1 Abstract

Liver fibrosis is a condition described by extensive accumulation of scar tissue in the liver. With further progression, it leads to cirrhosis or even to hepatocellular carcinoma. Liver fibrosis accompanies every chronic liver disease and its prevalence in adult European population is estimated to be around 4%. During my dissertation work, I studied the function of three members of Metzincin family of metalloproteinases - ADAM17, ADAM10 and MMP-19, in liver fibrosis and liver regeneration using mouse genetic models. ADAM17 and ADAM10 are important regulators of signalling pathways which are involved in immune response as well as differentiation. Both proteases are able to cleave ectodomains of their substrates from cell membrane, affecting bioavailability of ligands and functionality of receptors. Several of their substrates are involved in liver pathologies. MMP-19 on the other hand, is a metalloprotease mainly involved in extracellular matrix cleavage, important process in fibrosis development, as well as resolution of fibrosis.

Our results demonstrate that ablation of ADAM10 results in increased susceptibility to liver fibrosis in mice, both spontaneous and toxin induced. ADAM10 deficiency affected biliary epithelium, as we detected higher markers of biliary damage in serum of ADAM10 deficient mice. On the other hand, ADAM17 inhibition had protective effect in conditions involving biliary epithelial damage. ADAM17 deficiency did not influence development of fibrosis after CCl_4 intoxication, but it reverted exacerbating effect of ADAM10 deficiency on liver fibrosis. Interestingly, we showed that both studied ADAMs influenced levels of soluble TNF RI in serum, although in different manner. While ablation of ADAM17 inhibits cleavage of TNF RI into serum, deletion of ADAM10 leads to increased TNF RI release. Moreover, we show that ADAM17 and ADAM10 are involved in shedding of EGFR ligands and cMet receptor in partial hepatectomy, the model of liver regeneration. As a consequence, mice with combined deficiency of both proteases exhibited reduced EGFR signalling, but increased HGF/cMet signalling. Studies of MMP-19 whole body deficient mice revealed that ablation of MMP-19 is protective in CCl_4-induced fibrosis. Ablation of MMP-19 caused slower degradation of healthy extracellular matrix and reduced responsiveness to profibrotic TGF-β.

In conclusion, this work extends the knowledge of ADAM10/17-dependent release of EGFR ligands, cMet and TNF RI from liver cells in pathological states *in vivo.* Furthermore, we

described involvement of MMP-19 in liver fibrosis development. Our results demonstrate that inhibition of MMP-19 could be considered as potential treatment of liver fibrosis.