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Preview

Found in translation—core network preservation across liver diseases and species

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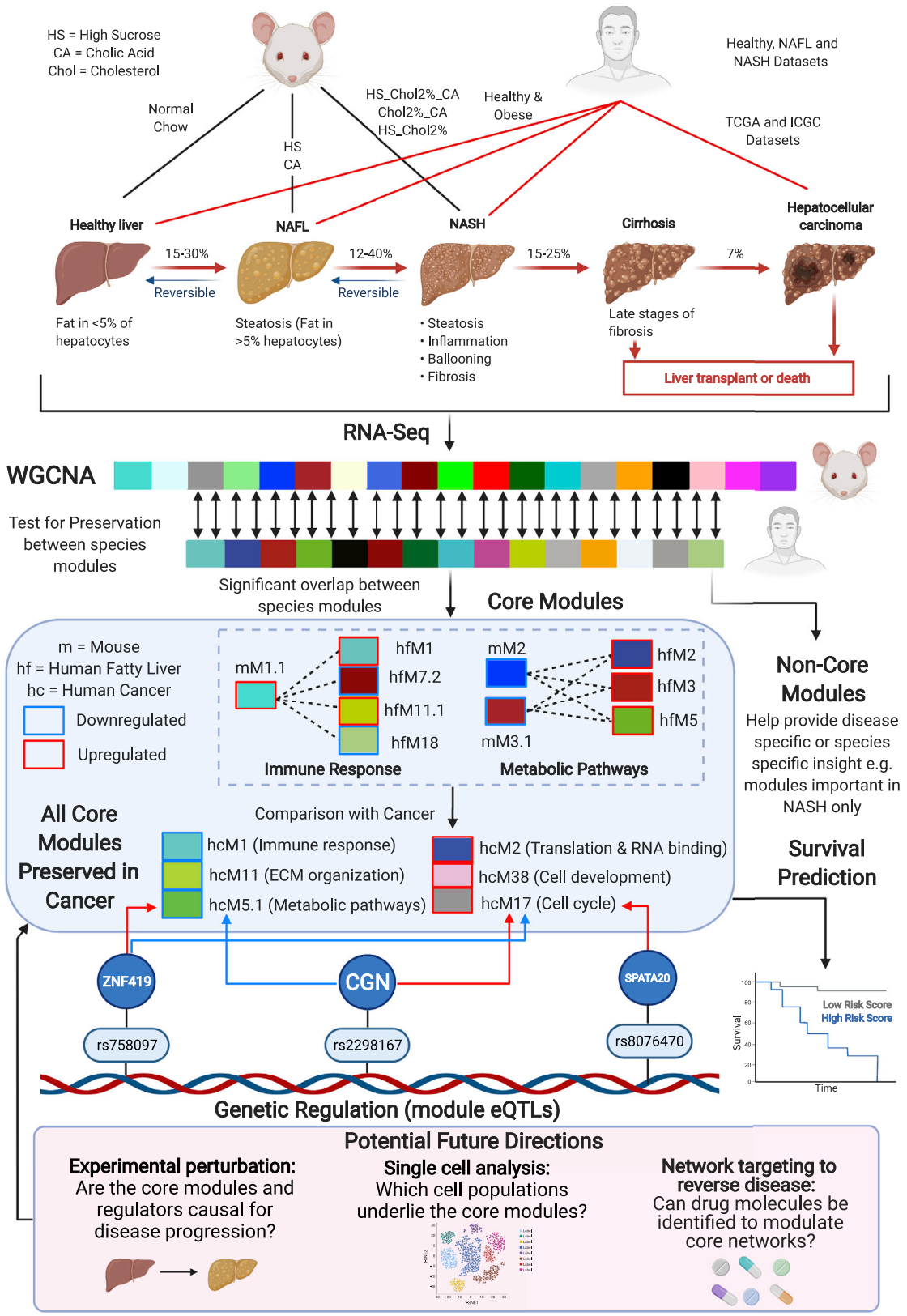
Esmaili et al.[1] conducted co-expression network analysis to uncover core homeostatic modules critical to a broad spectrum of liver diseases in mouse and human. Perturbation state of core modules may underlie disease stages across species and serve as therapeutic targets.

