NEXT GEN LIVER IMMUNOLOGY: BRIDGING BASIC SCIENCE AND CLINICAL PRACTICE

February 5-6, 2026

Symposium

FREIBURG, GERMANY

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6 credit hours (CME) have been awarded by the European Union of Medical Specialists (UEMS).

PREFACE

Welcome to the symposium NEXT GEN LIVER IMMUNOLOGY: Bridging Basic Science and Clinical Practice that brings together scientists, rising stars and clinicians dedicated to advancing the understanding of hepatic immunology across key disease areas. By integrating basic and translational research with clinical perspectives, this meeting aims to foster meaningful dialogue and collaboration across disciplines and career stages.

Central topics include **viral and autoimmune hepatitis**, **steatotic liver diseases**, **liver cirrhosis** and **hepatocellular carcinoma** (HCC). These conditions exemplify the complex immunological mechanisms that underlie liver pathology and demand innovative therapeutic strategies. As the field continues to evolve, insights into immune regulation, tolerance, inflammation, and tissue remodeling are becoming increasingly relevant for clinical translation.

A particular emphasis of this symposium lies in supporting early-career researchers. By offering a platform for young scientists to present their findings and engage with peers and senior experts, the event promotes the development of the next generation of liver immunologists and clinician-scientists.

A big thank you goes to all speakers and participants whose work and engagement shape this symposium for scientific exchange and future collaboration. Your contribution is key to advancing basic and translational liver immunology.

I am looking forward to welcoming you in the heart of the Black Forest, in Freiburg, a city blessed with more sunshine than any other German city and renowned for its academic tradition on hepatology and liver immunology that provides an ideal environment for focused exchange and new collaborations.

See you soon!

Robert Thimme

NEXT GEN LIVER IMMUNOLOGY: BRIDGING BASIC SCIENCE AND CLINICAL PRACTICE

February 5-6, 2026

Scientific Organization:
Prof. Dr. Robert Thimme
Director Klinik für Innere Medizin II
Universitätsklinikum Freiburg
Hugstetter Straße 55
79106 Freiburg
Germany

Congress Venue:
Konzerthaus Freiburg
Konrad-Adenauer-Platz 1
79098 Freiburg im Breisgau
Germany

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, February 5, 2026
12:00 – 18:00
at the congress office

Thursday, February 5, 2026

12:00	Registration
13:00	Welcome *Robert Thimme, Freiburg*

SESSION I

Viral and autoimmune hepatitis

Chairs:	*Maike Hofmann, Freiburg; Christoph Schramm, Hamburg*
13:10	Inducible Hepatic-Associated Lymphoid Tissue (iHALT): liver as a surrogate secondary lymphoid organ *Arash Grakoui, Atlanta*
13:35	T cell immunity in HEV infection *Tobias Böttler, Freiburg*
14:00	Immunology of HBV: Novel perspectives for immunotherapy *Matteo Iannacone, Milan*
14:25	NK cells and biliary tract inflammation in PSC *Britta Zecher, Hamburg*
14:50	Hepatic orchestration of local versus systemic T cell responses *Georg Gasteiger, Würzburg*
15:15	**Coffee break with ePoster session**

SESSION II

Steatotic liver diseases

Chairs:	*Natascha Röhlen, Freiburg; Frank Tacke, Berlin*
15:55	Modulation of the microbiome in steatotic liver diseases *Kai Markus Schneider, Dresden*
16:20	Macrophages and MASLD *Charlotte Scott, Ghent*
16:45	Spatial multiomics in MASLD *Paul Horn, Berlin*
17:10	Intermittent fasting in MASH and liver cancer *Suchira Gallage, Tübingen*
17:35	Liver specific determinants of antigen-specific immunity *Percy A. Knolle, Munich*
18:00	**Networking and ePoster session with light refreshments**

Friday, February 6, 2026

SESSION III	
Liver cirrhosis and portal hypertension	
Chairs:	*Marcus Cornberg, Hannover; Magdalena Filipowicz Sinnreich, Basel*
08:45	Systemic inflammation in liver fibrosis and cirrhosis *Thomas Reiberger, Vienna*
09:05	ILCs in liver fibrosis and cirrhosis *Jakob Nattermann, Bonn*
09:25	Immune cells in cirrhotic ascites: Friend or foe? *Christian Niehaus, Hannover*
09:45	Novel immunotherapies for liver cirrhosis *Stuart Forbes, Edinburgh*
10:05	Hepatic stellate cells: Novel functional aspects and therapeutic implications *Robert F. Schwabe, New York*
10:25	**Coffee break with ePoster session**

SESSION IV

Liver cancer

Chairs:	*Tom Lüdde, Düsseldorf; Charlotte Rennert, Freiburg*
11:00	HCC spatial single cell immune scoring system *Bertram Bengsch, Freiburg*
11:20	Immune therapy of liver cancer *Matthias Pinter, Vienna*
11:40	MAIT cells and HCC *Benjamin Ruf, Tübingen*
12:00	Novel immune approaches in HCC *Anna Pasetto, Oslo*
12:20	Presentation of poster awards
12:30	**Lunch with ePoster session**
13:15	**Opening of the annual meeting of the GASL**

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.

You will receive an automatic confirmation of registration by e-mail.
Please transfer the congress fee to the bank account listed in the e-mail within two weeks.

CONGRESS FEES

Scientific Program of Symposium	EUR 150
Students (copy of student ID required)	EUR 75

The congress fees include:
– Refreshments during coffee breaks
– Lunch on Thursday, February 5 and Friday, February 6, 2026
– Snacks during scientific discussion on Thursday, February 5, 2026
– A copy of the final program

CONGRESS OFFICE AND REGISTRATION

Opening Hours:

Thursday, February 5, 2026	12:00 - 18:00 h
Friday, February 6, 2026	8:00 – 12:30 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

Konzerthaus Freiburg
Konrad-Adenauer-Platz 1
79098 Freiburg im Breisgau
Germany

By car
From north and south via A5 Frankfurt-Basel Rhine Valley motorway, exit Freiburg-Mitte. Follow the signs. From east via the A81 Stuttgart-Singen motorway and B31 Donaueschingen, Titisee-Neustadt. Pass Freiburg on Schwarzwaldstrasse in the direction to motorway A5 and follow the signs. There is a huge underground car park belonging to Konzerthaus and Freiburg main station.

By plane
Basel-Mulhouse-Freiburg Airport (EuroAirport) is the nearest airport, just an hour's drive away. It offers international scheduled flights and charter flights. The airport bus runs directly to Freiburg main bus station, opposite the Konzerthaus. For more information see www.freiburger-reisedienst.de. Bigger airports like Zurich or Frankfurt offer good train connections to Freiburg main station.

By train
The Konzerthaus is ideally connected to public transport. Freiburg main railway station is directly opposite. The bus station and tram and bus stops are also located here. Taxis are available in front of the main entrance to the Konzerthaus Freiburg.

CONFLICTS OF INTEREST

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

Robert Thimme: no potential conflict of interest to report

POSTER ABSTRACTS

1. Morphometric profiling of immune cell populations in HCV-associated cirrhosis: Insights into spatial organization and clustering
   M. Aaa Hegazi, F. Pasqualini, M. Chiriva-Internati, F. Grizzi (Rozzano, IT; Houston, US)
2. Association of liver function tests, lipid profile and FibroScan findings in metabolic dysfunction-associated steatotic liver disease (MASLD)
   M. Alsenbesy, H. Sedeek (Manama, BH; Qena, EG)
3. BMP signaling dysregulation as a mechanistic link in alcohol-related hepatic osteodystrophy
   R. Aspera-Werz, M. Hammour, Y. Xin, A. Nussler (Tübingen, DE)
4. Distinct immune landscapes in autoimmune vs. checkpoint inhibitor-associated hepatitis revealed by spatial profiling
   S. Besson, L. Krimmel, N. Terway, J. Mitschke, F. Roettele, I. Godbole, H. Salie, P. Bronsert, D. Rafei-Shamsabadi, F. Meiss, U. Ehmer, A. Krackhardt, M. Schwabenland, R. Sankowski, M. Prinz, H. Luxenburger, M. Hofmann, T. Boettler, M. Schultheiss, T. Lowinus, R. Zeiser, C. Kreutz, R. Thimme, C. Mogler, B. Bengsch (Freiburg, Munich, DE)
5. Focal adhesion kinase (FAK)-dependent Immune escape in hepatocellular carcinoma
   S. Buechel, N. Vesper, L. Mack, F. Juehling, S. Sagar, B. Bengsch, R. Zeiser, C. Berlin, P. Holzner, P. Bronsert, T. Baumert, R. Thimme, M. Hofmann, N. Roehlen (Freiburg, DE; Strasbourg, FR)
6. MAIT cell recognition of disease-associated metabolite self-antigens in metabolic dysfunction-associated liver disease (MASLD)
   A. Chancellor, C. Rodrigues, T. Jaeger, J. Murle, M. Filipowicz Sinnreich (Basel, CH)
7. The expression and function of 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) in hepatocellular carcinoma
   H. Ehnis, A. Bosserhoff, C. Hellerbrand (Erlangen, DE)
8. Effects of hepatic stellate cells on melanoma cells
   V. Freutsmiedl, A. Bosserhoff, C. Hellerbrand (Erlangen, DE)
9. Microbiota-driven break of B cell tolerance promotes spontaneous anti-HBsAg seroconversion in HBV transgenic mice
   V. Fumagalli, M. Grillo, C. Perucchini, C. Beccaria, P. Di Lucia, M. Rava, C. Abbott, L. Giustini, S. Becattini, L. Guidotti, M. Iannacone (Milan, IT; Geneva, CH)
10. Microbiota-specific T cell responses in patients with immune checkpoint inhibitor therapy-associated hepatitis
    M. Goncharov, S. Jess, G. Rios Martini, C. Saggau, L. Rathjens, S. Schneiders, E. Kuhnke, C. Bartzke, C. Baldus, R. Guenther, P. Bacher (Kiel, DE)
11. T cell tolerance is maintained by liver sinusoidal endothelial cells in liver fibrosis
    C. Gottwick, P. Averhoff, C. Casar, S. Pilz, V. Haas, D. Krzikalla, S. Fleischer, A. Carambia, J. Herkel (Hamburg, DE)
12. Integrative systems biology identifies cell cycle – Immune crosstalk biomarkers in hepatocellular carcinoma through PPI network analysis
    F. Grizzi (Rozzano, IT)

13. Bile acid dysregulation impairs bone health: Evidence from human 3D co-culture and murine models of cholestasis
M. Hammour, K. Pejic, A. Molinari Colabelli, A. Nuessler, R. Aspera-Werz (Tübingen, DE)

14. Blood profile of innate lymphoid cells in HCC patients is cancer stage specific and undergoes functional switch during immunotherapy"
B. Heinrich, T. Ristic, L. Kusche, S. Chauhan, T. De Castro, S. Dey, L. Becker, S. Klein, S. Engelskircher, C. Po-Chun, P. Huang, F. Korangy, A. Saborowski, A. Vogel, T. Wirth, N. Woller, H. Wedemeyer (Hannover, DE; Bethesda, US)

15. Expression and function of stanniocalcin 2 in hepatocellular carcinoma
P. Hoefer, A. Bosserhoff, C. Hellerbrand (Erlangen, DE)

16. A peritoneal macrophage-Th1/Th17 axis drives inflammation in spontaneous bacterial peritonitis
O. Ibidapoobe, M. El Hassani, J. Reissing, M. Frissen, F. Haedge, M. Murad, K. Grosse, T. Bruns (Aachen, DE)

17. Lipid accumulation promotes tumorigenic and prometastatic characteristics of colorectal cancer cells
T. Itzenhaeuser, F. Schildt, J. Sommer, A. Bosserhoff, C. Hellerbrand (Erlangen, DE)

18. G protein-coupled receptor 37 as protumorigenic factor in hepatocellular carcinoma
S. Jochem, A. Bosserhoff, C. Hellerbrand (Erlangen, DE)

19. Investigating de novo virus-specific T cell immunity in the absence of PD-1 signaling
L. Kelsch, T. Boettler, M. Maas, J. Arnold, C. Neumann-Haefelin, R. Thimme, M. Hofmann, S. Sagar (Freiburg, Cologne, DE)

20. Comparing the role of gut microbiota in metabolic dysfunction-associated steatotic liver disease and alcoholic liver disease
R. Knut, L. Sydorchuk, I. Zabolotna, R. Sydorchuk, A. Sydorchuk, I. Hryhorchuk, I. Sydorchuk, I. Sydorchuk (Chernivtsi, Kyiv, UA; Neu-Ulm, Siegen, DE)

21. Reduced hepatitis B surface antigen (HBsAg) accumulation in hepatocytes of transgenic mice infected with Schistosoma mansoni
M. Kuisat, F. Stettler, S. Kaur, D. Glebe, V. Von Buelow, C. Grevelding, E. Roeb, M. Roderfeld (Giessen, DE)

