Project X: Tissue and immune cell communication in liver autoimmunity

Project leader: Prof. Dr. Johannes Herkel
Affiliation: I. Medizinische Klinik, UKE

Background and preliminary data:
Autoimmune liver diseases are difficult to treat chronic inflammatory conditions, which often progress to end stage liver disease. There is an urgent need for new therapies with improved efficacy, specificity and tolerability. To address that need, a more comprehensive knowledge of the disease mechanisms is needed. It is assumed that autoimmune liver diseases are caused by autoreactive lymphocytes that recognize liver antigens, producing tissue damage. Our recent single-cell and functional data suggest that autoreactive lymphocytes do not act alone, but in concert with innate immune cells and even with tissue cells. Apparently, autoreactive lymphocytes require confirmatory interactions with innate immune and tissue cells to fully deploy their pathogenic potential. Thus, while some tissue cells fall victim to autoimmunity, at least some other tissue cells seem to be complicit in driving autoimmune disease. Accordingly, autoimmune tissue damage seems to emerge from a network of cellular interactions involving both immune and tissue cells. However, the self-organization and regulation of this cellular network within the inflamed liver is not well understood. Elucidating these network interactions and its critical communication nodes might help to identify potential therapy targets. Based on our recent single-cell data, we have identified several cell states and candidate molecules awaiting functional confirmation.

Hypothesis:
The communication between autoreactive lymphocytes, innate immune cells and tissue cells is essential for the pathogenesis of autoimmune liver diseases. Targeted interference with critical communication signals can be used to prevent and treat autoimmune liver diseases.

Aims and Work Programme:

1. Identification and functional testing of critical signals in the communication between adaptive, innate and tissue cells driving autoimmune liver disease

2. Targeted interference with identified signalling pathways to validate their functional relevance and potential clinical use.

For Aim 1, we will use single-cell and spatial data from autoimmune liver diseases to identify critical cell types and candidate molecules of central importance for the cellular communication within the inflamed tissue, based on bioinformatic analyses. These cell types and molecules will be tested in functional experiments, using cells isolated both from human samples (blood and liver) and from mouse models that recapitulate critical characteristics of the human diseases, aiming for mutual confirmation of findings in mice and humans. Functional relevance of cell signalling molecules will be achieved by adding inhibitory antibodies if available, or CRISPR/Cas9-mediated inactivation. Additional confirmation of functional mechanisms will be obtained by histological and spatial analyses using human samples.

For Aim 2, we will assess the clinical relevance of molecules that were identified for Aim 1 as functionally relevant cell communication signals. This will be achieved by targeting those molecules in mouse disease models to validate their relevance for the clinical phenotype and their value as potential therapeutic targets.

We expect that this work programme will broaden our understanding of the cellular networks in autoimmune liver diseases, providing a rationale for novel therapies.

Project-related publications: (max. 5)

1. Lübbering D, Preti M, Schlott L, Schultheiß C, Weidemann S, Lohse AW, Binder M, Carambia A, Herkel J. Autoantigen-selected B cells are bystanders in spontaneous T cell-driven experimental autoimmune hepatitis. Immunology. 2023;170:214-229.
2. Müller AL, Casar C, Preti M, Krzikalla D, Gottwick C, Averhoff P, Rosenstiel P, Gelderblom M, Altfeld M, Lohse AW, Steinmann S, Sebode M, Krause J, Schwinge D, Schramm C, Carambia A, Herkel J. Inflammatory type 2 conventional dendritic cells contribute to murine and human cholangitis. J Hepatol. 2022;77:1532-1544.
3. Preti M, Schlott L, Lübbering D, Krzikalla D, Müller AL, Schuran FA, Poch T, Schakat M, Weidemann S, Lohse AW, Weiler-Normann C, Sebode M, Schwinge D, Schramm C, Carambia A, Herkel J. Failure of thymic deletion and instability of autoreactive Tregs drive autoimmunity in immune-privileged liver. JCI Insight. 2021;6:e141462.
4. Stein S, Henze L, Poch T, Carambia A, Krech T, Preti M, Schuran FA, Reich M, Keitel V, Fiorotto R, Strazzabosco M, Fischer L, Li J, Müller LM, Wagner J, Gagliani N, Herkel J, Schwinge D, Schramm C. IL-17A/F enable cholangiocytes to restrict T cell-driven experimental cholangitis by upregulating PD-L1 expression. J Hepatol. 2021;74:919-930.
5. Herkel J, Carambia A, Lohse AW. Autoimmune hepatitis: Possible triggers, potential treatments. J Hepatol. 2020;73:446-448.