Complex liver diseases such as metabolic-associated fatty liver disease (MAFLD) and liver cancer display heterogeneity in clinical manifestation, risk factors, and causal genes and pathways. MAFLD is a spectrum of hepatic abnormalities ranging from simple steatosis (or non-alcoholic fatty liver, NAFL), steatohepatitis (NASH) to fibrosis and cirrhosis, with potential to develop into hepatocellular carcinoma (HCC). Given the high mortality of HCC and that there are no FDA-approved drugs for MAFLD that encompasses over 25% of the general population and soon to be the most common cause for liver transplantation, we are at a critical stage to push the pace to better understand liver diseases. To date, factors governing the progression between different types and stages of liver diseases are unknown, and a unifying model to explain liver disease heterogeneity is lacking. Additionally, although animal models have been extensively used in human disease studies, ensuring the translational relevance from mouse to man is still a challenge.

To overcome the challenges in translational medicine for liver diseases, it is important to recognize the diverse genetic and environmental causal factors and broad molecular alterations involved. The complexity promotes an omnigenic disease model, which posits that numerous genes connected in networks work together to partake in homeostatic biological functions but, when perturbed, result in complex diseases.[2] Networks offer a bird's eye view of disease etiology by taking into account global data points and molecular interactions, thereby allowing for a higher level comparison between diseases and species to pave a better translational path.[3,4]

Esmaili et al. utilized network-based systems biology to explore the heterogeneity and between-species network preservation of liver diseases through a comparative study[1] (Figure 1). They hypothesized that there exists preservation of core homeostatic gene networks in the liver, and specific regulation and state of the core networks determine pathophysiological conditions in mouse and human. To test the hypothesis, they applied weighted gene co-expression network analysis (WGCNA)[5] to a large collection of liver transcriptomic datasets representing various dietary perturbations and pathophysiological conditions (healthy, obesity, NAFL, NASH, liver cancer) in different species (human versus mouse) to identify preserved network modules across species and disease conditions. WGCNA is a widely used network-modeling method to group genes into "modules," each consisting of numerous genes demonstrating highly coordinated expression patterns. The study not only uncovered core modules involved in immune response and metabolism to be preserved across liver conditions and species but identified disease- and species-specific perturbation states of the core modules along with non-preserved modules. Interestingly, the direction of correlation between the core modules and disease states is not necessarily consistent between species or disease conditions, and the state of the preserved modules can predict liver cancer survival. Lastly, they identified potential regulators of the preserved modules using module expression quantitative trait loci (eQTL) analysis, highlighting novel genes such as CGN, ZNF419, and SPATA20 that may alter the behavior of the core modules.

This study is comprehensive and significant in several ways. First, by challenging mice with six different diets consisting of mixtures of cholesterol, cholic acid, and/or sucrose, they generated valuable transcriptomic datasets informing dietary effects and molecular processes involved in MAFLD triggered by environmental risks. Their network analysis of these datasets uncovered preserved network modules that deviate from the homeostatic state across the MAFLD spectrum. As liver pathology becomes more severe, the immune modules become more upregulated and metabolic modules more downregulated. This knowledge of gene network dynamics provides valuable insights into MAFLD progression. Second, they performed similar network analysis on numerous transcriptome datasets for a spectrum of human liver pathologies from healthy to MAFLD to liver cancer in order to confirm the preservation of the core modules between species across liver diseases. Their observation that the direction of change in core modules was not necessarily consistent between species suggests that it is the specific degree and direction of deviation from network homeostasis that underlie different disease states in different species. These findings offer insights into the level of preservation between species; that is, there is preservation in module structure but not direction and degree of change.



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Finally, the study incorporated genetic information to identify "module eQTLs," which are genetic loci that potentially regulate module expression patterns and homeostasis. This analysis highlighted novel genes that may serve as potential targets to modulate gene network perturbations for liver disease treatment.

