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Effects of anti-fibrotic by RON receptor tyrosine kinase supression

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Objectives : Receptor tyrosine kinases play important roles in the pathogenic processes of renal fibrosis. However, the pathophysiological roles of recepteur d'origine nantais (RON), one of the receptor tyrosine kinase in kidney disease have not yet been identified. This study examined investigated whether the abnormal accumulation and activation of the RON and sequence-specific small interfering RNA (siRNA) suppression of the RON expression could regulate renal fibrosis, and investigated the involved molecular mechanisms.

Methods : Stable cell lines for RON overexpression and the transfected cells of siRNA for RON inhibition were developed for understand the renal fibrosis and molecular mechanisms by RON in human renal proximal tubular epithelial (HK-2) cells. The protein expression of epithelial-mesenchymal transition (EMT)-related proteins N-cadherin, E-cadherin, vimentin and fibrosis-related proteins TGF-β, α-smooth muscle actin (αSMA), fibronectin as well as Smad family and MAPK signal pathway was determined by semiquantitative immunoblotting. Staining of receptor tyrosine kinase family was evaluated using confocal laser microscopy.

Results : RON overexpression increased protein expression of EMT- and fibrosis-related proteins such as N-cadherin, E-cadherin, vimentin, TGF-β, αSMA, and fibronectin in HK-2 cells. Moreover, overexpression of RON increased phophorylation of Smad2/3 and smad-4, and Erk1/2, p38, and Jnk MAPK pathways. In contrast, RON inhibition by siRNA attenuated expression of EMT- and fibrosis-related proteins and decreased phosphorylation of Smad family and MAPK pathway. In addition, the siRNA silencing of RON attenuated expression of IGFR, VEGFR, and PDGFR.

Conclusions : Inhibition of RON may exert anti-fibrotic effect by suppression of EMT by controlling Smad and MAPK signal pathways in HK-2 cells.

Keywords : anti-fibrotic, RON, Receptor tyrosine kinases, Smad, MAPK