22. Non-selective beta blockers reduce inflammatory bystander CD8+ T cell activation in decompensated liver cirrhosis
A. Lietzau, I. Tapken, S. Kim, A. Kraft, S. Schuette, T. Tergast, B. Maasoumy, H. Wedemeyer, I. Drath, G. Zurek, E. Shin, M. Cornberg, C. Niehaus (Hannover, Bremen, DE; Daejeon, KR)

23. HBV-specific T-cell response and viral evolution in a transmission pair with acute-persistent HBV infection
M. Maas, A. Denecke, A. Walker, J. Lang-Meli, H. Luxenburger, J. Timm, R. Thimme, M. Hofmann, C. Neumann-Haefelin (Freiburg, Düsseldorf, Cologne, DE)

24. Characterizing the adaptive immune response to avian influenza H5 after seasonal influenza vaccination in patients with chronic liver disease
L. Mueller, W. Hailemichael, D. Reeg, K. Ciminski, P. Reuther, M. Schwemmle, R. Thimme, M. Hofmann, H. Luxenburger (Freiburg, DE)

25. Induction of TNF-α signaling in hepatocytes is reduced by ADAM17-mediated TNFR1 shedding through augmenter of liver regeneration (ALR)
A. Reithmeier, C. Voigt, M. Kubitza, M. Melter, T. Weiss (Regensburg, DE)

26. Viral load drives CD8+ T cell dysfunction in male versus female patients with chronic HBV infection
    C. Rogaczewski, M. Maas, M. Hofmann, R. Thimme, C. Neumann-Haefelin, D. Bettinger, J. Lang-Meli (Freiburg, Cologne, DE)
27. Identification and validation of gene expression pattern associated with inflammation in a cell culture model of Wilson's disease
    M. Sasula, A. Held, M. Krawczyk, A. Zibert, H. Schmidt, R. Broering (Essen, Münster, DE)
28. Loss of Interleukin-13 disrupts hepatic lipid homeostasis in mice
    F. Schmidt, V. Von Buelow, S. Riebeling, D. Felske, M. Hagen, F. Stettler, A. Tschuschner, H. Mueller, K. Eder, E. Most, G. Morlock, A. Haase, M. Roderfeld, E. Roeb (Giessen, DE)
29. Tumor-promoting and prometastatic characteristics of melanoma cells are enhanced by adipocytes
    B. Starke, J. Sommer, A. Bosserhoff, C. Hellerbrand (Erlangen, DE)
30. Inhibition of JNK worsens liver pathology in Schistosoma mansoni infected mice
    F. Stettler, L. Knedla, M. Hagen, V. Von Buelow, H. Mueller, A. Tschuschner, D. Zahner, S. Haeberlein, M. Moescheid, A. Windhorst, M. Burg-Roderfeld, D. Glebe, B. Pereira Moneira, C. Lesieur, A. Schmid, F. Falcone, C. Grevelding, E. Roeb, M. Roderfeld (Giessen, DE; Angers, FR)
31. Pro- and anti-inflammatory cytokines in metabolic dysfunction-associated steatotic liver disease may be influenced by different strains of microbiota
    A. Sydorchuk, I. Hryhorchuk, R. Sydorchuk, L. Sydorchuk, I. Zabolotna, I. Sydorchuk, A. Iftodiy, P. Kyfiak (Neu-Ulm, DE; Chernivtsi, Kyiv, UA)
32. The genetic connexions of immune cells, systemic inflammation, metabolism, hepatic dysfunction, and adipokines in MASLD
    L. Sydorchuk, A. Iftodiy, R. Sydorchuk, A. Sydorchuk, R. Knut, I. Sydorchuk, I. Plehutsa (Chernivtsi, Storozhynets, UA; Neu-Ulm, DE)
33. Fasting and diet-dependent changes of innate natural killer cells and pro-inflammatory cytokines in steatotic liver disease
    R. Sydorchuk, L. Sydorchuk, I. Zabolotna, A. Sydorchuk, I. Hryhorchuk, I. Sydorchuk, I. Sydorchuk, P. Kyfiak (Chernivtsi, UA; Neu-Ulm, Siegen, DE)
34. Spatial and proteogenomic niche deconvolution of hepatic crown-like structures in steatohepatitis progression and resolution
    S. Thomann, S. Basu, J. Schaf, N. Vornberger, M. Ashfaq-Khan, A. Rosenwald, T. Poth, D. Gruen (Würzburg, Heidelberg, DE)
35. A follicular T helper cell axis sustains antiviral CD4+ T cell immunity in chronic infection in humans
    J. Weisser, M. Reinscheid, N. Maier, D. Reeg, P. Hafkemeyer, L. Kelsch, G. Rusignuolo, J. Arnold, A. Walker, Y. Froehlich, A. Cherukunnath, J. Timm, B. Bengsch, S. Sagar, R. Thimme, T. Boettler, M. Hofmann (Freiburg, Düsseldorf, DE)

FULL CONTENT OF POSTER ABSTRACTS

Poster Numbers 1 – 35

1. Morphometric profiling of immune cell populations in HCV-associated cirrhosis: Insights into spatial organization and clustering

Mohamed Aaa Hegazi (Rozzano, IT), Fabio Pasqualini (Rozzano, IT), Maurizio Chiriva-Internati (Houston, US), Fabio Grizzi (Rozzano, IT)

Introduction: Chronic hepatitis C virus (HCV) infection triggers progressive liver injury, advancing from fibrosis and cirrhosis to hepatocellular carcinoma (HCC). This process is driven by persistent immune-mediated inflammation and aberrant fibrogenesis. Through continuous epitope variation in the E2 glycoprotein, HCV evades immune surveillance, promoting chronic infection. Disease progression depends on the balance between viral persistence and immune clearance: strong, coordinated $CD4^+$ and $CD8^+$ T-cell responses favor elimination, whereas weak responses sustain inflammation. We quantitatively analyzed the density, spatial distribution, and clustering of four immune cell subtypes ($CD4^+$, $CD8^+$, $CD68^+$, and $tryptase^+$) in HCV-cirrhotic liver tissue and correlated them with fibrosis severity.

Methods: Six liver biopsy samples (3 μm thick) from explanted livers of four male patients with HCV-induced cirrhosis undergoing orthotopic liver transplantation were analyzed. Immunohistochemistry was performed using monoclonal antibodies against $CD4^+$, $CD8^+$, $CD68^+$, and $tryptase^+$ markers. Stained sections were digitized and processed using a computer-assisted image analysis system applying the Delaunay triangulation algorithm. For each cell type, the total tissue area covered (AT, %) and the area occupied by cell clusters (AC, %) were measured. The AT/AC ratio at intercellular distances of 10–30 μm was calculated to assess clustering behavior. Fibrosis, quantified on Sirius Red–stained sections, was correlated with AT and AC values for each immune cell population. Polarized light microscopy (Zeiss AxioscanZ1, Zeiss, Italy) was employed to characterize collagen types, while multiplex fluorescence staining was used to assess the spatial interrelationships among the four immune cell populations. All data were expressed as mean ± standard deviation, and statistical analyses were carried out using JASP version 0.18.1 and Python version 3.12.

Results: Quantitative morphometric analysis revealed marked heterogeneity in immune cell infiltration across all examined liver sections from HCV-induced cirrhosis. The total inflammatory area (AT, %) varied among cell populations, averaging 0.56–0.93% for $CD4^+$ T cells, 2.83–3.58% for $CD8^+$ T cells, 2.38–3.18% for $CD68^+$ macrophages, and 1.32–1.67% for $tryptase^+$ mast cells, with coefficients of variation (CV, %) ranging from 28.6% to 66.1%, indicating pronounced inter-sample variability. The cluster area (ATI, %) progressively increased with larger intercellular distances, ranging for $CD4^+$ cells from 0.09% to 0.37%, $CD8^+$ T cells from 1.15% to 2.74%, $CD68^+$ macrophages from 0.70% to 2.49%, and $tryptase^+$ mast cells from 0.45% to 1.11%. The AT/AC ratio also rose proportionally with

increasing distances, reaching maximal values of 63.9% for $CD4^+$, 80.3% for $CD8^+$, 74.6% for $CD68^+$, and 60.9% for $tryptase^+$ mast cells. This pattern suggests the presence of scale-dependent clustering and fractal-like self-similarity in the spatial organization of inflammatory cell populations within fibrotic tissue. Moreover, morphometric quantification of fibrosis using Sirius Red staining demonstrated a significant positive correlation ($p < 0.01$) with both AT and AC parameters for all immune cell types, highlighting a close link between immune cell aggregation and the progression of hepatic fibrogenesis.

Discussion/Conclusion: HCV-induced cirrhosis exhibits a complex and heterogeneous immune landscape within a fibrotic liver microenvironment. $CD8^+$ cytotoxic T cells and $CD68^+$ macrophages represent the most abundant infiltrates, whereas $CD4^+$ helper T cells are less frequent, and mast cells preferentially localize within fibrotic regions. Morphometric analysis using Delaunay triangulation revealed scale-dependent, self-similar clustering of these immune populations, highlighting a structured spatial organization. The strong association between immune cell aggregation and fibrosis indicates that localized immune dynamics may actively contribute to fibrogenesis. These results identify immune clustering as a morphological hallmark of chronic liver injury and emphasize the interplay between inflammation and fibrotic remodeling in HCV-related cirrhosis. Studying the spatial distribution of immune cells, rather than focusing solely on their density, provides deeper insight into tissue organization and cellular interactions, and can be effectively integrated with modern spatial transcriptomic analyses to link structural patterns with gene expression profiles.

2. Association of liver function tests, lipid profile and FibroScan findings in metabolic dysfunction-associated steatotic liver disease (MASLD)

Mohamed Alsenbesy (Manama, BH), Hasan Sedeek (Qena, EG)

Introduction: Metabolic dysfunction-associated steatotic liver disease (MASLD) represents the hepatic manifestation of metabolic syndrome and is commonly associated with metabolic disturbances such as diabetes mellitus and dyslipidemia. FibroScan has emerged as a valuable non-invasive tool for assessing hepatic steatosis and fibrosis in MASLD patients. This study aimed to evaluate the correlation between liver function tests, lipid profiles, and FibroScan findings in patients with MASLD.

Methods: A prospective cohort study was conducted on 65 subjects, including 50 patients with MASLD and 15 healthy controls. Blood samples were analysed for liver function tests (ALT, AST, total and direct bilirubin), lipid profile, fasting blood glucose, HbA1c, and serology. Abdominal ultrasonography and FibroScan assessments were performed for all participants.

Results: The study included 65 participants, with 32.3% males and a mean age of 42 years. MASLD patients exhibited significantly higher values for diabetes mellitus, HbA1c, and hypertension compared to healthy controls ($p = 0.003$, 0.001, and 0.003, respectively). Laboratory investigations showed significantly elevated

levels of triglycerides, HDL, ALT, AST, direct bilirubin, and fasting blood glucose ($p = 0.001$) in the MASLD group, while total cholesterol levels were significantly lower ($p = 0.004$). Regression analysis demonstrated that FibroScan measurements were predictive of the presence of MASLD.

Discussion/Conclusion: This study demonstrates a strong correlation between liver function tests, lipid profile parameters, and FibroScan findings in patients with MASLD, supporting the role of FibroScan as a reliable diagnostic and predictive tool in assessing hepatic involvement and disease severity.

3. BMP signaling dysregulation as a mechanistic link in alcohol-related hepatic osteodystrophy

Romina Aspera-Werz (Tübingen, DE), Mohammad Majd Hammour (Tübingen, DE), Yuxuan Xin (Tübingen, DE), Andreas Nuessler (Tübingen, DE)

Introduction: Hepatic osteodystrophy (HOD), a common complication of chronic liver disease, involves impaired bone formation and an increased risk of fractures. Alcohol-related liver injury significantly contributes to this condition. However, the inter-organ mechanisms connecting hepatic dysfunction to bone loss remain unclear. The aim of this study was to investigate how alcohol-induced liver fibrosis affects bone metabolism through the liver-bone axis, focusing on the role of bone morphogenetic protein (BMP) signaling.

Methods: Our long-term human 3D in vitro liver-bone co-culture model integrates liver spheroids microorganoids composed of differentiated HepaRG cells, hepatic stellate cells (LX-2), and endothelial cells (HUVEC) with bone scaffolds containing bone-forming and -resorbing precursor cells (SCP-1, THP-1). The model was exposed daily to ethanol at a physiologically relevant concentration (50 mM) for 28 days. Functional assays, gene expression analysis, and protein profiling were performed to assess hepatic fibrosis, bone metabolism, and inter-organ signaling.

