Editorial Commentary

The vascular endothelial growth factor system—a new player in the pathogenesis and development of metabolic dysfunction-associated steatotic liver disease

Henning Grønbæk[1,2]^, Anders Mellemkjær[1,2]^, Søren Nielsen[2,3]^, Faidon Magkos[4]^

[1]Department of Hepatology & Gastroenterology, Aarhus University Hospital, Aarhus, Denmark; [2]Clinical Institute, Aarhus University, Aarhus, Denmark; [3]Steno Diabetes Center Aarhus, Aarhus University Hospital, Aarhus, Denmark; [4]Department of Nutrition, Exercise and Sports, University of Copenhagen, Frederiksberg, Denmark

Correspondence to: Henning Grønbæk, MD, PhD. Department of Hepatology & Gastroenterology, Aarhus University Hospital, 99 Palle Juul-Jensens Boulevard, 8200 Aarhus N, Denmark; Clinical Institute, Aarhus University, Aarhus, Denmark. Email: henngroe@rm.dk.

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The pathogenesis of liver disease from simple steatosis—metabolic dysfunction-associated steatotic liver disease (MASLD)—and the transition to inflammation and fibrosis—metabolic dysfunction-associated steatohepatitis (MASH)—is not well understood. However, cross-talk between subcutaneous white adipose tissue (WAT) and the liver may be of importance.

In a recent study, Falkevall *et al.* (1) focused on vascular endothelial growth factor B (VEGF-B) which controls tissue lipid accumulation by regulating the free fatty acid (FFA) transport properties across of the vasculature into tissue cells by upregulation of endothelial fatty acid transporter proteins. They investigated this using a translational approach in a set of elegant studies that combined experimental animal models of MASLD fed standard chow *vs.* a high fat diet (HFD) with adipocyte-specific overexpression or underexpression of VEGF-B, global deletion of VEGF-B, and antibody-mediated systemic inactivation of VEGF-B signaling. In addition, they obtained human visceral and subcutaneous WAT biopsies and clinical data from a pre-existing cohort of patients with obesity undergoing bariatric surgery with or without MASLD. Their main findings were that inhibition of VEGF-B signaling downregulates lipolysis in adipocytes by inactivating hormone-sensitive lipase (HSL) via yet unresolved mechanisms (reciprocal signaling and/or WAT inflammation), and thereby reduces the availability of FFA to the liver and ameliorating hepatic steatosis. Downregulation of hepatic de novo lipogenesis (DNL) was also evident, but the extent of this was comparably much smaller. Further, reduction of VEGF-B signaling improved MASLD by decreasing WAT inflammation and alleviating WAT insulin resistance to anti-lipolysis. These findings were supported by results from human subcutaneous and visceral WAT biopsies suggesting a potential contribution of VEGF-B signaling to MASLD development. VEGF-B expression levels in adipocytes from the two WAT depots correlated positively with development of dysfunctional WAT, markers of liver function, and MASLD severity. The authors concluded that a promising approach to combat

^ ORCID: Henning Grønbæk: 0000-0001-8998-7910; Anders Mellemkjær, 0000-0002-1909-9990; Søren Nielsen, 0000-0002-8624-5556; Faidon Magkos, 0000-0002-1312-7364.

MASLD would be to target hepatic steatosis through suppression of lipolysis via the VEGF system.

The study adds new knowledge on VEGF and MASLD development but is not without limitations. The authors used an HFD (60% of energy as fat) to induce MASLD. However, it is well known that HFDs in most animal models induces only mild MASLD changes. A better model would have been the Gubra Amylin NASH Diet (40% of energy fat, 22% fructose, 10% sucrose, 2% cholesterol) (2) which consistently induces steatosis, lobular inflammation, hepatocyte ballooning, MASH fibrosis and hepatic transcriptome changes similar to human MASH (3). Thus, the study by Falkevall (1) primarily investigated early and mild events in the pathogenesis of MASLD, such as the development of steatosis, hence the relevance of their findings to the transition and/or progression to MASH is less apparent. This was evident by the observation of limited inflammation and fibrosis in the HFD mouse model with a Non-alcoholic fatty liver disease (NAFLD) activity score (NAS) score of 3.5 and only mild fibrosis (F=0.7). Similarly, in the clinical study, MASLD patients were only diagnosed by ultrasound showing steatosis in the MASLD group and without steatosis in "controls" (4). As judged by fibrosis index based on four factors (FIB4) and aspartate transaminase-to-platelet ratio index (APRI) scores—two non-invasive methods that can diagnose advanced fibrosis and cirrhosis—fibrosis was absent or only mild and not different between the two groups. Thus, any conclusions regarding more advanced liver disease severity and aberrations in the VEGF axis in relation to inflammation and fibrosis are not possible.

