# Protease-activated receptor 4 is substantially involved in the progression of MAFLD to steatohepatitis and fibrosis as well as tumor-development


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## Abstract

Introduction The development of metabolically induced fatty liver disease (MAFLD) is now one of the most common causes of chronic liver disease and subsequently the development of liver fibrosis and cirrhosis and hepatocellular carcinoma (HCC). In this context, the molecular mechanisms underlying the progression of MAFLD/NAFLD to chronic inflammatory liver disease and the development of HCC are poorly understood.

Objectives: The aim of the present study was to investigate the role of protease-activated receptor 4, which is mainly expressed on platelets, in the development of MAFLD/NAFLD.

Methods Feeding series of wt and PAR4-/- mice on high-calorie western diet (WD) or standard diet for up to 50 weeks. Time-resolved analysis of histological changes, damage parameters in liver tissue and serum, and bile acids profiling and expression of transport proteins using among others rtPCR and HPLC-MS/MS.

Results The increase in AST, ALT, and LDH observed when fed a high-calorie diet was significantly reduced in PAR4-/- animals compared to control animals. This observation was associated with a decrease in fibrosis in the liver tissue. At the same time, the development of tumors observed from the 40th week of feeding with WD was significantly reduced in PAR4-/- animals. Depending on the time course, this was accompanied by a decreased increase in the expression of glycoprotein nonmetastic melanoma B (Gpnmb) in PAR4-/- animals compared with control animals, as well as a decrease in expression of the protein high-mobility group box 1 (Hmbg1) and serum levels of bile acids, particularly the taurine conjugates omega-muricholic acid and its derivative taurohyodeoxycholic acid. In addition, a significant reduction in the expression of multidrug resistance protein 4 (Mrp4/Abcc4) and organic anion transporting protein 1a4 (Oatp1a4/Slco1a4) at the transcriptional level was observed in PAR4-/- animals after 40 and 50 weeks of Western diet.

Conclusion: PAR4 plays an important role in the progression of MAFLD induced by a high-calorie diet to steatohepatitis, and in the development of fibrosis and cancer as a result of this diet.