Results: Liver spheroids exposed to alcohol showed a significant increase in transcript and protein levels of CYP3A4, alongside elevated levels of damage markers such as alkaline phosphatase, indicating enhanced metabolic activity and hepatocyte injury upon ethanol treatment. Ethanol exposure induced a fibrotic-like phenotype in liver spheroids, evidenced by stellate cell activation and an increase in TGF-β1 secretion levels, and Epithelial-Mesenchymal Transition markers. In the bone compartment, osteoblast activity (AP) and collagen synthesis (PINP) were significantly decreased, whereas osteoclast function remained unchanged upon alcohol-induced hepatic fibrotic phenotype. Additionally, the mineral density and stiffness of bone scaffolds decreased significantly. Mechanistically, ethanol exposure altered hepatic BMPs secretion—decreasing BMP2 and increasing BMP13—leading to the activation of the Smad1/5 and p38 MAPK pathways in bone cells. This signaling imbalance leads to a suppressed osteogenic and adiponegic master transcriptional factors (RUNX2 and PPARγ) expression while promoting chondrogenic lineage commitment (SOX9 upregulation).

Discussion/Conclusion: Our findings highlight the potential of BMP dysregulation as a key driver of alcohol-induced HOD, promoting a shift from osteogenesis to chondrogenesis. Our human in vitro 3D liver-bone co-culture model recapitulates key features of alcoholic liver fibrosis and its impact on bone metabolism, providing a powerful platform for mechanistic studies and therapeutic screening in liver–bone axis disorders.

4. Distinct immune landscapes in autoimmune vs. checkpoint inhibitor-associated hepatitis revealed by spatial profiling

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Introduction: Immune-related adverse events (IRAEs) resulting from checkpoint inhibitor therapy can be life-threatening, but their underlying immunopathology remains poorly defined. It is commonly assumed that the mechanisms driving immune-checkpoint-inhibitor-associated hepatitis (ICI-Hep) resemble those of spontaneous autoimmune hepatitis (AIH). To challenge this assumption, we compared the intrahepatic immune environments of ICI-Hep and AIH.

Methods: We performed high-resolution spatial single-cell and spatial transcriptomic analyses on inflamed liver tissue from patients with ICI-Hep and AIH. Cellular composition, spatial organization, and signaling pathway activity were evaluated to identify disease-specific immune interactions and molecular signatures.

Results: Spatial profiling revealed fundamentally distinct immune architectures between ICI-Hep and AIH. ICI-Hep was marked by strong spatial interactions between activated cytotoxic $CD8^+$ T cells and activated myeloid cells—features absent in AIH. In contrast, AIH displayed an enrichment of exhausted and tissue-resident T cells accompanied by abundant B cells. Pathway analysis demonstrated that the immune cell interactions in ICI-Hep were driven by active mTOR signaling. Pharmacologic inhibition of mTOR in two patients with steroid-refractory ICI-Hep reduced activation of $CD8^+$ and myeloid cells and led to clinical improvement of liver inflammation.

Discussion/Conclusion: These results highlight distinct cellular pathomechanisms in ICI-Hep and establish mTOR signaling trageting as a rational therapeutic option for severe ICI-Hep.

5. Focal adhesion kinase (FAK)-dependent immune escape in hepatocellular carcinoma

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Background and Aims: Immunotherapy represents the first line treatment for patients with advanced Hepatocellular Carcinoma (HCC). Yet, a high proportion of patients do not respond to immunotherapy and have a poor prognosis. The focal adhesion kinase (FAK), a non-receptor tyrosine kinase, is frequently overexpressed in HCC and associated with an immune-excluded tumor microenvironment. We aimed to evaluate the functional role of FAK for tumor immune escape in HCC.

Methods: We used imaging mass cytometry (IMC) and a 40-marker panel to investigate the FAK-associated tumor microenvironment and related immune neighbourhoods in n = 11 human HCCs. Moreover, 3D co-culture assays were used to functionally validate the role of FAK tumor cell signaling on certain immune cell populations.

Results: IMC analysis showed increased infiltration of CD204+ M2 macrophages and regulatory CD4+ T cells (Tregs) in tumors with high FAK expression. IMC neighbourhood analyses further revealed augmented co-localization of CK18+ tumor cells and CD8 T cells with CD68+ macrophages in FAK overexpressing tumor tissue. Interestingly, co-culture of THP1 cell line-derived M0 macrophages and Kupffer cells with Huh7 spheroids led to upregulation of M2 polarization markers (e.g. CCL22, CSF1R, Arginase 1), while the effect was reversed in macrophages co-cultured with FAK-inhibited Huh7 spheroids.

Discussion/Conclusion: Taken together, these data suggest FAK overexpression in tumor cells to be associated with a reorganized tumor immune microenvironment enriched in suppressive immune cell populations and to functionally drive M2 macrophage polarization.

6. MAIT cell recognition of disease-associated metabolite self-antigens in metabolic dysfunction-associated liver disease (MASLD)

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Introduction: MHC-related molecule 1 (MR1) is ubiquitously expressed in humans. Mucosal-associated invariant T (MAIT) cells are MR1-restricted, comprise up to 40% of T cells in the liver, and are conserved in humans with a well-described tissue maintenance function. However, their function is perturbed in liver disease, including metabolic dysfunction-associated steatotic liver disease (MASLD). MAIT

cells strongly respond to bacteria derived metabolite antigens (Ags) and also proinflammatory cytokines, making them unique players in intrahepatic inflammatory processes. Furthermore, recent work demonstrated MAIT cell recognition of self, and made the discovery of MR1-presented Ags derived from lipid peroxidation, a hallmark of MASLD. We hypothesize that metabolic alterations in Ag-presenting cells (APCs) generate MR1-presented Ags that perturb MAIT cell functions in an MR1/T cell receptor (TCR)-dependent fashion.

Methods: We isolated a library of MAIT cell clones from human liver samples and validated their MAIT cell status (expression of the Vα7.2+ TCR and reactivity toward the prototypic bacterial Ag 5-OP-RU). We further selected MAIT cell clones that produced IFN-γ in the presence of the tumour cell line A375 cultured under sterile conditions. These self-reactive MAIT cell clones were subsequently screened for altered activation toward different APCs, the latter treated with various agents used to perturb their metabolic profile.

Results: Our preliminary data demonstrate the existence of self-reactive MAIT cells within human liver. Moreover, some MAIT cell clones show increased reactivity to metabolic products of saturated and unsaturated lipid metabolism in an MR1-dependent manner.

Discussion/Conclusion: We intend to determine the molecular pathways responsible for Ag generation during disease and its impact on MAIT cell function. This represents the first investigation of direct T cell recognition of metabolites in a pathophysiologically relevant setting. Ultimately, this work aims to uncover the mechanisms underlying T cell-mediated liver injury, paving the way for novel therapeutic interventions.

7. The expression and function of 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) in hepato-cellular carcinoma

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Introduction: A hallmark of different types of cancer, including hepatocellular carcinoma (HCC), is metabolic reprogramming, such as glycolysis, even in aerobic environments (Warburg effect). The bifunctional enzyme 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) is key regulator of glycolysis. PFKFB3 has been associated with the progression of various cancers. However, its role in HCC remains unclear.

The aim of this study was to analyze the expression and function of PFKFB3 in HCC.

Methods: Different human HCC cell lines (Hep3B, PLC, SNU449 and Huh7) were analyzed by RT-qPCR and Western blotting. The expression of PFKFB3 was suppressed using RNAi technology.

Results: PFKFB3 mRNA and protein expression is significantly higher in various human HCC cell lines than in primary human hepatocytes. Increased PFKFB3 expression was observed in HCC cells under hypoxic conditions and in human HCC tissues. PFKFB3 showed a significant correlation with GLUT1, a glucose transporter and known marker for hypoxia. Suppression of PFKFB3 in HCC cells resulted in reduced glucose consumption and lactate production. Furthermore, PFKFB3 suppressed HCC cells showed significantly reduced colony formation and growth, proliferation and migratory activity. Similar results were found in HCC cells treated with a specific PFKFB3 inhibitor. In HCC patients, high PFKFB3 expression was associated with poorer progression free and overall survival.

Discussion/Conclusion: Our data suggest that increased PFKFB3 expression stimulates glycolysis and acts as a protumorigenic factor in HCC. Therefore, PFKFB3 appears as a promising prognostic marker and therapeutic target in HCC.

8. Effects of hepatic stellate cells on melanoma cells

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Introduction: The liver represents a very attractive niche for metastasis of different tumours including melanoma. However, the underlying molecular mechanisms are largely unknown. In primary liver cancer, it is known that activated hepatic stellate cells (HSCs) promote tumour progression. This study aimed to analyse the effects of HSCs on melanoma.

Methods: Primary human HSCs and human melanoma cell-lines were used in different in vitro systems. Melanoma cells were incubated with conditioned media (CM) from HSCs and spheroid formation assay was performed.

Results: Immunohistochemical (IH) analysis of alpha-smooth muscle actin (α-sma), a marker of activated HSCs, showed that HSCs surround and infiltrate the stroma of hepatic metastases from melanoma patients. In melanoma mouse models, HSC activation occurs early during hepatic colonisation of melanoma cells as demonstrated by IH of α-sma. In vitro, CM from HSCs induced proliferation and colony formation of melanoma cells and acted as a potent chemoattractant in Boyden chamber assays. Moreover, CM from HSCs induced the activity of protumourigenic pathways and protumourigenic gene expression of melanoma cells. Boiling the CM abolished these effects. The growth-promoting effect of HSCs on melanoma cells was also demonstrated in spheroid formation assays, in which mixed spheroids of melanoma cells and HSC formed significantly larger spheroids than the sum of either cell type alone. Furthermore, we observed that HSCs induced a significant induction of smad-1/5/8 phosphorylation in melanoma cells, indicating that bone morphogenetic proteins (BMPs) are involved in the protumourigenic effects of HSC on melanoma cells.

Discussion/Conclusion: Our data indicate protumourigenic effects of HSCs on melanoma cells and suggest that at least parts of these effects are mediated by secreted proteins potentially BMPs. We propose that our in vitro model system could

be used to identify further candidate factors secreted by HSCs as potential diagnostic markers and therapeutic targets for hepatic metastasis in melanoma patients.

9. Microbiota-driven break of B cell tolerance promotes spontaneous anti-HBsAg seroconversion in HBV transgenic mice

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Introduction: The liver is a unique immunological environment where tolerance and immunity are tightly balanced. In HBV-replication–competent transgenic mice (HBV Tg), hepatocytes express the full viral genome, and both T and B cells are traditionally considered tolerant to HBV antigens. Surprisingly, we reported that about 60% of HBV Tg mice spontaneously develop anti-HBsAg antibodies, leading to the clearance of circulating virions and subviral particles, and thus to seroconversion, revealing a spontaneous break of B cell tolerance. This model offers an opportunity to investigate mechanisms of immune reactivation that may inform strategies for chronic HBV.

Results: We investigated the mechanisms underlying this spontaneous seroconversion. HBsAg loss was strictly dependent on CD4+ T cell help, as HBV Tg mice deficient for MHC-II or CD40L failed to develop anti-HBsAg antibodies. Intriguingly, seroconversion often occurred among animals sharing the same cage, and fecal microbiota transplantation (FMT) from seroconverted donors induced seroconversion in recipients. This microbiota-driven effect depended on intact $CD4^+$ T cell-B cell cross-talk, since it was lost in CD40L-/- HBV Tg mice receiving FMT.

Shotgun metagenomic sequencing of fecal pellet revealed distinct microbial signatures in seroconverted mice, enriched in taxa with lactate- and GABA-producing pathways. These findings suggest that specific microbial metabolites may modulate immune activation and promote anti-HBsAg responses.

Discussion/Conclusion: Overall, our study identifies a novel link between gut microbiota and $CD4^+$ T cell help in breaking B cell tolerance against HBsAg in an HBV-tolerant host. This model offers new insight into how intestinal microbes can modulate peripheral tolerance and promote antiviral immunity. While direct translation to humans remains to be validated, this study may illuminate microbiota-dependent mechanisms of immune reactivation relevant to functional HBV cure.

10. Microbiota-specific T cell responses in patients with immune checkpoint inhibitor therapy-associated hepatitis

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Introduction: Cancer immunotherapy is a double-edged sword, effectively activating anti-tumor responses while also triggering immune-related adverse events (irAEs) in various organs. Emerging evidence links microbiota with immunotherapy efficacy and irAEs but the exact immune mechanisms involved remain elusive.

Methods: To explore this, we studied the role of microbiota-specific CD4+ T cells in the pathogenesis of hepatic irAEs using the Antigen-Reactive T cell Enrichment assay, which allows for high sensitivity isolation of antigen-specific CD4+ T cells that can be further studied with flow cytometry as well as multi-dimensional sequencing methods.

