group of patients with severe CD, the level of IL-23 was 1.6 times ($p < 0.05$) higher than in the group of patients with moderate CD.

Discussion/Conclusion: The median level of IL-17 was significantly higher by 1.5 times ($p < 0.05$) in patients with CD compared to UC. The level of IL-23 depended on the severity of both pathologies ($p < 0.05$). Thus, quantitative determination of IL-17 levels in the blood serum of patients with IBD may be a useful additional criterion for differential diagnosis between UC and CD, and IL-23 may be a clinical marker of disease severity.

43. JAK inhibition to target fibroblasts and IBD-related fibrosis

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Introduction: Intestinal fibrosis is a common complication of inflammatory bowel disease (IBD). Uncontrolled accumulation of extracellular matrix (ECM) deposited by fibroblasts is thought to be the underlying cause of fibrogenesis. While Janus kinases (JAK) inhibitors are effective anti-inflammatory therapies for IBD, their potential role in treating intestinal fibrosis remains unclear. We investigated the effects of JAK inhibition on intestinal fibroblasts in vitro and in vivo.

Methods: In vitro, human CCD-18Co and primary colonic fibroblasts were stimulated with cytokines in the presence of 10 uM tofacitinib or upadacitinib to assess JAK/STAT signaling by Western blot. For the T ell transfer colitis model, Rag-/- mice (n = 5–12/group) were used. After engraftment of donor T cells, the severity of colitis was evaluated with the mouse endoscopy score (MEICS) and mice were treated with upadacitinib (20 mg/kg, 4x/week intraperitoneal injection). Intestinal fibroblast subsets were analyzed by flow cytometry. Sirius red staining was performed to measure ECM deposition.

Results: Re-analysis of our previously published scRNA sequencing data from fibrostenotic tissue of Crohn's disease patients identified that a pathogenic subset of activated FAP+ fibroblasts was driven by STAT3 activation. Inflammatory cytokines activated the JAK-STAT pathway in human fibroblasts and both upadacitinib and tofacitinib strongly inhibited the pathway in a concentration dependent manner. Mice treated with upadacitinib reduced MEICS compared to controls (2.4 vs. 5.3). Interestingly, the CD90+PDGFR-β+ fibroblast subset were less abundant upon JAK-inhibition. Finally, upadacitinib restored the normal colonic ECM deposition.

Discussion/Conclusion: In conclusion, our study shows that the JAK-STAT pathway is activated in intestinal fibroblasts and upadacitinib inhibits this pathway in vitro. Furthermore, human data showed the JAK-STAT pathway activation in FAP+ fibroblasts and in mice, JAK inhibition has an effect on fibroblasts subsets and ECM deposition. This shows the potential of JAK-inhibitors to target more than immune cells.

44. Age-related T cell dynamics in patients with Crohn's disease reveal CD8+CD28- T cells as potential mediators of clinical remission

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Introduction: Aging has long been considered a contributing factor for the development of various inflammatory diseases such as osteoporosis and rheumatoid arthrosis. This is, however, not the case for inflammatory bowel diseases (IBD), where patients are usually diagnosed in their 20 s and 30 s. This study focuses on understanding age-related immune cell changes in patients with Crohn's disease, focusing on T cells as key mediators of inflammation.

Methods: Blood and tissue samples from patients with CD (age 19–80 years) were collected and evaluated markers for T cell maturation and co-stimulatory molecules using flow cytometry and immunohistological stainings. Disease activity of the patients was assessed using Harvey-Bradshaw-Index (HBI < 5 was considered remission; HBI ≥ 5, active disease).

