Inhibitory role of Nfe2l2 (Nrf2) in Tgf-beta1-Smad signaling through Smad7 elevation in mouse mesangial MES-13 cell

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Renal fibrosis is one of the principal processes underlying the progression of kidney diseases. Accumulating evidence indicates that oxidative stress plays a critical role in renal fibrotic diseases. Transforming growth factor-beta1 (Tgf-beta1) is well known as a central mediator in pro-fibrotic responses. Among them, Smad-dependent signaling is recognized as a major pathway of Tgf-beta1 signaling by expressing fibrosis markers such as extracellular matrix (ECM) and alpha-smooth muscle actin (Alpha-SMA) in progressive renal fibrosis. For these reasons, we investigated the potential involvement of nuclear factor (erythroid-derived 2)-like 2 (Nfe2l2; Nrf2) in renal fibrosis with Tgf-beta1-Smad signaling. Previously, we reported that Smad7, a negative regulator of Smad signaling, might be a molecular linking between the Nrf2 pathway and Tgf-beta1 signaling in human renal tubular epithelial HK2 cell. In this study, we confirmed that elevated protein level of Smad7 attenuates Tgf-beta1 signaling in Kelch-like ECH-associated protein 1 (Keap1) knockdown mouse mesangial MES-13 cell which is a cellular model of Nrf2 overexpression. As one of potentials underlying molecular mechanisms of Smad7 regulation by Nrf2, reduced level of Smad-ubiquitination-regulatory factor 1 (Smurf1), an E3 ubiquitin ligase for Smad7, was notable. Also, we showed that a Nrf2 inducer bardoxolone methyl ester (BARD) also elevated Smad7 level and attenuated Tgf-beta1 signaling in MES-13. Collectively, these results indicate that Nrf2 might be an effective inhibitor of Smad-dependent Tgf-beta1 signaling, and imply the anti-fibrotic role of Nrf2 in renal diseases.