Results: We identified microbiota species that induce high checkpoint expression on T cells in healthy donors. We subsequently tracked CD4+ T cell responses to immune-checkpoint-inducing species in 75 patients undergoing anti-PD-1/PD-L1-therapy and demonstrated altered T cell response signatures in 14 irAE-hepatitis patients.

In those patients, a pronounced Candida albicans-specific immune response was observed, characterized by upregulation of IL-17A, CTLA-4, and Ki-67, indicating ongoing immune activation at irAE onset. Similar immune responses were absent in a control cohort of 15 autoimmune hepatitis patients. Notably, the onset of C. albicans-specific responses aligned with irAE onset and diminished following resolution.

Discussion/Conclusion: Our study highlights a C. albicans-specific immune response with a proliferative Th17 phenotype as a characteristic of irAE-hepatitis. This immune response is not present in patients with non-irAE-associated liver inflammation nor in immunotherapy patients without irAE, suggesting microbiota-driven mechanisms underlying checkpoint inhibitor-induced liver toxicity.

11. T cell tolerance is maintained by liver sinusoidal endothelial cells in liver fibrosis

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Introduction: Liver sinusoidal endothelial cells (LSECs) are key players of hepatic immune tolerance by scavenging blood-borne molecules and restricting immune responses to those. Previously, we have shown that targeting of autoantigen peptides to LSECs using nanoparticles (NP) can be an effective therapeutic strategy for autoimmune diseases. In liver fibrosis, however, LSECs capillarize and acquire phenotypical and functional changes believed to lead to enhanced immunogenicity. Here, we explore whether fibrosis affects the scavenger and immune tolerance function of LSECs.

Methods: Utilizing the CCl4-induced and Mdr2KO mouse models of liver fibrosis, the scavenger function was examined by injection of Cy5-labelled NP, and the

ability of LSECs to cross-present ingested antigens was tested. To investigate immune tolerance induction, Treg conversion assays were performed and treatment of autoimmune diseases with autoantigen-coupled NP (provided by Topas Therapeutics) in the context of liver fibrosis was tested in murine models of experimental autoimmune encephalomyelitis (EAE) and autoimmune cholangitis. Furthermore, existing murine and human single cell sequencing data sets of LSECs in liver fibrosis were analysed with a focus on genes involved in scavenger function and induction of immune tolerance.

Results: In liver fibrosis, LSEC maintained their ability to scavenge autoantigen-coupled NP and to cross-present ingested antigen. Induction of Tregs was similar as with LSECs from healthy livers. Furthermore, NP-mediated targeting of autoantigen-peptide to LSECs in mice with established liver fibrosis was effectively preventing CD4+ T cell-driven EAE and CD8+ T cell-driven autoimmune cholangitis. Single-cell sequencing data confirmed that scavenger and tolerance functions of LSECs are maintained in humans as in mice, while transcriptional adaptions are found in pathways involved in fibrogenesis.

Discussion/Conclusion: Even though LSECs exhibit fibrotic changes, they maintain their distinct phenotype including their scavenging ability and their ability to induce specific T cell tolerance to autoantigen peptides. These findings suggest that the immune-regulatory function of LSECs is less susceptible to fibrosis than previously thought, supporting their continued therapeutic potential in autoimmune diseases even under fibrotic conditions.

12. Integrative systems biology identifies cell cycle – Immune crosstalk biomarkers in hepatocellular carcinoma through PPI network analysis

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Introduction: Hepatocellular carcinoma (HCC), the most prevalent primary liver cancer, remains a leading cause of cancer-related mortality worldwide. Early diagnosis markedly enhances patient outcomes, highlighting the importance of reliable biomarkers for detection, prognosis, and therapeutic monitoring. Among these, cancer-testis antigens (CTAs) are promising candidates owing to their limited expression in normal tissues and strong immunogenicity. In this study, we present a novel bioinformatic pipeline constructed around a protein–protein interaction (PPI) network centered on the hub gene Pituitary Tumor Transforming Gene 1 (PTTG1), a CTA previously associated with HCC and various other malignancies.

Methods: We analyzed the expression of PTTG1 and 10 functionally interconnected proteins and their corresponding genes (ESPL1, AURKA, CCNB2, BUB1, UBE2C, CCNB1, CDC20, CDK1, CDC27, and FZR1) to assess their clinical and prognostic significance and their association with the immune microenvironment in liver HCC. Data were obtained from the TCGA, UALCAN, K-M plotter, and TIMER-3 databases. Overall survival (OS) and relapse-free survival (RFS) were analyzed as survival metrics to determine the prognostic relevance of these candidate biomarkers.

Results: Comprehensive PPI analysis revealed that PTTG1 and most interacting partners (ESPL1, AURKA, CCNB1, CCNB2, BUB1, UBE2C, CDC20, CDK1, CDC27, FZR1) were significantly upregulated in primary hepatocellular carcinoma (HCC) versus normal liver ($p < 1\times10^{-12}$), confirming activation of cell cycle–related pathways. Expression of PTTG1, BUB1, CCNB1, CCNB2, CDK1, and CDC20 increased with tumor stage and grade ($p < 10^{-3}$), suggesting coordinated mitotic acceleration in HCC progression. Most hub genes strongly correlated with TP53 mutations (e.g., PTTG1 $p = 1.68\times10^{-10}$; CCNB1 $p = 1.00\times10^{-8}$), highlighting a close link between TP53 dysfunction and aberrant cell cycle activation. Subtype-specific analyses showed higher expression of AURKA, CCNB1, CCNB2, BUB1, UBE2C, CDC20, and PTTG1 in conventional HCC compared with mixed hepatocholangiocarcinoma ($p = 10^{-5}$–10^{-7}), while UBE2C and CDK1 remained elevated in advanced stages (Stage 3–4), reflecting sustained mitotic activity. CDC27, though upregulated ($p < 10^{-12}$), exhibited weaker associations with grade and stage. Minor ethnicity- and age-related variations were observed, AURKA, CCNB1, CCNB2, UBE2C, and CDK1 were higher in Caucasians ($p \approx 0.003$), and UBE2C differed between African American and Asian groups ($p = 0.018$). CCNB2, UBE2C, CDK1, and PTTG1 also varied by age ($p \approx 0.01$–0.04). Sex-based effects were limited, though FZR1 expression was slightly higher in males ($p = 0.015$). Survival analysis revealed that elevated expression of most hub genes, particularly PTTG1, ESPL1, AURKA, CCNB1, CCNB2, BUB1, UBE2C, CDC20, CDK1, and CDC27, was associated with reduced overall and relapse-free survival, underscoring their oncogenic potential. The strongest adverse prognostic effects were linked to PTTG1 (OS = 2.0×10^{-5}; RFS = 1.2×10^{-6}), CDC20 (OS = 1.1×10^{-6}), CDK1 (OS = 1.1×10^{-5}), and UBE2C (OS = 7.2×10^{-5}). In contrast, FZR1 showed a weak positive trend toward improved survival (OS $p = 0.1$; RFS $p = 0.077$), suggesting a potential tumor-suppressive role. Most PTTG1-network genes also exhibited significant positive correlations with immune cell infiltration in HCC. AURKA, BUB1, CCNB1, and CCNB2 correlated strongly with macrophages ($\rho \approx 0.32$–0.37), B cells ($\rho \approx 0.44$–0.45), and $CD4^+$ T cells ($\rho \approx 0.24$–0.25; all $p < 0.01$). CDC20, CDC27, and CDK1 showed similar patterns ($\rho \approx 0.32$–0.39 for macrophages; $\rho \approx 0.28$–0.40 for B cells; $p < 10^{-5}$). ESPL1 and FZR1 were moderately correlated with macrophage, B-cell, and $CD4^+$ T-cell infiltration, while PTTG1 and UBE2C demonstrated consistent immune associations, particularly with macrophages ($\rho = 0.256$–0.274) and B cells ($\rho = 0.396$–0.433; all $p < 10^{-6}$).

Discussion/Conclusion: PTTG1 expression shows a strong association with immune cell infiltration, suggesting its role in shaping the tumor microenvironment and contributing to immunotherapy resistance in HCC. The PTTG1 network reveals two prognostic clusters: a dominant oncogenic group linked to poor outcomes and a smaller regulatory subgroup, represented by FZR1, with potential protective effects. Overall, these findings highlight PTTG1 and its interacting cell cycle genes as key prognostic biomarkers and therapeutic targets involved in immune modulation and tumor–immune microenvironment remodeling in HCC.

13. bile acid dysregulation impairs bone health: Evidence from human 3D co-culture and murine models of cholestasis

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Background: Hepatic osteodystrophy is a common complication of chronic cholestatic liver diseases, yet the mechanistic link between bile acid imbalance and skeletal deterioration remains poorly understood. Bile acids act as signaling molecules beyond their digestive role, suggesting direct effects on bone cells.

Methods: In this study, we employed a 3D human bone co-culture system (osteoblast- and osteoclast-like cells) and a murine bile duct ligation (BDL) model of cholestasis. In vitro, cells were exposed to individual bile acids and mixtures mimicking healthy and cholestatic profiles. Receptor expression (FXR1α, VDR, FPR1, CHRM3) was assessed during differentiation. Functional assays included migration, viability, osteogenic and osteoclastic activity, and scaffold mineralization and stiffness.

Results: Expression analyses confirmed the presence of bile acid receptors in bone cells throughout their differentiation process, indicating potential direct responsiveness. Cholestatic bile acid mixtures significantly impaired mesenchymal stem cell migration and reduced osteoclast activity (TRAP). Whereas healthy bile acid mixtures preserved function. Glycochenodeoxycholic acid (GCDCA) emerged as a key mediator of osteoblast inhibition, reducing AP activity and mitochondrial function. Long-term exposure to cholestatic profiles decreased scaffold stiffness and mineral density. In BDL mice, bone mineral content and mechanical strength were reduced, mirroring in vitro findings. Importantly, ASBT inhibition partially restored bone mineralization and mechanical strength, suggesting that systemic bile acid reduction is a protective strategy.

Discussion/Conclusion: These findings demonstrate that altered bile acid composition in cholestatic liver disease directly disrupts bone homeostasis, primarily through receptor-mediated signaling in bone cells. The 3D co-culture model provides a relevant platform for mechanistic studies and therapeutic screening targeting the liver-bone axis.

14. Blood profile of innate lymphoid cells in HCC patients is cancer stage specific and undergoes functional switch during immunotherapy

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Introduction: Hepatocellular carcinoma (HCC) exhibits pronounced heterogeneity at clinical, immunological, and microenvironmental levels. Innate lymphoid cells (ILCs), which represent the innate counterparts of T cells, rapidly adapt to changes in the local milieu; however, their distribution and functional states across HCC progression and during immunotherapy remain insufficiently defined. In this study, we characterized ILC subsets within peripheral blood mononuclear cells (PBMCs) from HCC patients, stratified by disease stage and treatment status with the anti-PD-L1 antibody atezolizumab in combination with the anti-VEGF agent bevacizumab, the current first-line regimen. We postulated that ILC phenotypes display stage-dependent alterations and are modulated by immune checkpoint- and VEGF-targeted therapy.

Methods: Peripheral blood mononuclear cells (PBMCs) were obtained from 35 patients with advanced-stage HCC, 25 patients in follow-up without detectable tumor burden after local therapy, 8 patients with early-stage disease (NIH cohort), and 21 healthy donors. Samples from advanced-stage patients were collected longitudinally at baseline, after one treatment cycle, and approximately three months after therapy initiation, with clinical responses assessed according to RECIST criteria. ILC subsets—including ILC1-like/NK cells, ILC2s, and ILC precursors (ILCPs)—were quantified by multiparametric flow cytometry, while serum cytokine levels were determined using LEGENDplex assays. In a subset of patients, single-cell RNA sequencing (scRNA-seq) using the PARSE Evercode platform was performed. ILC profiles and states were integrated with therapeutic response and clinical outcome parameters.

Results: ILC composition varied markedly across healthy donors, early-stage HCC, tumor-free follow-up patients, and individuals with advanced disease. Advanced HCC was characterized by a pronounced reduction in cytotoxic NKp80^{+} NK-like ILCs, ILC2s, and ILC precursors (ILCPs). Functionally, advanced disease exhibited elevated IL-4 expression within ILC2s and a loss of IL-22 production in ILCPs. In tumor-free follow-up patients, disease relapse was associated with diminished frequencies of IL-13-producing ILC2s and IL-17^{+}/IL-22^{+} ILCPs, underscoring stage-dependent functional ILC heterogeneity.

During treatment with atezolizumab plus bevacizumab, ILC2 frequencies and absolute numbers increased after three months, accompanied by enhanced checkpoint molecule expression. Notably, immunotherapy induced granzyme-B production in ILC2s, which correlated with favorable clinical response and reduced serum AFP tumor marker levels. In contrast, non-responders displayed enrichment of IL-4-producing ILC2s and impaired liver function, as reflected by higher ALBI scores.