Results: Our data showed that aging did not impact the relative numbers relative numbers of CD4+ and CD8+ T cells. However, tSNE plots revealed age-related changes in clustering signatures in young (< 50 years old) CD patients compared to old ones (≥ 50 years old). Further analysis based on the disease activity indicated that young patients with disease in remission have significantly increased relative numbers of naïve CD8+ T cells that express CD27 and CD28 co-stimulatory molecule, while elderly CD patients in remission rather accumulate exhausted CD8+ T cells. We observed a similar phenotype in tissue samples from patients with CD, where CD8+CD28- T cells numbers significantly declined with age. Interestingly, increased numbers of CD8+CD27-CD28- T cells led to significantly less major adverse outcomes in patients with CD in remission monitored over a period of 18 months. In elderly patients with active CD, a specific cluster of cells with high expression of CD45RA and CD27, but not CD4 or CD8, was predominant, suggesting different modulatory mechanisms of disease in aging patients compared to the young ones.

Discussion/Conclusion: In conclusion, immune cell dynamics change during aging in patients with IBD, where CD8+CD28- T cells accumulation might be potential mediators for clinical remission. Understanding the functional role of these cells might help for the development of targeted therapies for CD.

45. Epithelial telomere shortening in the pathogenesis of ulcerative colitis

Oana-Maria Thoma (Erlangen, DE), Imen Larafa (Erlangen, DE), Markus Neurath (Erlangen, DE), Maximilian Waldner (Erlangen, DE)

Introduction: Aging is widely described as the loss of function at cellular and molecular level which occurs with time. It is not surprising therefore that aging is considered contributing factor to a variety of disorders including inflammatory bowel diseases (IBD). For example, it was shown that typical aging-like phenotypes such as telomere shortening can be often observed in intestinal epithelial cells (IECs) of patients with ulcerative colitis (UC). Nevertheless, the functional role telomere length in IECs is poorly understood. Here, we aim to evaluate the role of telomere attrition in IECs in the pathogenesis of UC.

Methods: We have used publicly available single cell RNA sequencing (scRNAseq) datasets (GSE214695, Nat Commun, 2023) to determine whether mucosal inflammation is associated with differential expression of telomerase-associated genes (TERC, TERT, etc.) in IECs from healthy individuals and IBD patients (n = 6 samples/group). Furthermore, we evaluated the response of telomerase-deficient mice (TERC-/-) to inflammation during aging and in acute and chronic DSS models.

Results: Our results show a downregulation of telomerase-associated genes expression in IECs from UC but not CD patients in comparison to healthy controls. Furthermore, Gen Set Enrichment Analysis (GSEA) of subtelomeric genes in IECs further revealed KEGG pathways associated with inflammation, proposing an influence of telomere shortening on immune regulation. In telomerase-deficient mice, telomere shortening occurs when the mice are bred over several generations (G1–G3). In steady state conditions, young Terc-/- mice showed reduced crypt size as early as G2, along with impaired bud formation in organoid cultures. Furthermore, old Terc-/- G2 mice (30 weeks old) show significant signs of inflammation, along with significantly decreased epithelial cell proliferation and increased cell death. Similarly, Terc-/- G2 mice developed significantly more inflammation than the control ones when exposed to DSS colitis models. Last, telomere attrition in aged Terc-/- G2 mice affected immune infiltration as well, where significantly increased CD4+ T cells and neutrophils were predominant.

Discussion/Conclusion: Overall, progressive telomere shortening in IECs can lead to inflammatory settings in the gut. In the future, studying the effects of therapeutics in modulating telomere length in epithelial cells might provide novel therapeutic strategies in IBD.

46. Epithelial CMAS is key to intestinal epithelial cell function and gut immune homeostasis

Ru Wang (Erlangen, DE)

Introduction: Growing evidence suggests that dysregulated sialylation contributes to the development and progression of inflammatory bowel disease (IBD). Cytidine monophosphate-N-acetylneuraminic acid synthetase (CMAS) catalyses the conversion of N-acetylneuraminic acid (Neu5Ac) to cytidine monophosphate-N-acetylneuraminic acid (CMP-Neu5Ac), which serves as a sialic acid donor substrate used by sialyltransferases to sialylate target molecules. However, CMAS has a unique nuclear localisation that distinguishes it from the sialyltransferases in the sialic acid biosynthetic pathway. Here we investigated the role of CMAS in intestinal epithelial cell homostasis and inflammation.

