Clinical relevance of animal models for NASH is crucial for the assessment of in vivo efficacy of compounds in preclinical development. The validity of efficacy assessment in animal models rests on histopathology of not only steatosis, ballooning and inflammation but also fibrosis. However, hepatic fibrosis varies from model to model, despite the adoption of fibrosis staging system for histopathology of not only steatosis, ballooning and inflammation but also fibrosis. However, hepatic fibrosis varies from model to model, despite the adoption of fibrosis staging system for animal models of NASH to evaluate the hepatic fibrosis and the antifibrotic activity of obeticholic acid (OCA), in particular the fibrous septa that are typical in the late stage of NASH-related, and they are the target of antifibrotic activities of NASH compounds with demonstrated clinical efficacies. Such septa could represent the bridging fibrosis as observed the fibrosis staging system for animal models of NASH to evaluate the hepatic fibrosis and the antifibrotic activity of obeticholic acid (OCA), in particular the fibrous septa that are typical in the late stage of NASH-related, and they are the target of antifibrotic activities of NASH compounds with demonstrated clinical efficacies. Such septa could represent the bridging fibrosis as observed the bridging fibrosis as observed the bridging fibrosis as observed the bridging fibrosis as observed the bridging fibrosis as observed the bridging fibrosis as observed the bridging fibrosis as observed the bridging fibrosis as observed the septa identified by the DP-AI system in the HFD+CCL4 model are the target of antifibrotic activities of NASH compounds.

In the mouse NASH model, after animals develop steatosis on feeding of high-fat diet (HFD), they are treated with carbon tetrachloride (CCL4) to induce hepatic fibrosis. Test compounds are administered during the CCL4 induction. The liver histopathology is analyzed for steatosis, ballooning, inflammation and fibrosis by the standard means. For DP-AI analyses, Second-Harmonic Generation (SHG)/Two-Photon Excitation Fluorescent (TPEF) microscopy is used for imaging of unstained liver sections. Collagen fibers (including septa) are identified and quantified by an AI-based algorithm that recognizes the portal tract (PT) and the central vein (CV) and by clustering heat map (top) and principal component (PC) analysis (bottom).

Our results demonstrate that the septa identified by the DP-AI system in the HFD+CCL4 model are NASH-related, and they are the target of antifibrotic activities of NASH compounds with demonstrated clinical efficacies. Such septa could represent the bridging fibrosis as observed the NASH patients. The HFD+CCL4 model is therefore clinically relevant in terms of histopathological presentation and targets of NASH compounds.

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