Single-cell RNA sequencing combined with LEGENDplex cytokine profiling revealed a cytokine-driven differentiation trajectory from ILCPs through ILC2s towards granzyme-B-producing ILC2/ILC1-like subsets, observed exclusively in HCC patients but absent in healthy controls. Among the cytokines, IL-18 and IL-27—along with their corresponding receptors—were identified as key mediators of ILC plasticity promoting the emergence of cytotoxic, granzyme-B-expressing ILC2 phenotypes.

Discussion/Conclusion: ILC profiles vary by disease stage and therapy, reflecting systemic responses to changes in the tumor microenvironment. Advanced disease is marked by low ILC2 frequencies and reduced cytotoxic ILCs, including NKp80^{+} NK-like cells. Atezolizumab + bevacizumab therapy increased granzyme-B-expressing ILC2s, whose cytotoxic shift correlated with better response to treatment. ScRNA-seq revealed IL-18- and IL-27-mediated plasticity driving this switch, suggesting potential for ILC-based cell therapy to enhance anti-tumor immunity. This aligns with prior high-impact reports of ILC-based therapies in solid tumors (Li et al., Cell 2024) and pancreatic cancer (Amasaki et al., Nature 2025). Our study fills a key knowledge gap in ILC responses across HCC stages and during immunotherapy, pointing to future ILC-targeted cell-based therapies in this lethal disease.

15. Expression and function of stanniocalcin 2 in hepatocellular carcinoma

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Introduction: Stanniocalcins (STCs) are glycosylated peptide hormones. In mammals there are two paralogs of stanniocalcins: STC1 and STC2. STC2 is expressed in several tissues and is involved in inflammation and cell proliferation. Research findings have indicated a correlation between dysregulation of STC2 and different types of cancer. In part protumorigenic as well as antitumorigenic effects were detected. The aim of this study was to investigate the expression and function of STC2 in hepatocellular carcinoma (HCC).

Methods: By using quantitative RT-PCR STC2 expression was analyzed. To suppress STC2 in HCC cells RNAi technology was applied. For in silico analyses of STC2 in human HCC tissues the databases Kaplan-Meier Plotter and GEPIA were used.

Results: Through in silico analysis an enhanced STC2 expression was found to be associated with a poor survival rate in HCC. A higher level of STC2 expression was detected in tumor samples compared to normal samples in a public data set. The expression of STC2 was elevated in different human HCC cell lines when evaluated against primary human hepatocytes. This was also the case in human HCC tissues compared with corresponding non-tumorous liver tissues. By transfection with siRNA-pools directed against STC2 a knockdown of STC2 was established in HCC cells. After STC2 depletion in HCC cell lines alterations in genes associated with tumor progression and metastasis such as VEGF and MMP2, as well as further glycolysis associated genes such as HK1 and LDHa were detected.

Discussion/Conclusion: The current data indicate a complex role of STC2 in HCC. In HCC cells it is compatible with a protumorigenic role. Further research is needed to provide a more comprehensive understanding of the potential of this secreted hormone as therapeutic target and diagnostic marker in HCC.

16. A peritoneal macrophage-Th1/Th17 axis drives inflammation in spontaneous bacterial peritonitis

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Introduction: Bacterial infections like spontaneous bacterial peritonitis (SBP) are a major cause of morbidity and mortality in cirrhosis. We investigated the phenotype and function of peritoneal T helper cells in ascitic fluid (AF) and their interaction with peritoneal macrophages during SBP.

Methods: We profiled blood and AF T helper cells from cirrhosis patients with and without SBP using unsupervised mass cytometry (CyTOF) and flow cytometry. Cytokines and chemokines were quantified in plasma and AF by Luminex and ELISA. Sorted AF T helper cell subsets were analysed by sequencing. To mimic peritoneal infection, we co-cultured AF $CCR6^+$ $CD4^+$ T cells with autologous macrophages and heat-killed E. coli.

Results: Peritoneal, resident-like $CD69^+$ T helper cells were abundant in AF compared to blood and showed heterogeneous CD127 expression. Unlike their CD127lo counterparts, $CD4^+CD69^+CD127^+$ cells displayed an activated effector phenotype, co-expressing CCR6 with CD161, CD49a, and CXCR3. Upon stimulation, these cells produced both IL-17 and IFN-γ, and gene profiling confirmed a pathogenic Th1/Th17 signature distinct from circulating T cells. During SBP, these Th1/Th17 cells ($CD4^+CXCR3^+CCR6^+$) were enriched in AF but not blood. Peritoneal levels of the CCR6 ligand CCL20 correlated with the severity of local and systemic inflammation. In vitro, E. coli-exposed macrophages produced CCL20 and pro-inflammatory cytokines, which enhanced IFN-γ and IL-17 production by co-cultured $CCR6^+$ T cells.

Discussion/Conclusion: Our findings reveal a macrophage-Th1/Th17 inflammatory circuit in SBP, driven by CCL20-mediated recruitment and sustained by macrophage-derived cytokines. Peritoneal $CCR6^+$ T helper cells represent a key driver of peritoneal inflammation and a potential target for modulating immunity in cirrhosis-associated infections.

17. Lipid accumulation promotes tumorigenic and prometastatic characteristics of colorectal cancer cells

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Introduction: The liver is the most prevalent site for metastases in colorectal cancer (CRC), these hepatic metastases are the main contributors to disease-specific mortality in patients with CRC. Obesity and hyperlipidemia are identified as risk factors for development of hepatic metastases. However, the underlying mechanisms are only incompletely understood.

The aim of the study was to investigate hyperlipidemic conditions on prometastatic characteristics of CRC cells and to assess the impact of lipid accumulation in human CRC tissues and liver metastasis.

Methods: To mimic hyperlipidemia in vitro, free fatty acids (FFA) complexed to albumin were added to the cell culture medium of human colon cancer cell lines.

Results: Time and dose dependent FFA uptake led to triglyceride accumulation, increased beta-oxidation and enhanced expression of proinflammatory genes. These metabolic changes resulted in increased proliferation and migratory activity, as well as altered expression of genes involved in lipid metabolism. Perilipin 2 (PLIN2), a structural component of lipid droplets, was identified as surrogate marker for lipid accumulation. Furthermore, PLIN2 expression in tumorous tissues of patients showed higher levels in obese compared to lean patients, and high PLIN2 expression correlated with poor overall survival. Moreover, the proliferation marker Ki67 was increased in metastases of obese patients.

Discussion/Conclusion: Our data indicate that hyperlipidemic conditions promote prometastatic characteristics of CRC cells and expression of PLIN2 might serve as a diagnostic marker for hepatic CRC metastasis. We propose that interference with exogenic high-fat supply could be a promising strategy to treat hepatic metastasis of CRC patients.

18. G protein-coupled receptor 37 as protumorigenic factor in hepatocellular carcinoma

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Introduction: G protein-coupled receptors (GPRs) play an important role in different types of cancers including hepatocellular carcinoma (HCC). GPR37 has been linked to tumor development and progression in several entities but its involvement in liver disease and liver cancer is unknown. The aim of this work is to analyze the expression and function of GPR37 in HCC.

Methods: GPR37 expression was measured at RNA and protein level in human HCC cell lines Hep3B, HepG2, PLC and SNU449 and compared with primary human hepatocytes (PHHs) using RT qPCR and Western blotting. For functional studies GPR37 expression was reduced in human HCC cells by RNA interference (RNAi).

Results: GPR37 expression was significantly higher in human HCC tissue than in corresponding non-tumorous liver tissue. In addition, in silico analyses showed that elevated GPR37 expression in HCC correlated with poor progression-free and overall survival. Human HCC cell lines showed higher GPR37 expression than primary human hepatocytes. Successful RNAi-mediated suppression of GPR37 expression was demonstrated. GPR37-suppressed HCC cells exhibited reduced proliferation and spheroid formation. Moreover, GPR37 suppression led to reduced activation of protumorigenic signaling pathways and reduced proinflammatory gene expression in HCC cells.

Discussion/Conclusion: Elevated GPR37 levels in HCC cells and correlation of high GPR37 expression with poor patient survival indicates this G protein-coupled receptor as a protumorigenic factor in HCC, which is supported by initial in vitro analyses. Further studies are required to identify the ligands that act via GPR37 on HCC cells and to assess their as well as GPR37's potential as a therapeutic target in HCC.

19. Investigating de novo virus-specific T cell immunity in the absence of PD-1 signaling

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Introduction: During self-limiting infections, virus-specific T cells typically undergo clonal expansion, contraction and establish long-lived memory. We have previously shown that hepatitis E virus (HEV)-specific T cell responses follow this pattern in acute-resolving infection. Immune checkpoint blockade (ICB) enhances T cell function by blocking inhibitory receptors such as PD-1 leading to enhance immune control of tumors but also causing immune-pathology. Using HEV infection as a model for antiviral immunity, we aimed to characterize de novo virus-specific T cell responses in the absence of PD-1 signaling.

Methods: We analyzed PBMCs from HEV-infected patients during both the acute and resolved phases, with (ICB) and without (Ctrl) checkpoint blockade (both n = 3). Acute-phase PBMCs were either left unstimulated or stimulated with customized HEV-specific peptides. Single-cell RNA sequencing of sorted non-naïve $CD3^+$ cells enabled detailed T cell profiling, while TCR sequencing served as a molecular barcode to trace clonally expanded populations and identify HEV-specific clones based on increased IFN-γ expression following stimulation.

Results: We found that the expanded clonotypes were predominantly $CD8^+$ T cells and mainly derived from ICB-treated patients. These HEV-specific clones displayed a strong effector signature during acute infection that persisted even after viral clearance. In contrast, resolved Ctrl patients exhibited features of memory development after viral clearance. We also had the unique chance to validate the impaired memory development after ICB treatment in one patient on the protein level using tetramer technology.

Discussion/Conclusion: Collectively, our results show that PD-1 blockade in the context of de novo T cell priming impairs development of T cell memory.

20. Comparing the role of gut microbiota in metabolic dysfunction-associated steatotic liver disease and alcoholic liver disease

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Introduction: Metabolic dysfunction-associated steatotic liver disease (MASLD and alcoholic liver disease (ALD) are principally different in various terms, emphasizing not only etiology, which is obvious, but clinical course and management strategy. ALD encompasses a broad spectrum of hepatic injuries including asymptomatic steatosis, alcoholic steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma. However, they share multiple common pathogenetic mechanisms including inflammation, systemic immune and partially metabolic changes, as well as morphology and clinical presentations. Naturally, this raises questions of finding similarities and peculiarities of both conditions that may assist in their management. Emphasizing the gut-liver axis, the human gastrointestinal lumen is the physiological habitat for a variety of microorganisms, and is the largest reservoir of microorganisms in the body. The gut microbiota is a vital component of homeostasis through not only direct involvement in nutrients and energy from ingested food, but also production of numerous metabolites that can regulate host metabolism and immunity. While the exact mechanisms of gut microbiota remain largely unexplored, it participates in vitamins and amino acid synthesis, energy providing, macromolecule catabolism, immune hemostasis, drug and toxin metabolism, and intestinal barrier preservation. Multiple studies showed that intestinal dysbiosis is associated with endotoxemia, deviated immune regulation and propagates liver injury in both MASLD and ALD. Therefore, the objective of the study is to analyze and compare the gut microbiota changes in MASLD and ALD, and find their common and distinguishing features.

Methods: Totally 87 individuals participated in the study, with 23 ALD and 31 MASLD patients, and 33 formed control. Male patients prevailed in both groups (49 males, 39 females, mean age 53.12 ± 7.09). MASLD and ALD diagnoses and management according to respective EASL and AGA/ACG Clinical Practice Guidelines. Colonic lumen and mucosal microflora studied microbiologically.

Results: Colonic microbiota changes significantly in all MASLD patients: significant decrease ($p < 0.05$) or elimination of autochthonic anaerobic microorganisms and hyperproliferation of conditionally pathogenic Enterobacteriacea: E. coli, including Hly+ – 9.31 ± 0.62 lg CFU/g against 7.39 ± 0.56 lg CFU/g in control; Klebsiellae – 5.17 ± 0.40 lg CFU/g against 3.48 ± 0.49 lg CFU/g in control, Proteus – 6.23 ± 0.35 lg CFU/g, and Serratia – 5.49 ± 0.74 lg CFU/g (not found in control). Similarly, in ALD patients significant ($p < 0.01–0.05$) decrease or elimination of autochthonic anaerobic microorganisms Bifidobacteriaceae and Lactobacillus species. and a higher abundance of Proteobacteriaceae and Fusobacteriaceae was found. However, in distinction to MASLD, ALD patients also had over-representation of Gram-negative endotoxin-producing Proteobacteriaceae and a particular increase in the Clostridia, and Firmicutes genus. Furthermore, both conditions were characterized by significant growth of both frequency and population levels of Candida yeasts.