Methods: IBD and control samples were analysed for CMAS expression. Newly generated intestinal epithelium-specific CMAS-deficient mice and intestinal organoids were used to dissect the function of CMAS in intestinal homeostasis in vitro and in vivo.

Results: We observed reduced CMAS expression in IBD patients, which was negatively correlated with S100A9 and IL6. Conditional deletion of Cmas in mice resulted in increased susceptibility to DSS-induced colitis, characterised by greater weight loss, severe histological damage and elevated levels of inflammatory cytokines. Notably, CmasΔIEC mice exhibited Paneth and goblet cell deficiencies and epithelial barrier dysfunction. In addition, CMAS deficiency impaired intestinal organoid formation and caused greatly increased levels of Neu5Ac in the colon and in small intestinal organoids, which could lead to a pro-inflammatory tissue environment and Paneth cell loss. Interestingly, stimulation of intestinal epithelial organoids with Neu5Ac for 24 hours, followed by RNA sequencing and Metascape-based gene

set enrichment analysis, revealed that Neu5Ac specifically induced inflammation-related pathways, including IL-17 signalling, cytokine production and inflammatory responses.

Discussion/Conclusion: Collectively, our results suggest that CMAS deficiency in the intestinal epithelium is a hallmark of UC and that CMAS-dependent processes are key to Paneth cell maintenance and resistance to intestinal inflammation.

47. Intestinal and liver fatty acid-binding proteins (I-FABP and L-FABP) and fibroblast growth factor (FGF-19) may be useful markers of impaired mucosal barrier and associated liver damage in inflammatory bowel diseases in children

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Introduction: In inflammatory bowel diseases (IBD) about 50% of patients develop liver disorders of different severity, one of the suggested causes is impaired mucosal barrier and the associated increased intestinal permeability.

The aim of the study was to assess the effect of phenotype of IBD on intestinal mucosal barrier and liver damage. Intestinal and liver fatty acid-binding proteins (I-FABP and L-FABP) and fibroblast growth factor (FGF-19), which are sensitive markers of mucosal and liver damage, and laboratory and imaging results were assessed.

Methods: There were 20 children with ulcerative colitis (UC) and 20 with Crohn's disease (CD) (22 boys, 18 girls, mean age: 14.3 years, range, 5.5–18) and 20 healthy controls enrolled into the study. Serum I-FABP, L-FABP and FGF-19 concentrations were assessed at the baseline, before the treatment and after 2 weeks of treatment, using ELISA immunoassays. Statistical analysis was performed with Statistica 13.0 software (TIBCO Software, USA) using Mann-Whitney U test, Wilcoxon signed rank test and Spearman's correlation rank test.

Results: We found significantly elevated serum I-FABP in active UC group when compared to active CD group and controls ($p < 0.05$), while in inactive UC group and inactive CD group they were comparable to controls (p = n.s.). Moreover, serum L-FAPB was significantly increased in active UC group and in active CD group when compared to controls ($p < 0.05$) and in inactive UC group when compared to inactive CD group and controls ($p < 0.05$). When we assessed serum FGF-19 concentrations, we found them significantly increased in active UC and active CD groups when compared to controls ($p < 0.05$), and in inactive UC group when compared to inactive CD group and controls ($p < 0.05$).

