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Rosuvastatin inhibits tubulointerstitial fibrosis via activating HOX13-BMP-7 pathway

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Objectives: Statins may exert anti-fibrotic effects to protect diseased kidney. This study evaluated anti-fibrotic effects of rosuvastatin(RSV) in chronic kidney fibrosis model and TGF-ß1 stimulated Madin-Darby canine kidney(MDCK) cells.

Methods: Mice subjected to unilateral ischemic reperfusion injury with contralateral nephrectomy(uIRIx) were treated with vehicle or RSV (10mg/kg, by oral gavage) daily for 4 weeks and kidneys were analyzed for fibrotic markers, bone morphogenetic protein-7(BMP-7), uterine sensitization-associated gene-1(USAG-1), and SMAD signaling. Control and homeobox protein Hox-A13(HOXA13) knocked down MDCK cells were stimulated with TGF- ß1(5 ng/ml) and then treated with RSV.

Results: Kidneys from uIRIx mice showed increased expression of α-SMA and Collagen 1, without changes in BMP-7(20.35±2.37 vs 1.00±0.27, $P<0.05$; 8.43±1.55 vs 1.00±0.35, $P<0.05$; 0.63±0.34 vs 1.00±0.38, $P=0.66$, respectively). In contrast, expression of USAG-1, most dominant BMP-7 antagonist in kidney, was markedly increased in fibrotic kidney (5.22±0.29 vs 1.00±0.33, $P<0.05$). RSV not only attenuated expression of USAG-1(1.33±0.77 vs 5.22±0.29, $P<0.05$) but also showed a tendency to activate expression of HOXA13(0.36±0.14 vs 0.51±0.15, $P>0.05$), and improved other markers of fibrosis. Moreover, RSV significantly reduced phosphorylated Smad3(p-Smad3, 3.94±0.81 vs 7.17±1.50, $P<0.05$) and increased phosphorylation levels of Smad1/5/9(p-Smad1/5/9, 0.67±0.10 vs 0.30±0.09, $P<0.05$). MDCK cells stimulated with TGF-β1 showed increased expression of fibrotic markers, USAG-1, and p-Smad3 as well as decreased expression of p-Smad1/5/9. RSV treatment reversed these changes as well as increased level of HOXA13(0.89±0.12 vs 0.33±0.08, $P<0.05$), which negatively regulates USAG-1, without changes in BMP-7 expression. In addition, effect of RSV on USAG-1 expression was significantly decreased in HOXA13 gene knocked down MDCK cells (1.01±0.19 vs 2.04±0.38, $P<0.05$; 1.66±0.13 vs 2.04±0.38, $P>0.05$; TGF-ß1+RSV vs TGF-ß1 and TGF-ß1+RSV+siRNA vs TGF-ß1, respectively).

Conclusions: Our results demonstrate that RSV inhibits kidney fibrosis in part by upregulating BMP-7-mediated signaling via HOXA13 expression and down regulation of USAG-1.