Discussion/Conclusion: Through different pathways, gut microbiota is strongly entangled in the pathogenesis and the progression of liver injury in both MASLD and ALD patients. The results of this study is supported by many other studies. However, few studies showed different data when decreased levels of Parabacteroides genus, Prevotella, and Clostridium, with higher values of Lactobacillus and Bifidobacterium were observed mostly in ALD.

21. Reduced hepatitis B surface antigen (HBsAg) accumulation in hepatocytes of transgenic mice infected with Schistosoma mansoni

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Introduction: Schistosomiasis, affecting over 250 million individuals worldwide, induces granulomatous liver inflammation through egg deposition within hepatic sinusoids. Chronic hepatitis B virus (HBV) infection remains a leading cause of hepatic necrosis, persistent inflammation, and hepatocellular carcinoma. This study examined how co-infection with Schistosoma mansoni modulates hepatic HBsAg accumulation and aggravates liver pathology.

Methods: HBsAg-transgenic and wild-type BALB/c mice were infected with S. mansoni at 17 weeks and sacrificed at 26 weeks of age. Alanine aminotransferase (ALT) as well as HBsAg levels were quantified in serum samples (functional assay; ELISA), while HBsAg-expression was assessed by Western blotting and morphometric analysis (ImageJ area fraction) of immunostainings in liver tissue. Statistical comparisons were performed between infected and non-infected control groups.

Results: Both male and female HBsAg-transgenic mice infected with S. mansoni showed significantly reduced hepatic HBsAg protein levels compared with non-infected transgenic controls. Serum HBsAg concentrations were decreased only in females. Infected males exhibited elevated serum ALT levels relative to non-infected counterparts, whereas ALT activity remained unchanged in females.

Discussion/Conclusion: Elevated ALT serum levels in infected male transgenic mice indicates enhanced hepatic injury, while the concurrent reduction in hepatic HBsAg accumulation suggests a modulatory effect of S. mansoni infection on HBsAg regulation. Ongoing studies aim to elucidate the contribution of autophagic pathways and other cellular mechanisms underlying this interpathogen interaction.

22. Non-selective beta blockers reduce inflammatory bystander CD8+ T cell activation in decompensated liver cirrhosis

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Introduction: Liver cirrhosis is characterized by immune dysfunction combining immunodeficiency and systemic inflammation. Bystander-activated $CD8^+$ T cells contribute significantly to this inflammatory state. Non-selective beta blockers (NSBB), routinely used to reduce portal hypertension, have been suggested to exert additional anti-inflammatory effects.

Methods: Beta-adrenergic receptor (ADRB) expressing $CD8^+$ T cells were analyzed by single-cell RNA sequencing. The immunomodulatory effects of NSBB therapy were assessed in paired blood and ascites samples from patients with decompensated cirrhosis (n = 31) using high-dimensional phenotyping and functional assays. Bulk RNA sequencing was performed to characterize NSBB-associated transcriptomic changes in $CD8^+$ T cells.

Results: $CD8^+$ T cells expressed ADRB1 and ADRB2, with ADRB2 enriched on effector/memory and bystander subsets compared to antigen-specific $CD8^+$ T cells. In vitro propranolol treatment reduced the proportion of bystander-activated ($CD69^+CXCR6^+$, $NKG2D^+$) $CD8^+$ T cells and decreased cytokine production after interleukin stimulation, while preserving antigen-specific responses. Transcriptomic analysis revealed suppression of interferon signaling via STAT1 downregulation. Consistently, patients receiving NSBB therapy exhibited reduced frequencies of bystander-activated $CD8^+$ T cells compared with untreated individuals. These findings were corroborated in a retrospective cohort of 624 patients with cirrhosis, where NSBB use was associated with lower serum ALT levels.

Discussion/Conclusion: NSBB selectively attenuates bystander-activated $CD8^+$ T cell responses in decompensated cirrhosis through inhibition of the interferon-STAT1 pathway, while maintaining antigen-specific immunity. These findings suggest an anti-inflammatory immunomodulatory role of NSBB therapy in cirrhosis.

23. HBV-specific T-cell response and viral evolution in a transmission pair with acute-persistent HBV infection

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Introduction: In acute HBV infection, T-cell responses are strong and broad, but they become weak and dysfunctional in chronic infection. The timing and role of viral escape in this transition are unclear. We thus longitudinally analyzed viral evolution and HBV-specific T-cell responses in a transmission pair with acute-persistent infection in the recipient.

Methods: PBMC and serum samples from an HBV genotype D transmission pair were collected at eight time points over eight years. PBMCs were screened for responses to overlapping peptides covering the full HBV proteome during both acute and chronic phases, and autologous viral sequences were analyzed over time.

Results: The recipient of the transmission event developed an acute infection with a maximum ALT level of 556 U/L and a viral load of 45 million IU/mL, followed by chronic infection. HBeAg seroconversion occurred after 6 years. OLP screening revealed T-cell responses to 4 epitopes, whose viral sequences remained unchanged during the transition to chronic infection. After seroconversion, a total of 10 amino acid mutations were detected (4 in the core and 6 in the polymerase protein), including 2 within recognized core epitopes and 6 within predicted epitopes.

Discussion/Conclusion: These findings are consistent with previous reports indicating that viral mutations occur more frequently in patients with HBeAg-negative chronic HBV infection than in those with HBeAg-positive infection, and indicate that viral escape temporally indeed coincides with HBe seroconversion. The contribution of viral escape to the progression from acute to chronic HBV infection will be further explored.

24. Characterizing the adaptive immune response to avian influenza H5 after seasonal influenza vaccination in patients with chronic liver disease

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Introduction: Patients with chronic liver diseases commonly display immune dysregulation and are therefore particularly vulnerable to infections such as influenza virus infections. Since 2024, the outbreak of a highly pathogenic avian influenza (HPAI) A virus has resulted in several severe human infections. Cross-reactive immune responses from seasonal influenza vaccination may offer protection against such emerging strains, particularly in vulnerable patients with chronic liver disease.

In the context of WHO pandemic preparedness, we aim to comprehensively characterize the humoral and cellular immune response to avian Influenza A virus H5N1 in patients with liver disease and healthy individuals following seasonal H1N1 vaccination to define cross-recognition against the circulating HPAI.

Methods: PBMCs from H1N1-vaccinated young, middle-age (< 60 years) and elderly healthy adults (> 60 years), patients with liver cirrhosis and liver transplant recipients (LTR) were stimulated with overlapping peptides covering the H5 protein (A/Astrakhan/3212/2020). CD4+ and CD8+ T cell responses were analysed via flow cytometry by measuring the secretion of IFNγ, TNF, CD107a and IL-2. CD4+ T cells subsets were then analyzed by an activation-induced

markers (AIM) assay. The characterization of the humoral immune response was conducted by a neutralization assay.

Results: Although neutralizing antibodies against the H1 and HPAI H5 proteins were comparable in all cohorts, T cell responses differed between patients with liver disease and healthy donors. Notably, elderly donors and individuals with cirrhosis exhibited slightly reduced CD4+ T cell responsiveness to H5-specific epitopes compared to younger, healthy individuals, though this difference was not statistically significant. Importantly, LTRs recognized a significantly narrower CD4+ T cell epitope repertoire, suggesting reduced cross-reactivity. CD8+ T cell responses were weak across all groups.

Discussion/Conclusion: Antibody responses against seasonal H1 and to a lesser degree against H5 were detectable in all cohorts. Cross-reactive H5-specific CD4+ T cells are reduced in H1N1-vaccinated cirrhotic patients and LTR, suggesting reduced cross-reactive cellular immunity against the currently circulating HPAI strain. These findings provide first insights into the influenza-specific cross-reactive adaptive immune response in patients with liver diseases and emphasize the importance of protective vaccinations in this vulnerable patient group.

25. Induction of TNF-α signaling in hepatocytes is reduced by ADAM17-mediated TNFR1 shedding through augmenter of liver regeneration (ALR)

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Introduction: Tumor necrosis factor alpha (TNF-α) is a key mediator of hepatic inflammation and cell death. The TNF-α signal transduction in hepatocytes is regulated by the availability of TNF-α and its receptor, TNFR1 (tumor necrosis factor receptor 1). TNFR1 can be cleaved by the sheddase ADAM17, which diminishes TNF-signaling. Previously, we demonstrated that ALR stimulates hepatocytes via a G-protein-coupled receptor (GPCR) and subsequent ADAM17 induction. ALR (augmenter of liver regeneration) is a multifunctional protein originally identified for its potent ability to stimulate hepatic regeneration following injury. Beyond its regenerative capacity, ALR has been implicated in regulating intracellular signaling pathways that control inflammation and apoptosis. However, the potential crosstalk between ALR and TNF-α signaling remains largely unexplored. The aim of this study is to elucidate the impact of ALR on TNF-α signal transduction, potentially mediated through ADAM17-dependent shedding of TNFR1.

Methods: We investigated the molecular signaling pathways of TNF-α in different hepatoma cell lines in the presence of ALR and specific ADAM17 inhibitors using western blot, RT-qPCR, and ELISA techniques.

Results: The amount of soluble ICAM-1 in the cell culture supernatant of Hep3B cells increased after treatment with TNF-α (20 ng/ml, 24 h), which was attenuated by pretreatment with ALR (100 ng/ml). Additionally, we observed reduced NF-κB

and p38 activation by TNF-α (20 ng/ml, 15 min) in presence of ALR. Furthermore, ALR treatment was found to reduce TNF-α-induced TNFR1 receptor complex formation, since TRADD recruitment to TNFR1 was decreased in Huh7 and HepG2 cells, which may be mediated by increased shedding of TNFR1, as shown by the reduced amount of TNFR1 in cell membrane fractions following ALR treatment.

Discussion/Conclusion: Taken together, our findings demonstrate that ALR can modulate TNF-α signaling in hepatocytes via ADAM17 activation, which provides a new perspective on how ALR may contribute to hepatoprotection and alleviate inflammatory liver diseases.

26. Viral load drives CD8+ T cell dysfunction in male versus female p atients with chronic HBV infection

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Introduction: Chronic Hepatitis B virus (HBV) infection causes > 1 mio deaths/year due to complications like liver cirrhosis and hepatocellular carcinoma (HCC). Disease progression can be prevented by long-term antiviral therapy with nucleoside-analogues. Male sex is associated with a higher HCC-risk, while the underlying mechanisms are unclear. It is also unclear, if there is a gender-effect in decision for antiviral therapy.

Methods: We observed 450 therapy-naive patients with chronic HBV infection retrospectively over 5 years (subgroup n = 282 over 10 years) with the primary endpoint "start of antiviral therapy". In 52 patients the phenotype of HBV-specific CD8+ T cells was analyzed by multiparametric flow cytometry after peptide/MHC-I tetramer enrichment.

Results: The primary endpoint was reached by 198 (44.0%) of patients, of which 75 were female and 123 male (start of therapy at median 2.7 vs. 3.1 months; p = 0,8870). Male sex was significantly associated with the start of antiviral therapy (p = 0,0005). Concerning indications for antiviral therapy, male patients showed a significantly higher viral load at baseline (male median 6622 [IQR, 4 724 277] vs. female 2020 [IQR, 54 800] IU/ml; p = 0.0030), while elevated liver enzymes were not significantly associated with gender. Immunological analysis revealed a more dysfunctional phenotype of HBV-specific CD8+ T cells in male patients, correlating with increased viral load.

Discussion/Conclusion: Higher risk for disease progression in male patients with chronic HBV infection is associated with a higher viral load, subsequent dysfunction of virus-specific CD8+ T cells and a higher chance of receiving antiviral therapy with implications for possible gender-sensitive clinical management of patients.

27. Identification and validation of gene expression pattern associated with inflammation in a cell culture model of Wilson's disease

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Introduction: Wilson disease (WD) is an autosomal recessive disorder caused by a defect in the ATP7B gene. ATP7B is an intracellular copper transporter that is highly expressed in the liver. The functional impairment of ATP7B results in a toxic hepatocellular copper accumulation, which ultimately causes impaired mitochondrial activity, autophagy, oxidative stress and the death of hepatocytes.

The objective of this study is to identify gene expression patterns associated with inflammation in HepG2 (WT and ATP7B-KO) cells and to investigate the effect of different copper levels on inflammatory processes.

Methods: Multivariance analysis of RNA-sequencing data (GSE107323) of $CuCl_2$-treated HepG2 (WT and ATP7B-KO) cells was performed, after which selected genes were analysed with STRING. Treatment of HepG2 (WT and ATP7B-KO) cells with CuCl2 was examined to measure cell viability (CCK8-Assay) and transcriptional changes of various immunology-related genes. In addition, NFKB- and AP1-promoter activity was measured in vitro after CuCl2 treatment using the luciferase reporter assays and a LEGENDPlexTM assay.