Discussion/Conclusion: Increased serum concentrations of I-FABP and L-FABP may be related to impaired mucosal barrier in IBD and may affect liver impairment. Increased serum FGF-19 concentration may be associated with liver damage in the course of IBD in children

48. TIM molecules and ITK-related signaling in the immunopathogenesis of microscopic colitis

Benno Weigmann (Erlangen, DE)

Introduction: Microscopic colitis (mC), an increasingly prevalent inflammatory bowel disease characterized by chronic watery diarrhea and a macroscopically normal colonic mucosa, is subclassified into collagenous colitis (CC) and lymphocytic colitis (LC) based on distinct histopathological features: subepithelial collagen deposition (> 10 µm) and intraepithelial lymphocytosis, respectively. This study investigates the differential expression and potential functional relevance of T cell immunoglobulin and mucin domain (TIM) family members, specifically TIM-1 (HAVCR1) and TIM-3 (HAVCR2), in the pathogenesis of mC subtypes, hypothesizing a role in disease-specific immune dysregulation.

Methods: Colonic tissue samples from a well-characterized mC cohort were analyzed using RNA-sequencing to determine the differential expression of HAVCR1 and HAVCR2. The cohort included patients with active

untreated CC (auCC), active untreated LC (auLC), budesonide-treated CC (itCC), and active refractory CC (aRCC). Immunofluorescence staining was performed to assess the distribution and expression levels of TIM-1 and TIM-3 on CD3+ T cells within the colonic lamina propria and epithelium of each patient group. Quantitative image analysis was used to determine the proportion of TIM-1/3+ CD3+ T cells.

Results: HAVCR2 mRNA expression was significantly upregulated in active, inflammatory LC compared to CC and a previously described channelopathic LC subtype, suggesting a specific role for TIM-3 in the immune response in LC. Interestingly, the ITK-related gene LCP2 was upregulated across all mC subtypes, irrespective of treatment status, implicating a common signaling pathway in mC pathogenesis. Differential expression of other ITK-related genes was observed; LCK, LCP2, and LGALS9 were enriched in inflammatory LC, while SPI1 and ZAP70 were enriched in CC. At the protein level, TIM-1 expression on CD3+ T cells was significantly elevated in auCC patients compared to LC patients and healthy controls. Budesonide treatment normalized the TIM-1 expression in responsive CC patients but not in aRCC patients.

Discussion/Conclusion: These findings suggest that TIM family molecules, particularly TIM-1 in CC and TIM-3 in LC, and downstream signaling components such as LCP2 and ZAP70, contribute to the distinct immunopathogenesis of mC subtypes. Aberrant TIM-1 expression in budesonide-refractory CC may represent a mechanism of treatment resistance. Targeting TIM signaling pathways represents a potential therapeutic strategy for mC, potentially allowing for more targeted and less immunosuppressive interventions in the future.

49. Epithelial IRF1 in shapes the intraepithelial lymphocyte niche

Stefan Wirtz (Erlangen, DE), Tamara Leupold (Erlangen, DE), Elahe Esmaeili (Erlangen, DE)

Introduction: The transcription factor Interferon Regulatory Factor 1 (IRF1) is encoded in the IBD5 locus and has been shown to be a key regulator of immune responses: It has benn implicated in the development and function of various immune cell populations, including natural killer (NK) cells, innate lymphoid cells (ILCs), and T cells.

Methods: Conditional knockout mouse models, bulk and single-cell RNA sequencing, organoid models and flow cytometry were used to analyse immune epithelial crosstalk in the small intestine.

Results: Wedemonstrate that intestinal epithelial cell (IEC)-specific rather than hematopoietic deletion of Irf1 significantly reduces in particular subsets of natuaral intraepithelial lymphocyte (IEL) populations. Mechanistically, we identify IRF1 as central regulator of butyrophilin-like (Btnl) molecule transcription in IECs. These molecules were previously identified as important for γδ IEL accumulation and maintenance in the gut. Further studies using an small intestinal inflammation model further established IRF1 as crucial epithelial regulator of IEL homeostasis in both steady-state and infectious/inflammatory diseases.

Discussion/Conclusion: This study provides new insights into the molecular mechanisms underpinning gut immune epithelial regulation and offers potential pathways for therapeutic intervention in diseases involving IEL dysfunction.

