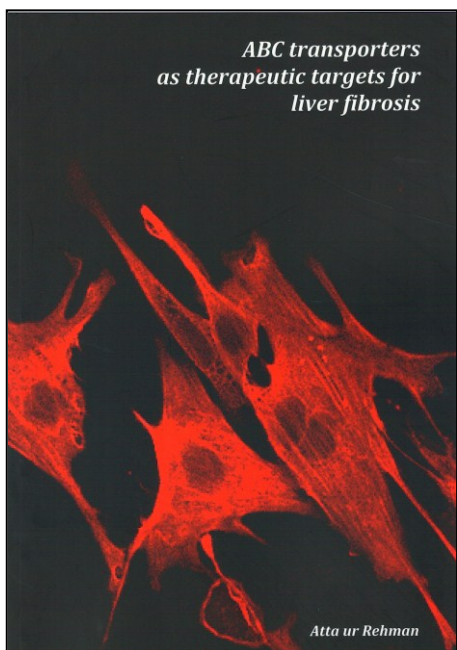




Nederlandse
Vereniging voor
Hepatology



Samenvatting proefschrift Atta ur Rehman

'ABC transporters as therapeutic targets for liver fibrosis'

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Liver fibrosis is the excessive healing response to chronic liver injury characterized by the loss of hepatocytes and expansion of fibroblasts that produce excessive extracellular matrix and may progress to cirrhosis and liver failure. There is no drug treatment for liver fibrosis/cirrhosis yet and liver transplantation is the only lifesaving treatment. Due to scarcity of liver donors, the development of antifibrotic drug therapy is of high importance.

Hepatic stellate cells (HSC) and portal myofibroblasts (PMF) are the main players in fibrosis and therefore potential targets for development of antifibrotic drugs. ABC transporters are substrate transporters for both endogenous (lipids, bile acids, leukotrienes) and exogenous (drugs) compounds. In this thesis, we studied the role of Mrp1 (ABCC1) and PMP70 (ABCD3) in HSC and PMF in vitro and in vivo.

We show that inhibition of Mrp1, the transporter of leukotriene C4, prevents the activation of HSC and its absence in mice attenuates liver fibrosis in mice. We show that Reversan is a selective inhibitor of Mrp1 and does not cause toxicity in hepatocytes and, thus, may be a potential drug to treat liver fibrosis. Moreover, we show that the antioxidant compound glutathione (also transported by Mrp1) and antioxidant enzymes, including glutathione peroxidase and catalase, have complementary roles in protecting HSC against oxidative stress.

Finally, we found that the peroxisomal membrane protein (PMP70) is required for the generation of the typical cytoskeleton in HSC and PMF made of alpha-smooth muscle actin. PMP70 shows a non-typical localization in HSC/PMF, residing in tubular structures instead of peroxisomes. These PMP70-containing tubules lay parallel to the α -SMA fibers, indicating a functional relationship between the two.

In conclusion, Mrp1 and Pmp70 promote liver fibrosis and are therefore potential drug targets for the treatment of liver fibrosis. ◀

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