Results: Multiple component analysis identified gene expression patterns in the HepG2 ATP7B-KO cells that are associated with liver function (ALB, TF, AFP), oxidative stress (HMOX1, DNAJB1, GADD45B) and inflammation (FOS, PLA2G2A, JUN, JUNB). Quantitative PCR partially validated the expression of selected genes. CuCl2 treatment resulted in upregulation of luciferase reporter activity in NFKB- and AP1- promoter assays. LEGENDplexTM Assay indicated CuCl2-upregulated TNF, IL1B and IL8 levels.

Discussion/Conclusion: Despite the potential for increased AP1 and NFKB sensitivity in HepG2 ATP7B-KO cells, copper triggered AP1- and NFKB-promoter activity in a minor way in both, HepG2 WT and ATP7B-KO cells. This study provides a more comprehensive understanding of the cellular processes involved in inflammatory responses in Wilson's disease and showed that in addition to metal ion transport and autophagy, genes involved in inflammation and liver function were also affected in HepG2 ATP7B-KO cells.

28. Loss of Interleukin-13 disrupts hepatic lipid homeostasis in mice

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Introduction: Metabolic dysfunction-associated steatotic liver disease (MASLD) represents the most prevalent chronic hepatic pathology within Western populations. Since the Th2-specific cytokine interleukin-13 (IL-13) acts as a key mediator in the interaction between metabolic and inflammatory processes, its regulatory role in systemic metabolism has attracted considerable scientific interest. In this study, the influence of IL-13 on hepatic lipid metabolism was investigated using an IL-13 knockout mouse model.

Methods: The experimental group consisted of 8-week-old female IL-13$^{-/-}$ BALB/c mice, with age-matched wild-type (WT) littermates as controls (n = 12 per group), all fed a standard chow diet. For biochemical evaluation, serum triglyceride (TG) concentrations were quantified utilizing a respons® 910 analyzer (DiaSys), while the comprehensive profile of lipid species was established through chromatographic methods. To assess molecular changes, gene expression in liver was examined using RT^2 Profiler Array, confirming the most relevant results by quantitative real-time PCR (RT-qPCR). The expression and localization of selected target proteins in liver sections were visualized and analyzed by immunohistochemistry (IHC). Differences between the groups were statistically validated using a two-tailed Student's t-test.

Results: IL-13$^{-/-}$ mice had significantly elevated serum triglyceride (TG) levels compared to their WT controls. Chromatographic lipid profiling revealed an accumulation of phosphatidylserine species and a marked change in the composition of polyunsaturated fatty acids (PUFA). Transcriptomic analyses suggested that IL-13 deficiency induces a lipogenic gene expression pattern: Transcripts controlling lipid uptake (Ldlr), de novo lipogenesis (Fasn, Acly), and cholesterol synthesis (Hmgcr) were upregulated, while β-oxidation-related transcripts (Ppard, Pdk4) were downregulated. Furthermore, expressions of the AP-1 transcription factors Fosl2 and Jun were reduced in the IL-13$^{-/-}$ group, as confirmed by immunohistochemistry (IHC).

Discussion/Conclusion: IL-13 deficiency significantly disrupts lipid homeostasis in the liver. The metabolic alterations observed could be related to an IL-13-dependent downregulation of Fosl2 and c-Jun, as confirmed by complementary in vitro data from our group.

29. Tumor-promoting and prometastatic characteristics of melanoma cells are enhanced by adipocytes

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Introduction: A different range of cancers including melanoma preferentially metastasise to the liver. Obesity and associated metabolic diseases are known to be a risk factor for cancer development and progression. Visceral adipose tissue, which is enlarged in obesity is considered to have an endocrine function and secretes soluble factors that also reach the liver via the portal vein. These factors may also have an influence on tumor cells in the liver environment.

The aim of the study was to analyse whether adipocyte secreted factors promote tumorigenicity of melanoma cells and (hepatic) metastasis.

Methods: The 3T3 in vitro model to mimic adipogenesis was used, consisting of 3T3-L1 cells, that can be differentiated to adipocytes and pre-adipocytes. Conditioned medium (CM) of adipocytes was generated after differentiation of adipocytes. Adipocyte maintenance medium was used as control. Melanoma cells were treated with CM or control medium to analyse gene expression and functional effects.

Results: After treatment with CM, we observed an increased expression of vascular endothelial growth factor (VEGF), which is a known pro-angiogenetic factor and a known marker for poor prognosis of melanoma patients with hepatic metastases. CM also induced the mRNA expression of EMT markers like SLUG and functional analyses revealed that adipocyte CM also led to an increased proliferation and spheroid volume of melanoma cells. Furthermore, we observed a chemoattractive effect of CM on melanoma cells and an activation of protumorigenic signaling pathways. Boiling of CM ameliorates these effects, indicating that proteins are mainly responsible for the chemoattraction.

Discussion/Conclusion: Soluble factors secreted by adipocytes in the tumor microenvironment enhance tumor-promoting and prometastatic properties of melanoma cells. This could contribute to understand the potential mechanism how obesity and expanded visceral adipose tissue promote hepatic metastasis. The model may be used to characterise adipocyte secreted factors for diagnostic and therapeutic purposes in patients with (hepatic) metastasis.

30. Inhibition of JNK worsens liver pathology in Schistosoma mansoni infected mice

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Introduction: Schistosomiasis is a neglected tropical disease that affects over 250 million people worldwide. The eggs of the parasitic helminth S. mansoni are responsible for significant pathological changes in the liver, spleen, and intestines. Egg secreted soluble egg antigens (SEA) stimulate the transcription factor c-Jun in hepatocytes, thereby driving the cell cycle, proliferation, and apoptosis. In this study, we investigated the effects of pharmacological inhibition of c-Jun N-terminal kinase (JNK) during infection with S. mansoni on the liver.

Methods: Eight-week-old male mice were infected with 100 S. mansoni cercariae of both sexes. Beginning at 14 weeks of age, the animals received SP600125

treatment via subcutaneously implanted osmotic pumps for three weeks. Liver and spleen tissues, as well as serum samples, were analyzed to assess hepatic injury, inflammation, fibrosis, and metabolic parameters.

Results: Binding of the chosen JNK inhibitor SP600125 to SmJNK had no adverse effect on parasite fitness. SP600125-treated mice infected with S. mansoni showed a parasite-induced elevation of serum aminotransferases as well as an increase in coagulative liver necroses compared to infected control animals. Additionally, hepatic Cd45, Tnfα, Il6 and Cxcl2 levels were increased in these mice indicating aggravated damage and inflammation in the liver.

Upregulation of hepatic Col3a1 in addition to that of hepatic stellate cell (HSC) markers αSMA and desmin in infected, inhibitor-treated animals may further contribute to the exacerbation of liver damage.

Furthermore, the combination of JNK-inhibition and S. mansoni infection causes an increased exploitation of hepatic glycogen stores compared to the infection alone.

31. Pro- and anti-inflammatory cytokines in metabolic dysfunction-associated steatotic liver disease may be influenced by different strains of microbiota

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Introduction: The metabolic dysfunction-associated steatotic liver disease (MASLD) remains the most common chronic liver disease worldwide, and its occurrence and progression involve the process from simple hepatic steatosis to metabolic dysfunction associated steatohepatitis, which could develop into advanced liver fibrosis, cirrhosis, or hepatocellular carcinoma. It is widely accepted that MASLD is multi-factorial and insufficiently understood condition, frequently believed to be a part of metabolic syndrome with both incidence and prevalence rising globally. Growing database suggests that both the pathogenesis and progression of MASLD are closely related to immune system, with the role of the pro- and anti-inflammatory cytokines in pathogenesis of MASLD generally established. However, influence of diet and dietary interventions including probiotics on immune disorders in relation to MASLD is still unclear. Potentially it may alleviate the changes of microbiota as a part of gut-liver axis and therefore, influence the pathogenesis. Moreover, existing information on probiotic use in liver diseases is confusing. We hypothesized that different probiotic compositions may have different influence on the intestinal microbiota and therefore also significant influence on immunity and inflammation in MASLD.

Methods: Sixty patients with verified NAFLD participated in the study (42 men and 18 women, mean age 57.9 ± 4.8 yrs). All patients were randomized into the following groups: 1st group included all patients before treatment, 2nd group –

23 patients after standard unmodified treatment (EASL/EASD/EASO), 3rd group – 17 patients after additional treatment with oral probiotic (composition of the Bifidobacterium longum and Enterococcus faecium), 4th group – 20 patients after additional treatment with another oral probiotic mix (Bacillus subtilis and Bacillus licheniformis). Selection of probiotic strains, their taxonomy and composition based on known metabolic and immune properties. Control group included 17 practically healthy individuals. For research purpose pro- and anti-inflammatory cytokines transforming growth factor beta (TGF-β), tumor necrosis factor alpha (TNF-α) and IL-1β were typified (ELISA) before and after 60 days of treatment in all groups.

Results: Before treatment IL-1β and TNF-α levels were almost twice higher than in practically healthy subjects; TGF-β level was generally 2.8 times higher than in control. IL-1β (pg/ml) levels were 92.1 ± 2.8 (1st group, $p < 0.001$); 70.9 ± 3.5 (2nd group, $p < 0.001$, $p1 < 0.05$); 65.6 ± 4.2 (3rd group, $p < 0.001$, $p1 < 0.05$); 72.2 ± 3.7 (4th group, $p < 0.001$, $p1 < 0.05$); 50.7 ± 3.6 (control, p value compared to control; p1 compared to the 1st group data). TNF-α (pg/ml) levels were 86.1 ± 2.2 (1st group, $p < 0.001$); 71.7 ± 3.5 (2nd group, $p < 0.001$, $p1 < 0.05$); 83.3 ± 3.5 (3rd group, $p < 0.001$, $p2 < 0.05$ compared to the data of the 2nd group); 93.7 ± 4.2 (4th group, $p < 0.001$, $p2 < 0.05$), and 46.3 ± 4.3 (control). TGF-β: 150.4 ± 5.0 (1st group, $p < 0.001$); 142.1 ± 7.4 (2nd group, $p < 0.001$); 72.0 ± 3.9 (3rd group, $p < 0.001$, $p1 < 0.05$, $p2 < 0.05$); 63.5 ± 4.1 (4th group, $p1 < 0.05$, $p2 < 0.05$), and 53.1 ± 3.6 control. In 2nd group IL-1β and TNF-α levels decreased by 22.9% and 16.8% accordingly, with still higher values compared to control group's results. TGF-β level did not statistically differ in the 2nd group after standard treatment. Probiotic administration in 3rd group caused IL-1β level decrease by 28.7%, TGF-β level decrease 2.1 fold with regard to 1st group, but all data were still higher than in control group – 29.4%, 35.6%, accordingly, especially TNF-α level – 79.9%. Probiotic administration in fourth group caused IL-1β level decreasing by 21.6%, TGF-β level decreased 2.4 times and did not differ reliably from the control group; TNF-α level became certainly higher, comparatively to second and control groups.

Discussion/Conclusion: Existing standard therapy for MASLD causes significant lowering of the IL-1β and TNF-α levels concentration without certain influence on TGF-β level. However, the oral probiotic administration leads to the statistically reliable decrease of the IL-1β and TGF-β levels, with non-significant changes of the TNF-α concentration.

32. The genetic connexions of immune cells, systemic inflammation, metabolism, hepatic dysfunction, and adipokines in MASLD

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Introduction: Metabolic dysfunction-associated liver disease (MASLD) is a fatty infiltration of liver often leading to inflammatory damage to hepatocytes, closely related to metabolic syndrome, obesity, insulin resistance, type 2 diabetes

mellitus, arterial hypertension, and hyperlipidaemia. Pathogenesis of MASLD is complex and combine metabolic, inflammatory, and immune components. Common mechanisms for hepatic steatosis include reduced synthesis of very low density lipoprotein, and increased triglyceride synthesis; inflammation may result from lipid peroxidative damage to cell membranes, stimulating hepatic stellate cells, leading to liver failure and fibrosis. Number of experimental and clinical studies suggest that leptin (adipokine responsible for regulating body weight and energy expenditure) plays a key role to balance energy expenditure and nutritional status in the immune system. Moreover, leptin is also a crucial regulator of immunity and functions as a pro-inflammatory cytokine, influencing T-cell general population, particularly CD4+ cells proliferation, and balance between Th1 and Th2 phenotypes. Nonetheless, genetic background of orchestration apropos of leptin, hepatic function, metabolism and immune cells in MASLD is mostly unclear. Therefore, the aim of this study was to analyze the associations of the ACE (I/D), PPAR-γ2 (Pro12Ala) genetic polymorphisms with hepatocytes' functional activity, leptin and immune cells in patients with MASLD.

