Ultrasound-microbubble-mediated gene transfer of inducible Smad7 blocks transforming growth factor-beta signaling and fibrosis in rat remnant kidney

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摘要

Abstract

Transforming growth factor (TGF)-β1 has been shown to play a critical role in hypertensive nephropathy. We hypothesized that blocking TGF-β1 signaling could attenuate renal fibrosis in a rat model of remnant kidney disease. Groups of six rats were subjected to 5/6 nephrectomy and received renal arterial injection of a doxycycline-regulated Smad7 gene or control empty vector using an ultrasound-microbubble-mediated system. Smad7 transgene expression within the kidney was tightly controlled by the addition of doxycycline in the daily drinking water. All animals were euthanized at week 4 for renal functional and histological examination. Hypertension of equivalent magnitude (190 to 200 mmHg) developed in both Smad7- and empty vector-treated rats. However, treatment with Smad7 substantially inhibited Smad2/3 activation and prevented progressive renal injury by inhibiting the rise of 24-hour proteinuria ($P < 0.001$) and serum creatinine ($P < 0.001$), preserving creatinine clearance ($P < 0.05$), and attenuating renal fibrosis and vascular sclerosis such as collagen I and III expression ($P < 0.01$) and myofibroblast accumulation ($P < 0.001$). In conclusion, TGF-β/Smad signaling plays a critical role in renal fibrosis in a rat remnant kidney model. The ability of Smad7 to block Smad2/3 activation and attenuate renal and vascular sclerosis demonstrates that ultrasound-mediated Smad7 gene therapy may be a useful therapeutic strategy for the prevention of renal fibrosis in association with hypertension.

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