Medical University of Graz

p53 regulation of lipid-associated macrophage infiltration upon fasting in liver disease

Summary

Andreas Prokesch, Gottfried Schatz Research Center, Cell Biology, Histology and Embryology, Medical University of Graz

Supervisor:	PD Dr. Andreas Prokesch
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between August 03, 2022 00:00 and September 20, 2022 23:59 (Europe/Zurich)

Description

Background:

Metabolic derangements solicited by unhealthy lifestyle-choices such as sedentariness and overnutrition are predominant causes of liver disease[1,2] and other metabolic disorders. Intermittent fasting (IF) has been shown to mitigate many of these metabolic derangements[3,4]. Lipid-associated macrophages (LAMs), positive for markers such as Trem2, Mmp12, and Gpnmb, have been identified in various stages in the progression of liver disease, from hepatosteatosis, fibrosis, cirrhosis to hepatocellular carcinoma (HCC)[5–8]. LAMs develop from infiltrating monocytes and, once infiltrated, localise to pathologic lesions and are suggested to curtail disease severity[9]. Yet, the primary signals that elicit the recruitment of these macrophages under various cirumstances remain elusive.

Hypothesis and Objectives:

Unpublished data from our lab show that LAMs are strongly recruited in adipose tissue upon an IF regimen applied to obese mice. Importantly, this IF-driven recruitment is entirely dependent on expression of the transcription factor p53 in parenchymal adipocytes. Based on preliminary data from livers of IF mice, we hypothesize that IF may ameliorate liver disease through recruitment of LAMs and that hepatic p53 regulates LAM infiltration in response to fasting.

Methodology:

We have established several fasting protocols for mice and a transgenic, conditional and hepatocyte-specific mouse model for knock-out of p53 (AlbCreERT2-p53fl/fl)[10]. This model will be subjected to treatments that model non-alcoholic fatty liver disease (high fat high fructose diet) or HCC with and without fibrosis background (DEN+/-CCl_4), with or without clodronate-mediated macrophage depletion. In these models we will asses the effects of loss of hepatocyte p53 on LAM infiltration upon IF. We will employ single-cell sequencing methods (established in our lab), immuno-histochemistry, and spatial transcriptomics (HybridISS[11], available through an in-house collaborator). Liver function will be analysed through liver-specific blood markers (e.g. AST, ALT) and HCC progression will be assessed via number and size of tumor nodules.

Finally, we will characterize macrophage infiltration and p53 status in biopsies from cirrhotic HCC patients (ethical approval and on-site clinical collaborations are already established).

In sum, this project aims to reveal mechanisms of p53-driven macrophage infiltration that underlie the effects of fasting in the etiology of liver disease. Understanding this axis is poised to deliver novel therapeutic avenues to fight the growing threat of metabolic liver diseases.

References:

1. Brunt, E. M. *et al.* Nonalcoholic fatty liver disease. *Nat. Rev. Dis. Prim.* 15080. **2015**. doi:10.1038/nrdp.2015.80

2. Younossi, Z. M. & Henry, L. Epidemiology of non-alcoholic fatty liver disease and hepatocellular carcinoma. *JHEP Reports* 3, 100305. **2021**. doi:10.1016/j.jhepr.2021.100305

3. De Cabo, R. & Mattson, M. P. Effects of intermittent fasting on health, aging, and disease. *N. Engl. J. Med.* 381, 2541–2551. **2019**. doi:10.1056/NEJMra1905136

Medical University of Graz

4. Patterson, R. E. & Sears, D. D. Metabolic Effects of Intermittent Fasting. *Annu. Rev. Nutr.* 37, 371–393. **2017**. doi:10.1146/annurev-nutr-071816-064634

5. Ramachandran, P. *et al.* Resolving the fibrotic niche of human liver cirrhosis at single-cell level. *Nature* 575, 512–518. **2019**. doi:10.1038/s41586-019-1631-3

6. Hendrikx, T. *et al.* Soluble TREM2 levels reflect the recruitment and expansion of TREM2+ macrophages that localize to fibrotic areas and limit NASH. *J. Hepatol.* **2022**. doi:10.1016/j.jhep.2022.06.004

7. Jaitin, D. A. *et al.* Lipid-Associated Macrophages Control Metabolic Homeostasis in a Trem2-Dependent Manner. *Cell* 178, 686-698.e14. **2019**. doi:10.1016/j.cell.2019.05.054

8. Guilliams, M. *et al.* Spatial proteogenomics reveals distinct and evolutionarily conserved hepatic macrophage niches. *Cell* 185, 379-396.e38. **2022**. doi:10.1016/j.cell.2021.12.018

9. Deczkowska, A., Weiner, A. & Amit, I. The Physiology, Pathology, and Potential Therapeutic Applications of the TREM2 Signaling Pathway. *Cell* 181, 1207–1217. **2020**. doi:10.1016/j.cell.2020.05.003

10. Krstic, J. *et al.* Fasting improves therapeutic response in hepatocellular carcinoma through p53-dependent metabolic synergism. *Sci. Adv.* 8, eabh2635. **2022**. doi:10.1126/sciadv.abh2635

11. Gyllborg, D. *et al.* Hybridization-based in situ sequencing (HybISS) for spatially resolved transcriptomics in human and mouse brain tissue. *Nucleic Acids Res.* 48, E112. **2020**. doi:10.1093/nar/gkaa792

To get more information or to apply online, visit https://mug.glowbase.com/positions/249 or scan the the code on the left with your smartphone.