Despite the strengths, the study has a few limitations, including the lack of functional validation of the causal importance of the core modules and regulators, and what the directional inconsistencies mean from a translational perspective. As module changes can be either protective or pathogenic, it is possible that a protective module is upregulated in one species but downregulated in another species. Additionally, as the liver is a heterogenous tissue with various cell types, it is important to dissect the cellular contributions to the core modules identified through single-cell studies. Furthermore, it would be interesting to identify drugs or agents that reverse network perturbations to homeostatic state.

Overall, the work by Esmaili et al. opens the door to translational medicine by providing a dynamic understanding of a broad spectrum of liver diseases between species and uncovering potential targetable gene candidates and networks. Previous studies have shown that disease genes identified from mouse and human do not necessarily overlap.[6] Instead of hunting for consistent disease causal genes, targeting preserved core networks is likely a more productive path, although caution is needed because of the directional inconsistency. The findings of this study are in line with recent network-based disease studies that uncovered preserved networks across diseases and/or species[6–10] and supports the value of systems biology in translational medicine.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Esmaili, S., Langfelder, P., Belgard, T.G., Vitale, D., Azardaryany, M.K., Alipour Talesh, G., Ramezani-Moghadam, M., Ho, V., Dvorkin, D., Dervish, S., et al. (2021). Core liver homeostatic co-expression networks are preserved but respond to perturbations in an organism- and disease-specific manner. Cell Syst. *12*, 432–445.
2. Boyle, E.A., Li, Y.I., and Pritchard, J.K. (2017). An Expanded View of Complex Traits: From Polygenic to Omnigenic. Cell *169*, 1177–1186.
3. Yang, X. (2020). Multitissue Multiomics Systems Biology to Dissect Complex Diseases. Trends Mol. Med. *26*, 718–728.
4. Barabási, A.L., Gulbahce, N., and Loscalzo, J. (2011). Network medicine: a network-based approach to human disease. Nat. Rev. Genet. *12*, 56–68.
5. Zhang, B., and Horvath, S. (2005). A general framework for weighted gene co-expression network analysis. Stat Appl Genet Mol Biol. *4* https://doi.org/10.2202/1544-6115.1128.
6. von Scheidt, M., Zhao, Y., Kurt, Z., Pan, C., Zeng, L., Yang, X., Schunkert, H., and Lusis, A.J. (2017). Applications and Limitations of Mouse Models for Understanding Human Atherosclerosis. Cell Metab. *25*, 248–261.
7. Mardinoglu, A., Uhlen, M., and Borén, J. (2018). Broad Views of Non-alcoholic Fatty Liver Disease. Cell Syst. *6*, 7–9.
8. Swarup, V., Hinz, F.I., Rexach, J.E., Noguchi, K.I., Toyoshiba, H., Oda, A., Hirai, K., Sarkar, A., Seyfried, N.T., Cheng, C., et al.; International Frontotemporal Dementia Genomics Consortium (2019). Identification of evolutionarily conserved gene networks mediating neurodegenerative dementia. Nat. Med. *25*, 152–164.
9. von Scheidt, M., Zhao, Y., de Aguiar Vallim, T.Q., Che, N., Wierer, M., Seldin, M.M., Franzén, O., Kurt, Z., Pang, S., Bongiovanni, D., et al. (2021). Transcription Factor MAFF (MAF Basic Leucine Zipper Transcription Factor F) Regulates an Atherosclerosis Relevant Network Connecting Inflammation and Cholesterol Metabolism. Circulation *143*, 1809–1823.
10. Wang, I.M., Zhang, B., Yang, X., Zhu, J., Stepaniants, S., Zhang, C., Meng, Q., Peters, M., He, Y., Ni, C., et al. (2012). Systems analysis of eleven rodent disease models reveals an inflammatome signature and key drivers. Mol. Syst. Biol. *8*, 594.

Figure 1. Overview of Esmaili et al. study and potential future directions

Esmaili et al.[1] conducted a cross-disease, cross-species study to understand the heterogeneity and between-species network preservation of a broad spectrum of liver diseases. A few potential future directions include functional validation of the core modules and regulators, identifying cellular components contributing to the core modules, and uncovering agents and drugs that may modulate the perturbed core modules to homeostatic state.