The transition from simple/mild MASLD to MASH includes activation of inflammatory cells where macrophages seem to be of significant importance not only for inflammation but also fibrosis progression (5,6). Of interest, in the Falkevall *et al.* study (1), inflammation in liver biopsies from mice studies showed a reduction in F4/80 expression as well as reduction in liver inflammation (and ballooning) and fibrosis on histology following anti-VEGF treatment. This may point to inhibition of inflammatory and fibrotic pathways of significance for liver disease progression.

The cross-talk between WAT and the corresponding improvement in MASLD was substantiated by significant effects of anti-VEGF treatment on reductions in WAT lipolysis and improved insulin sensitivity in WAT, and to a lesser extent by inhibition of lipogenic enzymes in the liver. The latter was observed without changes in insulin or glucose levels. In humans, MASLD is associated with increased export of triglyceride in very-low density lipoproteins and unchanged or somewhat increased hepatic fatty acid oxidation, suggesting that its pathogenesis involves increased intrahepatic triglyceride synthesis rather than decreased hepatic triglyceride mobilization (7). Increased availability and hepatic uptake of FFA from the systemic circulation and increased *de novo* synthesis of fatty acids in the liver from simpler precursors are likely key important culprits (8). Hepatic DNL is directly related to circulating glucose and insulin concentrations and to intrahepatic triglyceride accumulation (7,9). VEGF-B antagonism (1) did not significantly alter circulating glucose and insulin concentrations in animal models, and did not affect hepatic fatty acid oxidation and triglyceride secretion, and only mildly downregulated hepatic DNL, reinforcing the primary role of adipose tissue lipolysis in the beneficial effects of VEGF-B antagonism in MASLD.

Of note, WAT inflammation was reduced as determined by reduced messenger RNA (mRNA) expression of key inflammatory markers [tumor necrosis factor (TNF), interleukin (IL)6, IL1b]. Concomitantly, anti-VEGF treatment reduced hepatic expression of fibroblast growth factor 21 (FGF21) and peroxisome proliferator-activated receptor (PPAR)-alpha pathways. These effects may be instrumental for the beneficial hepatic effects of VEGF-B antagonism in MASLD and/or MASH. In fact, pharmacological downregulation of adipocyte lipolysis by acipimox—a nicotinic acid analogue—reduces systemic and intrahepatic fatty acid availability and attenuates HFD-induced histological changes in the livers of experimental animal models of MASLD, without affecting intrahepatic triglyceride content (10). These inflammatory WAT aberrations have also been associated with liver inflammation and fibrosis as determined by the macrophage activation markers soluble CD163 (sCD163) (11). Of interest, sCD163 levels correlated with FFA levels, glycerol rate of appearance (i.e., lipolysis) and WAT insulin resistance, but not with hepatic insulin resistance. This observation further supports a link between WAT metabolic derangements and liver inflammation with macrophage activation and fibrosis, possibly in response to fatty acid overflow from WAT to the liver, and to the extent these excess fatty acids cannot be stored as 'benign' triglycerides but instead are converted to lipotoxic lipid intermediates (e.g., diacylglycerols, short-chain ceramides).

Taken together, there is strong evidence for a pathogenic and clinically relevant cross-talk between metabolic changes

in WAT and the development and progression of MASLD to MASH with fibrosis and subsequent cirrhosis (12). The study by Falkevall *et al.* (1) further supports such links, highlights the potential physiological relevance of the VEGF system, and suggests a therapeutic role for its antagonism.

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