Targeting TGF-β2 in chronic liver diseases

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BACKGROUND

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

MATERIALS & METHODS

Three CLD mouse models (CCL4, BDL & MDR2-KO) were investigated representing different types of CLD background. Dynamics of TGF-β2 and TGF-β1 expression were compared in these models by quantitative realtime (qRT)-PCR. In vivo, we selectively inhibited TGF-β2 using specific 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 in parallel 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 by tissue morphology and on protein and mRNA level. Typical fibrotic markers are currently investigated using qRT-PCR.

RESULTS

TGF-β2 selective AON treatment of MDR2-KO mice reduces liver damage

CONCLUSIONS

Taken together, our results suggest a role of TGF-β2 in the process of CLD. We further conclude that in vivo application of a TGF-β2 directed AON to CLD mouse models could contribute to fibrogenesis attenuation. 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.