Methods: This study fully conforms to international bioethical standards and involved 96 patients (mean age 53.70 ± 5.34 yrs) with MASLD, 56 (58.33%) women and 40 (41.67%) men. Diagnosis and management according to EASL-EASD-EASO Clinical Practice Guidelines. The liver function was assessed by detoxification, protein-synthetic function of hepatocytes indices, by the presence/absence of cytolysis, mesenchymal inflammatory syndrome, or cholestasis. Leptin and adiponectin were measured in ELISA. Leptin resistance (LR) was calculated as the leptin/triglycerides ratio. Quantification of CD4+ T-cells was performed by fluorescence microscopy after Acridine Orange staining following 3-step immunomagnetic cell separation in samples of EDTA anticoagulated blood. PCR was used to study the SNPs of PPAR-γ2 (Pro12Ala, rs1801282) and ACE (I/D, rs4646994) genes.

Results: Liver protein synthesizing function did not suffer, regardless of the genes' SNPs. In ACE DD genotype, direct bilirubin, AST/ALT, and CD4+ were higher than in II/ID-genotypes. Conjugated bilirubin was higher by 22.24% and 20.55% ($p < 0.05$), AST – 2.12 and 1.71 times ($p < 0.05$); ALT – 1.32 times ($p < 0.05$); CD4+ by 14.56% ($p < 0.05$). Ala-allele carriers had higher rates of AST, ALT as well as CD4+ compared to Pro12-genotype of the PPAR-g2 gene – by 35.21%, 38.64%, 29.81% and 12.95%, respectively ($p < 0.05$). The fasting glucose level was higher in all patients regardless of type 2 diabetes, requiring further clarification. Leptin is higher in women, regardless of MASLD type and obesity by 1.74–2.39 times ($p < 0.001$). In MASLD men, leptin was 25.39% higher than in men with MASH, $p < 0.05$. In case of 3rd degree obesity, leptin was higher than in 1 and 2 degrees, regardless of gender: in men by 48.99% ($p = 0.022$) and 43.55% ($p = 0.034$); in women by 53.34% ($p < 0.001$) and 50.98% ($p = 0.002$). Obesity was associated with high leptin content in men ($F = 77.95$, $p < 0.001$) and women ($F = 341.43$, $p < 0.001$), with LR increase ($F = 103.17$, $p < 0.001$) and decrease of adiponectin ($F = 44.84$, $p < 0.001$). In female D-allele carriers of the ACE gene, leptin exceeded the one in II-genotype by 22.19% ($p = 0.048$) and 28.73% ($p = 0.036$). In Pro12 genotype of

the PPAR-γ2 gene, leptin exceeded that of the Ala-allele carriers regardless of sex: in men 1.99 ($p = 0.036$) and 3.75 times ($p = 0.008$), in women by 32.79% ($p = 0.015$) and 27.81% ($p = 0.043$). LR prevailed exclusively in male homozygous Pro-allele carriers, over Ala-allele carriers – 2.23 and 3.16 times ($p < 0.01$), in contrast to women, where such dependences were not found, despite higher initial level of both leptins itself and LR rate.

Discussion/Conclusion: Immunity and nflammation are closely associated with the development of MASLD. Multiple factors including metabolic dysfunction, oxidative stress, and lipotoxicity have been confirmed to initiate inflammation in MASLD. Moreover, different studies demonstrated subpopulations of T-cells are involved in MASLD through interacting/supporting factors mentioned above. It is known that CD4+ cells can either protect the liver from infections, or act a responsible actor in autoimmune hepatocellular injury. This study confirmed many previous findings and showed associations of adipocytokines activity, bilirubin, transaminases, and CD4+ in MASLD with shared genetic polymorphisms.

33. Fasting and diet-dependent changes of innate natural killer cells and pro-inflammatory cytokines in steatotic liver disease

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Introduction: Metabolic dysfunction-associated liver disease (MASLD) ranges from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), progressing to cirrhosis and hepatocellular carcinoma. Compared to MASLD, patients with MASH are more likely to develop advanced stages of liver fibrosis, cirrhosis and carcinoma. Although the pathogenetic mechanisms of disease progression remain uncertain, growing evidence suggests that the immune system participate in this process. Natural killer (NK) T-cells, an innate immune cells, are abundant in the liver, accounting for 20–35% of total hepatic lymphocytes in rodent experimental models and can specifically recognise glycolipid antigens, and produce both Th1 and Th2 cytokines when activated, and sharing characteristics with both T-cells and natural killer cells However, the role of NK T-cells in hepatic fibrogenesis is poorly understood. Moreover, while the role of diet in progression of MASLD and MASH is well established, the role of these immune cells remains unclear as only few studies have addressed the question of whether influence on NK T-cells' activity by nutritional alteration is of practical benefit Therefore, the aim of this study was to analyze the associations of different diets with NK T-cells, proinflammatory cytokines and liver fibrosis in MASLD.

Methods: The study fully conforms to international bioethical standards and performed experimentally on rodent model. Prior to the start of the experiment, mice were allowed ad libitum access to food. Fifty adult Wistar-line rats received 16 weeks of either Methionine-Choline-Deficient Diet (MCD, containing high

sucrose and fat without methionine and choline, which are essential for hepatic mitochondrial β-oxidation and for synthesis of VLDL) diet, which is the classic dietary model for studying MASH, or the Fast-Food diet (FFD, containing high fat, high cholesterol, high fructose), which recently becomes another dietary tool for MASLD modelling. In addition, 20 fasted mice were deprived of food for 1 to 3 days to study the effects of starvation. Fifteen animals formed control, receiving normal diet with not more than 10–12% of calories from fat. Liver histology, NK T-cells, fibrosis, and proinflammatory cytokines were studied in liver bioptates.

Results: All diets significantly impacted body mass: expectedly fasting diet reduced it by 41.10 ± 5.41% ($p < 0.05$), but FFD increased it by 95.36 ± 12.71% ($p < 0.01$), and MCD decreased it by 37.14 ± 11.09% ($p < 0.05$), supporting previous findings. Further changes in body mass were insignificant. No significant histological changes were observed in fasting animals similarly to control, whereas FFD fed animals developed mainly perisinusoidal/pericellular histological changes associated with mild to moderate NASH 1 stage fibrosis, and MCD fed animals presented with paraacinar macrovesicular steatosis, severe inflammation, hepatocellular ballooning, more advanced stage of fibrosis (mostly 2–3 stages), occurring in a perisinusoidal/pericellular, perivenular or bridging fibrosis patterns, associated with severe MASH. FFD diet animals showed significant decrease of NK T-cells compared to both control and MCD group ($0.01 < p < 0.05$), while difference between control and MCD group was insignificant ($p = 0.11$). Changes in fasting animals were insignificant ($p = 0.09$), too. IL-4 remained unchanged in the FFD ($p = 0.19$) and fasting group ($p = 0.08$), while being significantly higher in MCD animals compared to control ($p < 0.01$).

Discussion/Conclusion: It is well known that inflammation and immune response play a key role in the pathogenesis of obesity-associated metabolic diseases, including MASLD/MASH. Studies on pathogenic and protective role of NK T-cells in MASLD are controversial: it was shown that lack of NK T-cells may promote steatosis, inflammation, and liver fibrosis in high-fat or choline-deficient diets, whereas other studies showed NK T-cells play a role in promoting liver fibrogenesis and cirrhosis. This study confirms existing associations of dietary habits and development of metabolism associated liver conditions. Moreover, we found low to absent influence of fasting diet on immune mechanisms like NK T-cells and IL-4.

34. Spatial and proteogenomic niche deconvolution of hepatic crown-like structures in steatohepatitis progression and resolution

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Introduction: Proinflammatory macrophage responses in steatohepatitis lead to the development of hepatic crown-like structures (hCLS), that may govern tissue fibrosis – yet these lesions remain poorly studied. To resolve hCLS development and resolution, we generated a spatial and proteogenomic single-cell

RNA sequencing (scRNA-seq) reference to spatiotemporally map macrophage responses.

Methods: The choline deficient, ethionine-supplemented (0.05%; CDE) diet was given to male C57BL/6J mice for up to 21 days or for 8 days followed by a recovery period. A CDE scRNA-seq atlas with matched spatial transcriptomics data (ST, Xenium platform) was generated. CITE-seq enabled the simultaneous detection of 84 cell surface proteins in inflammatory macrophage subsets. Experimental validation was performed by multicolor immuno-fluorescence, immunohistochemistry, qPCR, FACS analysis and liver function tests. Selected findings were validated using the western diet model (32 weeks).

Results: CDE-induced steatohepatitis was associated with elevated transaminases and the development of numerous hCLS, that were characterized by heterogeneous expression of the marker proteins Clec4f, Gpnmb, F4/80, CD11b, CD11c and CD172a. scRNA-seq captured hepatocyte disease progression, the recruitment of lipid-associated macrophages (LAM) following a distinct trajectory, and the existence of a LAM-Kupffer cell (KC)-specific communication node. ST analysis of hCLS development confirmed a dynamic LAM-KC relationship with unique stage-specific compositional changes in hCLS.

Discussion/Conclusion: Current work focuses on the pharmacological perturbation of LAM- and KC-specific expression programs through inhibition of cell-specific regulons in vivo. These experiments aim to resolve cell type-specific roles in hCLS and their contribution in initiating, maintaining and potentially resolving profibrotic responses in steatohepatitis.

35. A follicular T helper cell axis sustains antiviral CD4+ T cell immunity in chronic infection in humans

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Introduction: Virus-specific CD4+ T cells are key orchestrators of adaptive immunity, yet their differentiation trajectories and long-term maintenance during chronic infection remain incompletely defined. Using human hepatitis C virus (HCV) as a model, we investigated how infection outcomes shape virus-specific CD4+ T cell fates.

Methods: We longitudinally analyzed HCV-specific CD4+ T cells from individuals across acute, acute-resolved, chronic, and direct-acting antiviral (DAA) therapy cured infection states. MHC class II tetramer-based enrichment enabled characterization of virus-specific CD4+ T cells phenotypically, transcriptionally and functionally using high-dimensional flow cytometry, single-cell RNA and TCR sequencing, and PMA-ionomycin stimulation assays, respectively.

Results: In chronic infection, a population of stem-like TCF-1+Bcl-2+ CD4+ T cells with T follicular helper (Tfh)-biased features gave rise to T-bet+ Th1-like effector cells. Shared TCR clonotypes between these subsets and trajectory analysis supported a linear differentiation hierarchy. Functionally, CD4+ T cells from chronic infection exhibited diminished cytokine secretion compared to acute-resolving infection. Following HCV cure, stem-like CD4+ T cells persisted as a stable memory pool for up to eight years but retained transcriptional imprints of chronic infection.

Discussion/Conclusion: In conclusion, CD4+ T cell responses in chronic infection are sustained by a stem-like subset that gives rise to effector cells and persists long term after HCV cure. These cells retain transcriptional features of chronic antigen exposure, a chronic scar, in contrast to bona fide memory cells obtained after acute-resolved infection. These results reveal similarities in the differentiation of CD4+ and exhausted CD8+ T cells with implications beyond chronic HCV infection.

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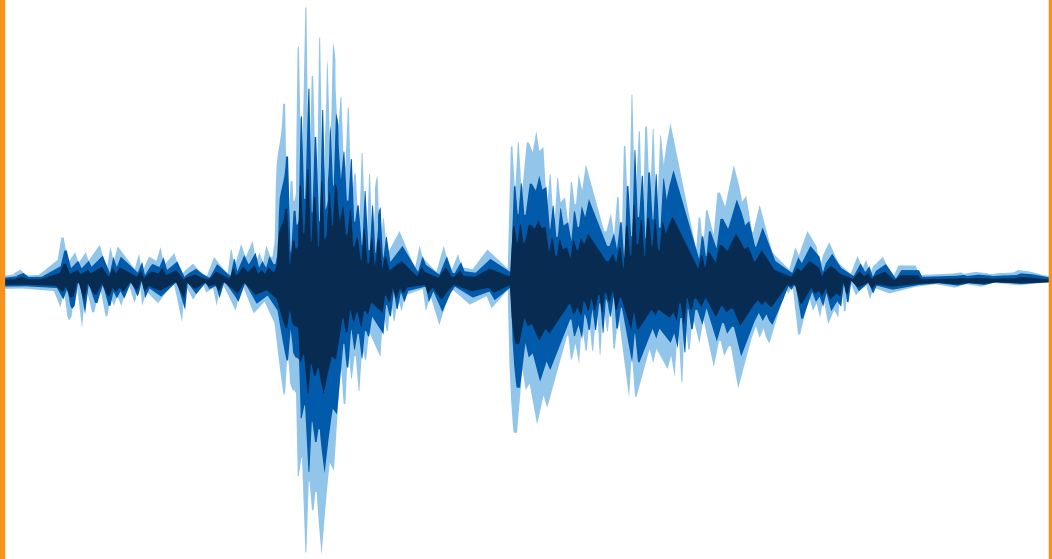

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