Targeting TGF-β2 in chronic liver diseases

Anne Dropmann1, Hanna Korhonen1, Frank Jaschinski2, Michel Janicot2, Nadja Meindl-Beinker1, Steven Dooley1

Department of Medicine II, Section Molecular Hepatology, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; 2 Isarna Therapeutics GmbH, Munich, Germany

Background and aims:
Expression and function of TGF-β2 have not been investigated thoroughly in chronic liver disease (CLD) progression and HCC. Upon providing further evidence that TGF-β2, like TGF-β1, plays a putative role in fibrogenesis, we now aim to selectively target TGF-β2 expression or both, TGF-β2 and TGF-β1 together using antisense oligonucleotides (AONs) for attenuation or even blockage of human liver disease progression.

Methods
For our study three CLD mouse models (CCl4, BDL & Mdr2-/-) were investigated representing different types of CLD background. TGF-β2 expression was compared to TGF-β1 expression by quantitative realtime (qRT)-PCR. In vivo, we selectively inhibited TGF-β2 using AONs. In detail, for induction of chronic liver damage, 12 weeks old mice were injected intraperitoneally (i.p.) with 0.2 ml/kg BW CCl4 twice per week for four weeks. After 2 weeks, subcutaneous AON application started parallelly with a dosage of 30 mg/Kg twice per week. In the MDR2-KO mouse model the AON was administered for 4 weeks. The effect and efficacy of AON treatment was evaluated on protein and mRNA level. Typical fibrotic markers are currently investigated using qRT-PCR.

Conclusion
Taken together, our results indeed suggest a role of TGF-β2 in the process of CLD. We further conclude that in vivo application of TGF-β2 directed AON to CLD mouse models attenuates fibrogenesis. Further studies are currently performed to determine mechanistic details of AON effects and define specifications of a potential AON based treatment of CLD, e.g. dosage and stage of disease, when application is feasible.