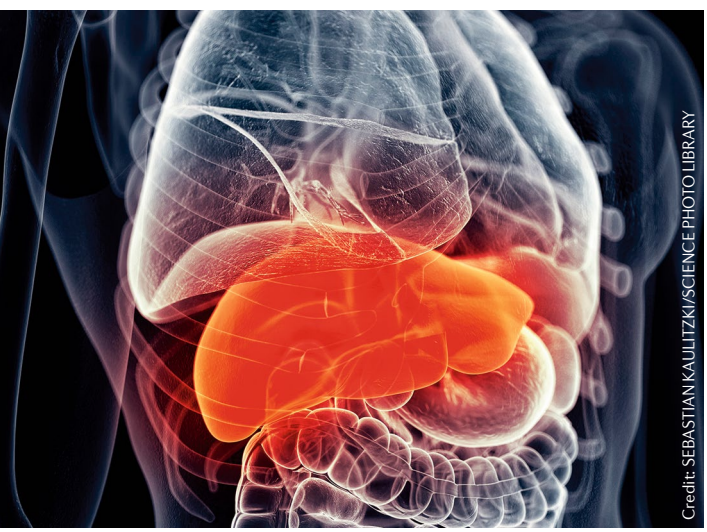
NASH

Novel regulatory pathway in NASH identified

> These pieces of evidence encouraged the team to investigate whether BMP8B was involved…in the progression of NASH

A new study published in *Nature Metabolism* has identified a novel regulatory pathway that contributes to the progression of nonalcoholic steatohepatitis (NASH). Michele Vacca, Antonio Vidal-Puig and colleagues report that bone morphogenetic protein 8B (BMP8B), a poorly characterized member of the BMP–TGFβ superfamily, is a major contributor to NASH progression. The team show that BMP8B controls the level of activation of the two counteracting branches of the BMP–TGFβ pathway, which regulate the progression of liver damage in NASH.

During the past decade, Vidal-Puig's team have had a keen interest in BMP8B. "We previously described its metabolic-associated role in brown and white adipose tissue where, via ALK7 (which is not expressed in the liver), BMP8B mediates the β-adrenergic signalling, thus promoting energy expenditure," explains Vidal-Puig. "At that point, we believed that BMP8B was almost absent in the normal liver and 'healthy' fatty liver." When Vacca, who has a background in liver disease, joined Vidal-Puig's team he found that BMP8B was selectively upregulated in animal models of NASH, especially when they display a severe phenotype. "We went on to confirm this observation in two independent human cohorts," adds Vacca.


Credit: SEBASTIAN KAULITZKI/SCIENCE PHOTO LIBRARY

Next, the team conducted a literature search of relevant omics papers and discovered associations between the polymorphisms or expression of BMP8B with hepatitis C and chronic cholestasis, respectively. "These findings were suggestive of a more general role in liver disease," explains Vacca. "BMP8B was also peculiar in being able to activate the two branches of the BMP–TGFβ pathway that exert opposing roles in NASH and chronic liver disease." These pieces of evidence encouraged the team to investigate whether BMP8B was involved in the transition of nonalcoholic fatty liver disease (NAFLD) to NASH, and in the progression of NASH.

To test this hypothesis, Vacca, Vidal-Puig and colleagues began by investigating the cells that produced and/or sensed BMP8B in humans and murine models of NASH. "We observed that hepatocytes and hepatic stellate cells (HSCs) both synthesize BMP8B, but only HSCs sense it," says Vidal-Puig. "Therefore, we decided to study the autocrine and/or paracrine role of BMP8B on HSCs in vitro using primary cells from wild-type as well as *Bmp8b*-knockout mice."

These experiments indicated that BMP8B modulated the transactivation of HSCs into pro-inflammatory and pro-fibrotic myofibroblasts, which was suggestive of a strong link between BMP8B and hepatic wound-healing response. "We confirmed this connection in vitro and in vivo (via acute carbon tetrachloride model and partial hepatectomy), showing that BMP8B promotes inflammatory and proliferative pathways (and, in some conditions, extracellular matrix remodelling)," adds Vacca.

Next, the team set about validating the relevance of BMP8B in the wound healing mechanism in NASH. This step was of particular importance to their findings because the chronic activation and propagation of the wound-healing response is crucial for NASH progression. "To validate BMP8B's mechanism of action, we took advantage of the 3D NASH micro-tissues developed by CN bio," explains Vacca. "This system is highly reminiscent of human liver and enabled us to model NASH in vitro." The data generated allowed the team to confirm their initial observations in the context of NASH.

The team now intend to investigate BMP8B as a potential target for the management of liver disease in the clinic. "We need to elucidate how BMP8B is regulated to identify the best targeting strategy as BMP8B is expressed in multiple organs and information about its tissue-specific function is still limited," concludes Vidal-Puig. "We also want to study whether BMP8B is relevant for other hepatic diseases, such as viral hepatitis or hepatic cholestasis, and the basis for the sex differences we and others have described as this information could have implications for personalized treatment strategies in NASH."

Alan Morris

ORIGINAL ARTICLE Vacca, M. et al. Bone morphogenetic protein 8B promotes the progression of non-alcoholic steatohepatitis. *Nat. Metab.* **2**, 514–531 (2020)