testing. As they point out, routinely used molecular assays for HEV diagnostics or blood donor screening would not be able to detect HEV-C1.[3] Although we demonstrated that the Wantai HEV immunoglobulin M (IgM) and immunoglobulin G kits (Wantai, Beijing, China) may cross-react with the sera of patients with HEV-C1,[1] HEV-A/HEV-C1 discriminatory assays would be a valuable asset to HEV diagnostics.

For 40 of the HEV IgM-positive/RNA-negative patients with sufficient sample volume, we also attempted conventional RT-PCR using universal consensus primers as described previously.[3] These primers would theoretically be able to detect highly divergent species within the family *Hepeviridae*, but all samples tested negative. As noted in our study, our real-time PCR primers and probes were specific for HEV-C genotype 1, which circulates in rats.[1] However, HEV-C is very diverse, with four putative genotypes circulating in a variety of rodents and ferrets.[4] Our HEV-C1 real-time PCR would not detect HEV-C genotypes 3 and 4, which circulate in field mice and voles.[4] However, we judge that urban dwellers in Hong Kong are less likely to be exposed to these genotypes.

The route of transmission of HEV-C1 between rats and humans is elusive. None of our patients had a history of rat meat consumption, and the practice is uncommon in Hong Kong. Indeed, almost all of them even denied rat infestation in their domestic premises. We considered adulteration of food products or natural HEV-C1 infection of pigs to be possibilities, so we tested for HEV-C1 in 212 pork products and samples. However, none of the samples tested positive.[1] We agree that extensive epidemiological investigations are required to identify the definitive source of HEV-C1 infection.

Siddharth Sridhar, FRCPath[1-4]
Kwok-Yung Yuen, M.D.[1-4]
[1]Department of Microbiology
Li Ka Shing Faculty of Medicine
The University of Hong Kong
Hong Kong, China
[2]State Key Laboratory of Emerging Infectious Diseases
The University of Hong Kong
Hong Kong, China
[3]Carol Yu Centre for Infection
The University of Hong Kong
Hong Kong, China
[4]The Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases
The University of Hong Kong
Hong Kong, China

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View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep.31237

Potential conflict of interest: Nothing to report.

Letter to the Editor: Does Augmenter of Liver Regeneration Deficiency Pave the Way for Nonalcoholic Steatohepatitis Progression?

TO THE EDITOR:

We read with interest the recent article by Kumar et al.[1] on the impact of augmenter of liver regeneration (ALR) deficiency on nonalcoholic fatty liver disease (NAFLD) progression from steatosis to nonalcoholic steatohepatitis (NASH). By using hepatocyte-specific ALR knockout/knockdown high-fat/high-

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carbohydrate mouse models, they demonstrated an involvement of ALR in lipid metabolism, oxidative stress, and inflammatory response leading to fibrosis. However, ALR is expressed in three isoforms (15, 21, 23 kDa),[2] and their specific roles in this "loss-of-function" strategy is not addressed. In earlier publications, using an overexpression approach ("gain-of-function") of the mainly mitochondrial 23-kDa ALR, a reduction in hepatic fibrosis and ischemia reperfusion injury (IRI) in steatotic livers was shown.[2] Expression of cytosolic 15-kDa ALR reduced severity of liver injury in a methionine-choline–deficient NASH mouse model.[2] Furthermore, it was shown that cytosolic 15-kDa ALR, different from exogenously applied 15-kDa ALR, diminished triacylglycerol levels and lipoapotosis *in vitro* by attenuating endoplasmatic stress, increasing lipolytic and decreasing lipogenic gene expression.[3] Additionally, treatment with exogenous ALR reduced hepatic IRI in mice by reducing neutrophil infiltration through less hepatocytic chemokine expression.[4] More detailed knowledge of the function of individual ALR isoforms is necessary for future therapeutic interventions.

Kumar et al. found decreased ALR levels in human NASH patients (tissue and serum) and pointed to a lack of information about ALR regulation. This was addressed earlier, demonstrating reduced hepatic ALR mRNA levels in patients with steatosis and even more with NASH.[2,3] ALR is regulated, among others, by forkhead box A2 (FOXA2; hepatocyte nuclear factor 3β), which translocates from the nucleus to the cytosol upon treatment with free fatty acids, and whose expression correlates with ALR expression in NAFLD patients.[3] Nuclear factor erythroid 2–related factor 2 (Nrf2), another ALR-regulating transcription factor,[2] was shown to attenuate liver steatosis and therefore it is likely that FOXA2 and Nrf2 diminished endogenous ALR levels in hepatic steatosis/NASH. However, the conclusion that ALR deficiency may be a major determinant of accelerated progression of NASH to end-stage liver disease, that is, cirrhosis, is not supported by enhanced ALR levels in patients with cirrhosis[2] or by clinical characterization of patients with mutations in the growth factor erv1-like (GFER) gene (encoding for ALR) showing almost no distinctive feature regarding hepatic function[2] and therefore should to be taken with caution.

Thomas S. Weiss, Ph.D.
Michael Melter, M.D.

Rania Dayoub, Ph.D.
Children's University Hospital (KUNO)
University Hospital Regensburg
Regensburg, Germany

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DOI 10.1002/hep.31248

Potential conflict of interest: Nothing to report.

REPLY:

We appreciate the important points raised by Weiss et al.[1] Our data indicate that the loss of 21/23 kDa Augmenter of liver regeneration (ALR), in mice and humans, renders the liver compromised to develop NASH.[2] Administration of 21/23 kDa ALR to hepatocyte-specific ALR-knockout (ALR-H-KO) mice between 1 and 2 weeks postpartum mitigated steatohepatitis.[3] The 15 kDa ALR is absent (Fig. 8)[2][Ref. 71 in (4)] or expressed at a very low level[5] in human liver and absent in mouse liver.[2,4,6] However, further investigation of ALR isoform(s) that can be of therapeutic intervention is important.

Hepatic ALR is down-regulated in steatosis regardless of its etiology in wild-type (WT) mice,

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