Abstract Type : Poster exhibition
Abstract Submission No.: A-0412
Abstract Topic : Basic Research

Preventing Kidney Tubulointerstitial Fibrosis: Effect of Atorvastatin on the HOXA13-USAG-1-BMP7 Pathway

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Objectives : Statins have been suggested to exert antifibrotic effects in kidney disease, but their preventive potential remains unclear. Therefore, we aimed to investigate whether statin pretreatment can attenuate kidney fibrosis in a bilateral ischemia-reperfusion injury (bIRIx) model.
Methods : Mice were pretreated with atorvastatin (10 mg/kg/day) or vehicle for three days before bIRIx, and kidneys were collected three days later for fibrosis marker analysis. To investigate underlying mechanisms, MDCK cells were transfected with HOXA13-specific siRNA, treated with atorvastatin, and stimulated with TGF-β1 (5 ng/mL), followed by assessment of fibrosis markers.
Results : Mice subjected to bIRIx developed significant severe tubulointerstitial fibrosis, as evidenced by elevated expression of TGF-β1 (2.5 ± 0.2 vs. control, $p<0.001$), collagen (2.8 ± 0.2 vs. control, $p<0.001$), and monocyte chemoattractant protein-1 (MCP-1; 3.3 ± 0.1 vs. control, $p<0.001$), along with marked collagen deposition, α-smooth muscle actin (α-SMA) expression, and F4/80-positive macrophage infiltration. Atorvastatin pretreatment significantly attenuated kidney fibrosis and inflammation, reducing TGF-β1 (2.5 ± 0.2 vs.1.7 ± 0.1, $p<0.01$), collagen (2.8 ± 0.2 vs. 1.8 ± 0.1, $p<0.001$), MCP-1 (3.3 ± 0.1 vs. 2.0 ± 0.1, $p<0.001$) compared to bIRIx alone. In vitro, atorvastatin attenuated TGF-β1-induced upregulation of collagen (2.9 ± 0.2 vs. 6.8 ± 0.3, $p<0.001$), α-SMA (2.3 ± 0.2 vs. 5.0 ± 0.3, $p<0.001$), and USAG-1 (3.4 ± 0.4 vs. 7.4 ± 0.4, $p<0.001$). Importantly, HOXA13 knockdown abolished the inhibitory effect of atorvastatin on USAG-1 (3.4 ± 0.4 vs.5.6 ± 0.2, $p<0.001$) and reversed its antifibrotic effects on collagen (2.9 ± 0.2 vs. 4.9 ± 0.1, $p<0.001$) and α-SMA (2.3 ± 0.2 vs. 3.8 ± 0.1, $p<0.001$), suggesting a critical role for HOXA13 in mediating these responses.
Conclusions : Our results suggest that atorvastatin pretreatment prevents kidney fibrosis, partly by regulating HOXA13, USAG-1, and BMP-7. These findings indicate statins may have therapeutic potential to prevent kidney fibrosis by modulating profibrotic pathways.