Capsaicin receptor TRPV1 maintains quiescence of hepatic stellate cells in the liver via recruitment of SARM1

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Abstract

Background & aims: Capsaicin receptor, also known as transient receptor potential vanilloid 1 (TRPV1), is involved in pain physiology and neurogenic inflammation. Herein, we discovered the presence of TRPV1 in hepatic stellate cells (HSCs) and aimed to delineate its function in this cell type and liver fibrosis.

Methods: TRPV1 expression was examined in liver biopsies from patients with liver fibrosis using quantitative real-time PCR and immunostaining. Its contribution to liver fibrosis was examined in Trpv1-/- mice, upon lentiviral delivery of the TRPV1 gene, and in human and mouse primary HSCs, using patch clamp, intracellular Ca2+ mobilization determination, FACS analyses and gain/loss of function experiments. Binding of sterile alpha and Toll/interleukin-1 receptor motif-containing protein 1 (SARM1) to TRPV1 was determined using mass spectrometry, co-immunoprecipitation, surface plasmon resonance, bioluminescence resonance energy transfer, and NanoBiT.

Results: TRPV1 mRNA levels are significantly downregulated in patients with liver fibrosis and mouse models, showing a negative correlation with F stage and α-smooth muscle actin expression, a marker of HSC activation. TRPV1 expression and function decrease during HSC activation in fibrotic livers in vivo or during culture. Genetic and pharmacological inhibition of TRPV1 in quiescent HSCs leads to NF-κB activation and pro-inflammatory cytokine production. TRPV1 requires binding of its N-terminal ankyrin repeat domain to the TIR-His583 (Toll/interleukin-1 receptor) domain of SARM1 to prevent HSCs from pro-inflammatory activation. Trpv1-/- mice display increased HSC activation and more severe liver fibrosis, whereas TRPV1 overexpression is antifibrotic in various disease models.

Conclusion: The antifibrotic properties of TRPV1 are attributed to the prevention of HSC activation via the recruitment of SARM1, which could be an attractive therapeutic strategy against liver fibrosis.

Impact and implications: We identified the neuronal channel protein TRPV1 as a gatekeeper of quiescence in hepatic stellate cells, a key driver of liver fibrogenesis and chronic liver disease. Physiologically expressed in healthy liver and consistently downregulated during liver fibrosis development, its therapeutic re-expression is expected to have few side effects, making it an attractive target diagnostic tool and drug candidate for industry and clinicians.

Keywords: HSC; SARM1; TRPV1; liver fibrosis.