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Targeting the TGF-β pathway for normalisation of chronic liver diseases

Autor: Julia Antonia Charlotte Werle
Institut / Klinik: II. Medizinische Klinik
Doktorvater: Prof. Dr. S. Dooley

The concept of reversing chronic liver disease (CLD) has been intensively studied over the past decade. As the prevalence of end-stage liver disease is constantly on the rise, the lack of established anti-fibrotic therapies is a considerable unmet need in clinical practice. TGF-β has been identified as a master regulator of liver fibrogenesis. It promotes ECM deposition and is responsible for an invasive and aggressive phenotype of HCC. Galunisertib, a small molecule inhibitor of the TGF-β1 pathway, exerts, in contrast to many other small molecule inhibitors of the TGF-β pathway, good safety and tolerability with no cardiac or hemorrhagic side effects. Thus, it is used in preclinical and clinical studies, e.g., in HCC patients in combination with Sorafenib. The applied animal model, *Abcb4Ko* mouse, is a well-established model for CLD. Deletion of the *Abcb4* (Mdr2) gene leads to the loss of the canalicular phospholipid transporter MDR2 expression, an ATP-binding cassette transporter. Therefore, *Abcb4Ko* mice develop spontaneously progressive biliary liver fibrosis, cirrhosis and eventually HCC.
Herein, data sets are provided for disease stage-related morphological signatures in the *Abcb4Ko* mice over time. Portal invasion of immune cells and only little ductular injury and fibrosis are shown in the young animals expanding into portal damage and septal bridging of the fibrosis. In the late stages, the inflammation and fibrosis lead to obliteration of bile ducts and therewith cholestasis. This strengthens the development of fibrosis in turn. Typical histopathological features of this development are found, e.g., onion-skin-fibrotic bands, in the first experiment.
In the second experiment, the impact of Galunisertib on the pheno- and genotype of 6 month old *Abcb4Ko* mice with fibrosis of at least stage F1 is demostrated. It is proven that Galunisertib intervenes the TGF-β pathway by downregulation of Smad2 phosphorylation. This leads to deregulation of TGF-β target genes and results in less collagen transcription and therewith ameliorates the fibrosis of *Abcb4Ko* mice. Due to the treatment with the TGF-β inhibitor, reorganization of ECM components is found, which impedes the building of an HCC favourable microenvironment. Galunisertib induces bile duct reaction, one of the main features of *Abcb4Ko* mice. There is no remarkable influence on the inflammatory phenotype under treatment. The data give reasonable hope for the use of Galunisertib in patients with liver fibrosis, not only to strengthen fibrosis regression but to prevent disease progression into HCC.