Galectin-3 in NAFLD: therapeutic target or non-causal biomarker?

Raymond E. Soccio, MD, PhD

Department of Medicine, Division of Endocrinology, Diabetes, and Metabolism; Institute for Diabetes, Obesity and Metabolism; Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA

Correspondence: soccio@pennmedicine.upenn.edu

DISCLOSURE STATEMENT: The author has nothing to disclose.

Keywords: Galectin-3, Non-alcoholic fatty liver disease, Mendelian randomization, Phenome wide association study

© The Author(s) 2021. Published by Oxford University Press on behalf of the Endocrine Society. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
Human genetics is a powerful tool to probe disease mechanisms and therapeutics. A prominent example is PCSK9 in hypercholesterolemia: identification of individuals with genetically low PCSK9 levels and protection from cardiovascular disease helped pave the way for anti-PCSK9 monoclonal antibody drugs (1). Furthermore, cell and animal studies of PCSK9 revealed a hitherto unappreciated pathway of LDL receptor degradation. Non-alcoholic fatty liver disease (NAFLD) is a condition ripe for such genetic studies of mechanism, and in great need of therapeutics. The study by Tremblay et al. in this issue (2) deploys Mendelian Randomization (MR) to investigate galectin-3 in NAFLD, and phenome-wide association studies (PheWAS) to look for other disease associations. The key background to this study is that galectin-3 inhibitors like belapectin are candidates for treatment of progressive NAFLD, nonalcoholic steatohepatitis with liver fibrosis and cirrhosis. A large multicenter phase 2b/3 study (NCT04365868) of over 1000 patients is investigating belapectin for prevention of esophageal varices, a complication of portal hypertension from cirrhosis.

Galectin-3 is a beta-galactoside binding protein, one of fourteen mammalian lectin family carbohydrate binding proteins, and it functions in diverse biological processes including cell adhesion and growth. Galectin-3 is located intracellularly and on the cell surface, and in the extracellular space such that it is also found in circulation. There is an expansive literature on galectin-3 in a host of diseases (3), including fibrotic diseases, cardiovascular disease, heart failure, neurodegeneration, and various cancers. Thus, galectin-3 is considered a drug target for many such diseases, and there was even a recent suggestion that galectin-3 inhibition could be beneficial in COVID-19 (4). Some animal models support a causal role of galectin-3 in pathology, but this remains an open question as it may be more relevant as a biomarker of diverse disease processes (5).

To test a causal role of galectin-3 in disease, Tremblay et al. first identified genetic variants (single nucleotide polymorphisms, SNPs) that are associated with higher levels of circulating galectin-3. They focus upon SNPs with significant effects in the LGALS3 locus (encoding galectin-3), indicating cis-acting variants affecting gene expression. Of course,
the elevations in circulating galectin-3 found in various diseases could reflect post-transcriptional effects, but the analysis in this study was designed to ask whether higher galectin-3 *per se* causally affects disease risk.

Next, the authors used MR to test whether these SNP alleles affecting circulating galectin-3 levels are associated with NAFLD at the population level. MR relies on the random inheritance of alleles during meiosis, and powerfully controls for confounding and reverse causality which can plague epidemiological studies. Here the authors found no difference in NAFLD risk associated with circulating galectin-3 levels. This negative result was consistent with the quite low mRNA expression levels of galectin-3 in liver relative to other tissues – though it notably remains unknown which tissues contribute most to circulating galectin-3.

Finally, the authors performed PheWAS to test whether the galectin-3 SNPs associate with any diagnoses based on electronic medical record (EMR) interrogation. They note the importance of this analysis, as belapectin could be repurposed for other diseases. After correction for multiple testing, the results were again negative, with no apparent difference in risk of any disease in people with genetic differences in circulating galectin-3 levels.

In aggregate, these results suggest that the association of galectin-3 with NAFLD and other diseases may reflect reverse causality, with disease processes increasing galectin-3 levels, but not higher galectin-3 levels increasing disease risk. If this is true, then therapeutic strategies to block galectin-3 will likely prove ineffective. Therefore, the authors present valuable negative data regarding galectin-3 as a causal factor in NAFLD and other diseases.

There are several caveats to this study. Regarding NAFLD, the authors acknowledge the potential of misclassification in EMRs, with a likely underestimate of the prevalence of NAFLD, and the lack of imaging or biopsy to confirm pathology or assess disease severity. For NAFLD and other diseases, there are theoretical models whereby genetically higher circulating galectin-3 may not increase disease risk, yet blocking galectin-3 in affected
tissues could nonetheless ameliorate disease processes. Imagine for instance that circulating galectin-3 is normally derived nearly entirely from adipose tissue, yet an inhibitor of galectin-3 could still affect local fibrotic disease processes in liver, lung, or kidney, or affect tumor galectin-3 in cancer. The mechanism of potential benefits in fibrosis and cancer remains unclear but would be local and tissue autonomous in this model, and thus would not correlate with circulating galectin-3. Therefore, as the authors note, clinical trials are still necessary to test galectin-3 blockers. If such trials fail, the analysis here would support the hypothesis that galectin-3 is more a biomarker of disease rather than a therapeutic target.
References:

1. Cohen JC. Using human genetics to discover new therapeutic targets for plasma lipids. *J Intern Med* 2016;280(5):487–495.

2. Tremblay M, Perrot N, Ghodsian N, Gobeil É, Couture C, Mitchell PL, Thériault S, Arsenault BJ. Circulating galectin-3 levels are not associated with non-alcoholic fatty liver disease: A Mendelian randomization study, 2020 In Press. *The Journal of Clinical Endocrinology & Metabolism* 2020.

3. Sciacchitano S, Lavra L, Morgante A, Ulivieri A, Magi F, De Francesco GP, Bellotti C, Salehi LB, Ricci A. Galectin-3: One Molecule for an Alphabet of Diseases, from A to Z. *Int J Mol Sci* 2018;19(2). doi:10.3390/ijms19020379.

4. Caniglia JL, Asuthkar S, Tsung AJ, Guda MR, Velpula KK. Immunopathology of galectin-3: an increasingly promising target in COVID-19. *F1000Res* 2020;9:1078.

5. Hara A, Niwa M, Noguchi K, Kanayama T, Niwa A, Matsuo M, Hatano Y, Tomita H. Galectin-3 as a Next-Generation Biomarker for Detecting Early Stage of Various Diseases. *Biomolecules* 2020;10(3). doi:10.3390/biom10030389.