HEPATOLOGY

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

CORRESPONDENCE | HEPATOLOGY, VOL. 00, NO. 00, 2016

Aquaporin Gene Therapy for Cholestasis

TO THE EDITOR:

This is regarding the editorial "Aquaporin gene therapy for disorders of cholestasis?" by Tradtrantip and Verkman.[1] We thank the authors for their comments in our recent studies.[2,3] Nevertheless, we believe that an analysis of the role of aquaporins (AQPs) in hepatocyte canalicular water transport and bile secretion should take into account several published contributions that were not cited in the editorial.

Two independent studies using the polarized rat hepatocyte couplet as *in vitro* model for bile secretion indicate that the osmotically driven transepithelial transport of water is largely transcellular by AQPs with a minor paracellular contribution.[4,5] In line with this is the assessment of the osmotic water permeability of hepatocyte basolateral and canalicular plasma membranes.[6] Studies in bile-canaliculi-forming, human-hepatocyte-derived HepG2 cells provide key additional support by demonstrating that the gene silencing of canalicular AQP8 markedly reduced osmotically driven and bile-agonist-induced canalicular water secretion.[7] Altogether, these experimental evidences support the notion that canalicular AQP8 is implicated in bile formation and that a defective expression of this AQP contributes to bile secretory dysfunction. In line with this is the fact that different animal models of cholestasis show defective canalicular AQP protein expression.[9-12] In this context, it is conceivable that AQP gene transfer may help to improve certain cholestatic disorders.

According to the editorial, studies in AQP8 knockout mice provide evidence against a role of canalicular AQP8 in bile secretion.[8] In that study, bile was not collected, and the conclusion was based on the fact that AQP8 knockout mice show only mild dietary fat misprocessing.[8] Although this finding may suggest a preserved excretion of bile salts for lipid digestion, direct studies on bile secretion must be done in order to conclude whether AQP8 knockout mice have any alteration in the flow of bile.

In the editorial, it is questioned that only a subset of AQP1-expressing hepatocytes was able to increase bile flow. The transduction efficiency of 20% was estimated considering the total number of hepatocytes within the lobule (i.e., periportal, central, and perivenous). Nevertheless, the retrograde biliary vector administration allowed that most of the periportal hepatocytes were transduced with AQP1.[2,3] This is relevant because periportal hepatocytes are exposed to the highest blood concentrations of bile salts and thus are the primary cells involved in bile-salt-dependent bile secretion.

We think it may be premature to judge whether the hepatic gene transfer of AQPs is a credible approach for treatment of cholestasis. We anticipate that further studies will clarify its impact as a novel therapeutic strategy.

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REFERENCES

1) Tradtrantip L, Verkman AS. Aquaporin gene therapy for disorders of cholestasis. HEPATOLOGY 2016;64:344-346.
2) Marrone J, Soria LR, Danielli M, Lehmann GL, Larocca MC, Marinelli RA. Hepatic gene transfer of human aquaporin-1 improves bile salt secretory failure in rats with estrogen-induced cholestasis. HEPATOLOGY 2016;64:535-548.
3) Marrone J, Lehmann GL, Soria LR, Pellegrino JM, Molinas S, Marinelli RA. Adenoviral transfer of human aquaporin-1 gene to rat liver improves bile flow in estrogen induced cholestasis. Gene Ther 2014;21:1058-1064.
4) Huebert RC, Splinter PL, García F, Marinelli RA, LaRusso NF. Expression and localization of aquaporin water channels in rat hepatocytes. Evidence for a role in canalicular bile secretion. J Biol Chem 2002;277: 22710-22717.
5) Jessner W, Zsembery A, Graf J. Transcellular water transport in hepatobiliary secretion and role of aquaporinas in liver. Wien Med Wochenschr 2008;158:565-569.
6) Marinelli RA, Tietz P, Caride A, Huang B, LaRusso NF. Water transporting properties of hepatocyte basolateral and canalicular plasma membrane domains. J Biol Chem 2003;278:43157-43162.
7) Larocca MC, Soria LR, Espelt MV, Lehmann GL, Marinelli RA. Knockdown of hepatocyte aquaporin-8 by RNA interference induces defective bile canalicular water transport Am J Physiol 2009;296:G93-G100.
8) Yang B, Song Y, Zhao D, Verkman AS. Phenotype analysis of aquaporin-8 deficient mice. Am J Physiol 2005;288:C1161-C1170.
9) Carreras FI, Gradilone SA, Mazzone A, García F, Ochoa JE, Tietz P, et al. Rat hepatocyte aquaporin-8 water channels are down-regulated in extrahepatic cholestasis. HEPATOLOGY 2003; 37:1026-1033.

10) Carreras FI, Lehmann GL, Ferri D, Tioni MF, Calamita G, Marinelli RA. Defective hepatocyte aquaporin-8 expression and reduced canalicular membrane water permeability in estrogen-induced cholestasis. Am J Physiol 2007;292: G905-G912.
11) Lehmann GL, Carreras FI, Soria LR, Gradilone SA, Marinelli RA. LPS induces the TNFα-mediated down-regulation of rat liver aquaporin-8: role in sepsis-associated cholestasis. Am J Physiol 2008;294:G567-G575.
12) Lehmann GL, Marinelli RA. Peritoneal sepsis down-regulates liver expression of aquaporin-8, a water channel involved in bile secretion. Liver Int 2009;29:317-318.

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DOI 10.1002/hep.28734

Potential conflict of interest: Nothing to report.