Letter to the Editor

Cancer Research

Lipid Metabolism Signatures in NASH-Associated HCC—Letter

Sonja M. Kessler[1], Stephan Laggai[1], Ahmad Barghash[2], Volkhard Helms[2], and Alexandra K. Kiemer[1]

An article published recently in *Cancer Research* elegantly performed lipidomic and gene expression analyses in a murine model of nonalcoholic steatohepatitis (NASH)–associated hepatocellular carcinoma (HCC) and compared the findings with serum samples from patients with fibrosis and HCC (1).

The study reports that the expression of the C18 fatty acid producing elongase (*ELOVL6*) is elevated in a mouse NASH model. The animals also exhibited elevated oleic acid (18:1n9) and vaccenic acid (18:1n7) abundance in livers and serum. Thereby, the study supports findings about increased hepatic *ELOVL6* expression in other models of NASH, such as a fructose feeding model (2) and low-density lipoprotein receptor (LDLR) knockout animals fed on a Western-type diet (3). In line with these findings, a causal role for ELOVL6 in the development of NASH was published recently in a comprehensive work using overexpression and knockdown strategies (4).

HCC represents a rare but important complication of NASH (5). The study by Muir and colleagues reports an increased expression of ELOVL6 not only in murine NASH but also in murine NASH–associated HCC. Because lipidomic analyses of sera of 15 patients with HCC showed a higher prevalence of the C18 vaccenic acid (18:1n7) than serum of patients with cirrhosis, the authors suggested elevated ELOVL6 expression in human HCC. Although they observed lower levels of the more abundant linoleic acid (18:2n6) and they do not show any data on ELOVL6 expression in patients with HCC, they propose ELOVL6 as a pharmacologic target for patients predisposed to HCC.

We investigated differential *ELOVL6* gene expression between HCC ($n = 247$) and nontumor ($n = 239$) samples of a Gene Expression Omnibus dataset (GSE14520; see Fig. 1). Interestingly, in contrast to Muir and colleagues, our results from this large dataset revealed significantly decreased levels of *ELOVL6* gene expression in the majority of human liver tumors compared with nontumorous tissue. We also observed a decreased expression of *Elovl6* in the widely accepted murine diethylnitrosamine (DEN) HCC model (see Fig. 2; ref. 5).

Taken together, different recent reports from the literature suggest a pathophysiologic role for ELOVL6 in steatohepatitis. Still, a role for ELOVL6 in HCC is as yet elusive and our data show ELOVL6 expression to be reduced in a common murine non-NASH–associated HCC model as well as in a large proportion of patients with HCC. In our opinion, the data available on ELOVL6 in HCC do not justify proposing ELOVL6 as a therapeutic target in either prevention or treatment of HCC.

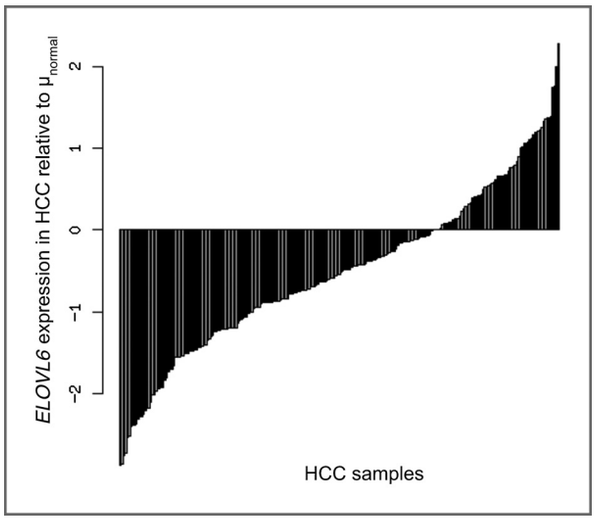

Figure 1. mRNA levels of *ELOVL6* in 247 human HCC samples relative to the mean of 239 nontumor liver tissue (μ_{normal}). Samples of dataset GSE14520 [$\log_2$ (expression) values from GEO after Robust Multi-array Average normalization] were mapped to hgu133a.db using bioconductor. Significance values: $P = 3.8E{-}11$, Kolmogorov–Smirnov test; $P = 6.7E{-}11$, *t* test; 5.1E−11, Mann–Whitney *U* test.

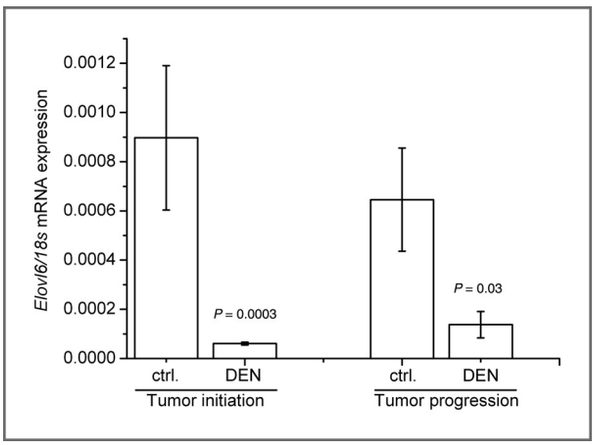

Figure 2. Wild-type mice were treated with the carcinogen DEN at the age of 2 weeks. Livers were analyzed after 24 weeks to assess the tumor initiation state. Analyses in the tumor progression stadium were done after 36 weeks. *Elovl6* mRNA expression as determined by real-time reverse transcriptase PCR with $n = 8$–18 per group. Data were normalized to *18S*. Statistical differences compared with untreated animals of the same age (ctrl.) were calculated by Mann–Whitney *U* test.

Authors' Affiliations: [1]Pharmaceutical Biology; and [2]Center for Bioinformatics, Saarland University, Saarbrücken, Germany

Note: The authors of the original article declined to submit a response.

Corresponding Author: Alexandra K. Kiemer, Pharmaceutical Biology, Saarland University, P.O. Box 15 11 50, 66041 Saarbrücken, Germany. Phone: 49-681-302-57301; Fax: 49-681-302-57302; E-mail: pharm.bio.kiemer@mx.uni-saarland.de

doi: 10.1158/0008-5472.CAN-13-2852

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Received October 8, 2013; revised November 19, 2013; accepted November 22, 2013; published OnlineFirst April 28, 2014.

References

1. Muir K, Hazim A, He Y, Peyressatre M, Kim DY, Song X, et al. Proteomic and lipidomic signatures of lipid metabolism in NASH-associated hepatocellular carcinoma. Cancer Res 2013;73:4722–31.
2. Mori T, Kondo H, Hase T, Murase T. Dietary phospholipids ameliorate fructose-induced hepatic lipid and metabolic abnormalities in rats. J Nutr 2011;141:2003–9.
3. Hoekstra M, van der Sluis RJ, Kuiper J, Van Berkel TJC. Nonalcoholic fatty liver disease is associated with an altered hepatocyte microRNA profile in LDL receptor knockout mice. J Nutr 2012;23:622–8.
4. Matsuzaka T, Atsumi A, Matsumori R, Nie T, Shinozaki H, Suzuki-Kemuriyama N, et al. Elovl6 promotes nonalcoholic steatohepatitis in mice and humans. Hepatology 2012;56:2199–208.
5. Li Y, Tang ZY, Hou JX. Hepatocellular carcinoma: insight from animal models. Nat Rev Gastroenterol and Hepatol 2012;9:32–43.