Participation of miR-200a in TGF-β1-mediated hepatic stellate cell activation

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Abstract  Hepatic stellate cell (HSC) activation is a pivotal event in the initiation and progression of hepatic fibrosis since it mediates transforming growth factor beta 1 (TGF-β1)-driven extracellular matrix (ECM) deposition. MicroRNAs (miRNAs), small non-coding RNAs modulating messenger RNA (mRNA) and protein expression, have emerged as key factors to regulate cell proliferation, differentiation, and apoptosis. Although the function of miR-200a has been discussed in many cancers and fibrotic diseases, its role in hepatic fibrosis is still poorly understood. The aim of this study is to investigate whether miR-200a could attenuate hepatic fibrosis partly through Wnt/β-catenin and TGF-β-dependant mechanisms. Our study found that the expression of endogenous miR-200a was decreased in vitro in TGF-β1-induced HSC activation as well as in vivo in CCl4-induced rat liver fibrosis. Overexpression of miR-200a significantly inhibited α-SMA activity and further affected the proliferation of TGF-β1-dependent activation of HSC. In addition, we identified β-catenin and TGF-β2 as two functional downstream targets for miR-200a. Interestingly, miR-200a specifically suppressed β-catenin in the protein level, whereas miR-200a-mediated suppression of TGF-β2 was shown on both mRNA and protein levels. Our results revealed the critical regulatory role of miR-200a in HSC activation and implied miR-200a as a potential candidate for therapy by deregulation of Wnt/β-catenin and TGFβ signaling pathways, at least in part, via decreasing the expression of β-catenin and TGF-β2.

Keywords  miR-200a · Hepatic stellate cells · TGF-β · α-SMA · β-Catenin

Abbreviations
HSC  Hepatic stellate cell
ECM  Extracellular matrix
α-SMA  α-Smooth muscle actin
TGF-β  Transforming growth factor-β
β-catenin  Cadherin-associated protein beta
3′-UTR  3′-Untranslated region
PBS  Phosphate-buffered saline
SDS  Sodium dodecyl sulfate
Wt  Wild type
ZEB  Zinc-finger E-box-binding homeobox
One-step qRT-PCR  One-step quantitative real-time PCR

Introduction
Liver fibrogenesis represents the common responses of the liver to toxic, infectious, or metabolic agents and is characterized by excessive accumulation of extracellular matrix (ECM). Hepatic stellate cells (HSCs), the major mesenchymal cells in the liver, are well known for their critical functions in liver fibrosis [1, 2]. Activated HSC is the principal cell type promoting synthesis and deposition of ECM proteins in response to increased levels of circulating inflammatory signals derived from damaged parenchymal cells. The HSCs are found within the perisinusoidal space of Disse in a quiescent state, but upon hepatic injury, they...