**Hyaluronan-TLR4 pathway regulation of NASH and cancer**

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The progression of chronic liver disease is characterized by liver injury, inflammation, and fibrosis, which ultimately cause cancer. Toll-like receptor 4 (TLR4), a pattern-recognition receptor, stimulates innate immune signaling through adaptor proteins myeloid differentiation factor 88 (MyD88) and TIR-domain containing adaptor-inducing interferon- (TRIF). MyD88 and TRIF pathways have distinct roles in the development of nonalcoholic steatohepatitis (NASH). The TLR4-MyD88 pathway promotes liver steatosis, inflammation, and fibrosis in NASH, whereas TLR4-TRIF pathway inhibits inflammation and NASH-mediated fibrosis. We utilized a mouse model of hepatocyte-specific TAK1 knockout (*Tak1Hep*), which recapitulates human HCC progression. Deletion of either TLR4 or MyD88 inhibits the liver inflammation-fibrosis-cancer axis. Hyaluronan (HA), an extracellular matrix component, is another TLR4 ligand. TLR4 regulates HA-induced hepatic stellate cell profibrogenic phenotypic change. This contributes to NASH-mediated liver fibrosis as well as metastatic niche formation in NAFLD. Taken together, our results reveal the role of TLR4 and their downstream molecules in NASH, fibrosis, and cancer. Better understanding of TLR4 signaling will provide new insight into the management and prevention of chronic liver diseases.