cmgh
CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

A Molecular Signature of Mouse NASH: A Step Closer to a Human Predictive Biomarker?

Fibrosis is the single best predictor of clinical outcomes in patients with nonalcoholic steatohepatitis (NASH).[1,2] Advanced fibrosis portends liver-related mortality and determines the need for liver transplantation.[3] Current diagnostic tools assess the presence of hepatic fibrosis but do not predict its development in patients at risk. Risk stratification based on propensity for liver fibrosis is a key factor for the selection of patients who benefit from close follow-up evaluation and medical therapy once approved. Liver biopsy remains the gold standard for fibrosis detection and staging but is invasive, and has the potential for sampling error. Radiologic assessment of liver stiffness has gained credibility over the past decade as a diagnostic and staging tool for liver fibrosis with magnetic resonance and vibration transient elastography. Simple predictive model of fibrosis including the aspartate aminotransferase–to-platelet ratio index), fibrosis-4 (age, platelet count, alanine aminotransferase, and aspartate aminotransferase), nonalcoholic fatty liver disease fibrosis score, and serologic panels of combined biomarkers to predict the presence of fibrosis has been established. These noninvasive tools have been reviewed thoroughly elsewhere[4] and overall have moderate accuracy in identifying patients with fibrosis stage 2 or greater on the Metavir scale, but good accuracy in excluding advanced fibrosis, and could be used to identify individuals at low risk for advanced disease. Notably, all of these tests have been developed with liver biopsy staged fibrosis as the reference standard. Therefore, by definition, these tests do not discriminate those who are at risk for fibrosis development from those who are not.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, in an effort to establish a molecular signature of fibrosis, van Koppen et al[5] performed an integrated transcriptomic and proteomic analysis of gene expression and protein turnover in a murine model of NASH over time. RNA sequencing of whole-liver mRNA in high-fat diet (HFD)-fed, low-density lipoprotein receptor knockout mice identified that the key categories of signaling pathways up-regulated in this model are lipid metabolism, inflammation, oxidative stress, and fibrosis/extracellular matrix (ECM). Over the time-resolved evolution of NASH, lipid metabolic pathways were the most up-regulated at week 6 (14 of 24 pathways). At this early time point, neither inflammation nor matrix remodeling were significantly induced. However, by 12 weeks of feeding there was increasing representation of inflammation (12 of 24 pathways), and by 18 weeks there was the appearance of matrix remodeling (2 of 24 pathways). Interestingly, using deuterated water to label newly formed protein ECM turnover was evident at 12 weeks of HFD feeding well before the transcriptomic signature and the histopathology reflected this. Next, using a reductive approach to identify differentially expressed genes that correlate with the dynamic protein data, that are up-regulated significantly at 12 weeks and persist for the duration of the study, the investigators identified a proteomic-transcriptome signature consisting of 232 genes and 8 proteins to predict fibrosis before its histologic onset in murine NASH. The top 20 of these genes and proteins had a high correlation with histologic fibrosis at week 24 of HFD feeding. Although some of the top 20 hits were predictable, it is notable that several of these top 20 hits have not been identified previously as biomarkers for either NASH or fibrosis.

A comparison with publicly available human microarray data showed that 71 of the 123 differentially expressed genes in human NASH were regulated in this murine model.[6] Furthermore, pathway analysis showed that the top pathways regulated in this murine model were similar to those in human NASH. Previous transcriptomic comparisons of murine and human NASH have not shown this degree of overlap, suggesting that the HFD-fed, low-density lipoprotein receptor knockout mouse model may more closely mimic human NASH.[6] However, the extreme hypercholesterolemia in these mice might not provide an accurate assessment of the biological changes in wild-type mouse models of NASH. For example, in a recent kinetic study of fibrosing NASH in wild-type mice, a significant increase in the messenger RNA expression of collagen was evident as early as 2 weeks after initiating dietary feeding.[7]

To be translated to a widely available blood-based biomarker panel, this gene panel will need to be refined further down to the most important targets that can be detected without the need for liver biopsy. The proteomic data are most intriguing in this regard and a biochemical ECM turnover signature seems promising. Validation of this proteomic signature in larger independent human NASH cohorts is feasible and may be able to stage fibrosis accurately and also predict those at greatest risk of fibrosis onset and progression.

SAMAR H. IBRAHIM, MB, ChB
Department of Pediatrics
Mayo Clinic
Rochester, Minnesota

HARMEET MALHI, MBBS
Division of Gastroenterology and Hepatology
Mayo Clinic
Rochester, Minnesota

References

1. Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, Mills PR, Keach JC, Lafferty HD, Stahler A, Haflidadottir S, Bendtsen F. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2015;149:389–397 e10.
2. Hagstrom H, Nasr P, Ekstedt M, Hammar U, Stal P, Hultcrantz R, Kechagias S. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. J Hepatol 2017, Epub ahead of print.
3. Wong RJ, Aguilar M, Cheung R, Perumpail RB, Harrison SA, Younossi ZM, Ahmed A. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology 2015;148:547–555.
4. Alkhouri N, Feldstein AE. Noninvasive diagnosis of nonalcoholic fatty liver disease: are we there yet? Metabolism 2016;65:1087–1095.
5. van Koppen A, Verschuren L, van den Hoek AM, Verheij J, Morrison MC, Li K, Nagabukuro H, Costessi A, Caspers MPM, van den Broek TJ, Sagartz J, Kluft C, Beysen C, Emson C, van Gool AJ, Goldschmeding R, Stoop R, Bobeldijk-Pastorova I, Turner SM, Hanauer G, Hanemaaijer R. Uncovering a predictive molecular signature for the onset of NASH-related fibrosis in a translational NASH mouse model. Cell Mol Gastroenterol Hepatol 2018;5:83–98.
6. Teufel A, Itzel T, Erhart W, Brosch M, Wang XY, Kim YO, von Schonfels W, Herrmann A, Bruckner S, Stickel F, Dufour JF, Chavakis T, Hellerbrand C, Spang R, Maass T, Becker T, Schreiber S, Schafmayer C, Schuppan D, Hampe J. Comparison of gene expression patterns between mouse models of nonalcoholic fatty liver disease and liver tissues from patients. Gastroenterology 2016;151:513–525 e0.
7. Krishnan A, Abdullah TS, Mounajjed T, Hartono S, McConico A, White T, LeBrasseur N, Lanza I, Nair S, Gores G, Charlton M. A longitudinal study of whole body, tissue, and cellular physiology in a mouse model of fibrosing NASH with high fidelity to the human condition. Am J Physiol Gastrointest Liver Physiol 2017;312:G666–G680.

Correspondence
Address correspondence to: Harmeet Malhi, MBBS, Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905. e-mail: Malhi.Harmeet@mayo.edu.

Conflicts of interest
The authors disclose no conflicts.

Funding
Supported by the North American Society of Pediatric Gastroenterology Hepatology and Nutrition Young Investigator Award/Nestle Nutrition Award and National Institutes of Health grant K08DK111397 (S.I.). Also supported by National Institutes of Health grants DK111378 and DK107402, the Mayo Foundation, Gilead Sciences, and the Palumbo Foundation (H.M.).

Most current article

2352-345X
https://doi.org/10.1016/j.jcmgh.2017.10.005