50. QingChangHuaShi Granules improve mucosal immunity in the treatment of ulcerative colitis by regulating Th17/Treg via dendritic cells

Kai Zheng (Nanjing, CN), Jia Jia (Nanjing, CN)

Introduction: Mucosal immune disorders play an important role in the occurrence and development of ulcerative colitis (UC), and restoring immune tolerance is helpful in the treatment of UC. The type of immune response is dependent on the maturity of dendritic cells (DCs). Immature DCs hold the function of inducing immune tolerance through promoting the balance of Th17/Treg. The Chinese patent medicine QingChangHuaShi Granules (QCHSG) is clinically used for the treatment of UC and can improve the mucosal T cell immunity of UC patients. However, the mechanisms of QCHSG remain unclear. The aim of this study was to explore the effect of QCHSG on mucosal immunity in UC models.

Methods: We carried out QCHSG intervention in vitro experiments on T cells and in vivo experiments on IL-2-/- UC animal models. Surface antigen expression of DCs (MHC II and CD86) and IL-12, as indicators of mature DCs after LPS stimulation in the absence or presence of QCHSG were detected. Then, the effect of QCHSG-treated DCs on T cells and IL-2-/- mice was observed. Th17/Treg proportions, the expression levels of IL-17 and IL-10 were detected.

Results: QCHSG inhibited the up-regulation of MHC II and CD86, decreased IL-12 secretion. DCs exposed to QCHSG reduced Th17 proliferation and expression of IL-17mRNA, while induced CD25+Foxp3+Treg differentiation from naive CD4+ T cells and enhanced production of IL-10mRNA. Histological improvements in IL-2-/- mice were found in response to QCHSG and QCHSG-treated DCs. QCHSG and QCHSG-treated DCs also elevated levels of IL-10 and Foxp3, decreased expression of IL-17 and Th17/Treg proportion in IL-2-/- mice.

Discussion/Conclusion: These results indicate that QCHSG can treat UC effectively, through improving mucosal immunity by inhibiting maturation of DCs to regulate the balance of Th17/Treg.

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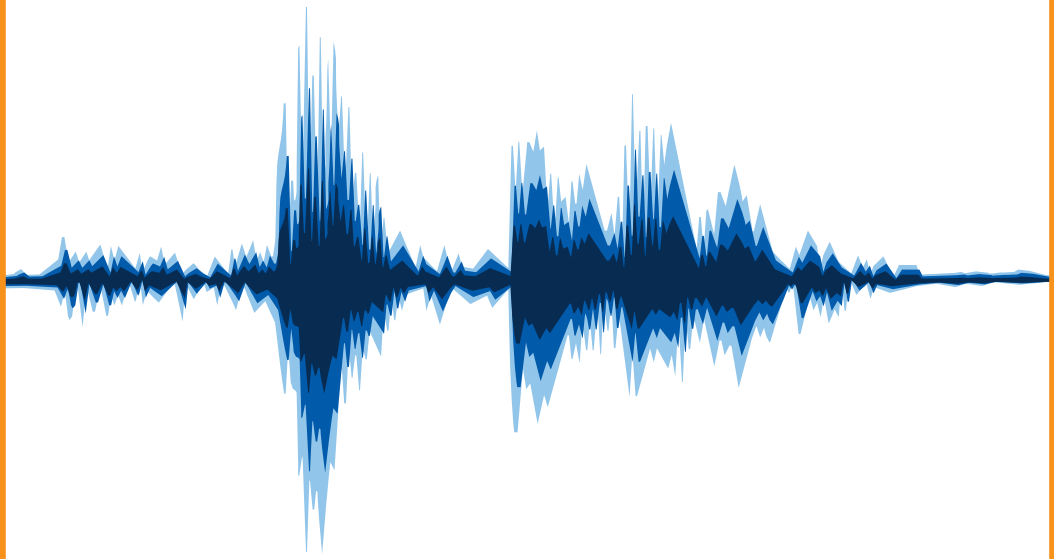

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P241E/2025/300St