PROJECT

Supervisor: Prof. Matteo Iannacone, M.D., Ph.D.

Title: The role of liver lymphatic vessels in health and disease

Curriculum: _____

Link to the personal page of the University or relevant hospital site website: https://www.iannaconelab.com/

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Liver lymphatic vessels are increasingly recognised as important regulators of tissue fluid homeostasis and immune cell trafficking. However, their specific role in liver physiology and pathology remains poorly understood. While lymphatic vessels have been shown to modulate immune responses in other organs, their contribution to liver inflammation, regeneration, and cancer progression is largely unexplored. This represents a critical gap in our understanding of hepatic immune regulation and tissue homeostasis.

Rationale and hypothesis

We hypothesise that liver lymphatic vessels are active regulators of immune responses and tissue function, rather than passive drainage structures. We propose that their phenotype and function are dynamically remodelled in response to disease, thereby influencing leukocyte trafficking, inflammatory responses, and tissue repair. Furthermore, dysregulation of lymphatic vessel function may contribute to disease progression in chronic liver conditions and cancer.

Objectives and specific aims

The overall objective of this project is to define the functional role of lymphatic vessels in liver homeostasis and disease.

Aim 1: Phenotypic and spatial characterisation of liver lymphatic vessels in health and disease

Aim 2: Functional role of lymphatic vessels in regulating liver immune responses

Aim 3: Identification of molecular regulators of lymphatic vessel function

Expected outcomes

This project will generate a comprehensive and integrated understanding of liver lymphatic vessel biology across multiple disease contexts. It will identify how lymphatic vessels regulate immune cell behavior, tissue damage, and repair, and will uncover key molecular pathways controlling their function. By combining *in vivo* models, advanced imaging, and single-cell transcriptomics, the study will provide mechanistic insights into lymphatic–immune interactions in the liver.

Ultimately, these findings are expected to reveal novel therapeutic targets and strategies aimed at modulating lymphatic vessel function to improve outcomes in liver diseases, including inflammatory conditions and cancer.

Skills that the student should acquire (max. 600 characters including spaces):

The PhD student will be required to work with *in vivo* animal models to recapitulate the complexity of the liver environment. The student will learn animal husbandry and be involved in animal care, including handling and breeding of sophisticated genetic mouse models. The student will also learn how learn how to work with mouse models of liver disease and advanced dissection techniques. They will be trained to perform spectral flow cytometry for immunological analysis including understanding panel design and high parameter analysis techniques. The student will also learn confocal and intravital imaging techniques, flow-cytometric cell sorting, and RNA sequencing techniques. The student will also learn the importance of experimental design and planning and be involved in lab meetings to be involved in discussions about all the projects ongoing in the lab.

References (max. 15)

1. M. Tanaka, Y. Iwakiri. The Hepatic Lymphatic Vascular System: Structure, Function, Markers, and Lymphangiogenesis. Cell Mol Gastroenterol Hepatol. 2016 Sep 14;2(6):733-749. doi: 10.1016/j.jcmgh.2016.09.002

2. L.G Guidotti, D. Inverso, L. Sironi, P. Di Lucia, J. Fioravanti, L. Ganzer, A. Fiocchi, M. Vacca, R. Aiolfi, S. Sammicheli, et al. Immunosurveillance of the Liver by Intravascular Effector CD8+ T Cells. Cell. 2015 Apr 23;161(3):486-500. doi: 10.1016/j.cell.2015.03.005

3. J. Jeong, M. Tanaka , Y. Iwakiri . Hepatic lymphatic vascular system in health and disease. J Hepatol. 2022 Jul;77(1):206-218. doi: 10.1016/j.jhep.2022.01.025.

4. S. Xie, X. Fan, Y. Liu, H. Li, C. Zhou, C. Guo, X. Tang , Y. Ming, P. Zhang. Intrahepatic Lymphangiogenesis Is Associated with Early Post-Hepatectomy Liver Regeneration, in Part via IL-6/STAT3 Signaling. Int J Med Sci. 2026 Jan 14;23(2):646-660. doi: 10.7150/ijms.106849.

5. S. Roy, P. Banerjee, B. Ekser, K. Bayless, D. Zawieja, G. Alpini, S. S Glaser, S. Chakraborty. Targeting Lymphangiogenesis and Lymph Node Metastasis in Liver Cancer. Am J Pathol. 2021 Dec;191(12):2052-2063. doi: 10.1016/j.ajpath.2021.08.011.

6. M.A Burchill, J. M Finlon, A. R Goldberg, A. E Gillen, P. A Dahms, R. H McMahan, A. Tye, A. B Winter, J. A Reisz, E. Bohrnsen, J. B Schafer, A. D'Alessandro, D. J Orlicky, M. S Kriss, H. R Rosen, R. L McCullough, B. A Jirón Tamburini. Oxidized Low-Density Lipoprotein Drives Dysfunction of the Liver Lymphatic System. Cell Mol Gastroenterol Hepatol. 2021;11(2):573-595. doi: 10.1016/j.jcmgh.2020.09.007.