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CKD & associated complications

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Rosuvastatin attenuates tubulointerstitial fibrosis in a model of ischemic acute kidney injury induced chronic kidney disease

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Background: Tubulointerstitial fibrosis plays an important role in progressive chronic kidney disease (CKD). Lysyl oxidase like-2 (LOXL2), a member of the lysyl oxidase (LOX) family, promotes crosslinking of collagen and elastin that has been implicated in liver and lung fibrosis. Statin's pleiotropic actions include anti-fibrotic effects in the diseased kidneys. Aim of the study was to investigate the effect of rosuvastatin on renal LOXL2 activity and tubulointerstitial fibrosis in a model of CKD induced by ischemic acute kidney injury (AKI) followed by contralateral nephrectomy.

Methods: Male FVB mice were subjected to 42 minutes of unilateral ischemic AKI and after 2 weeks mice underwent contralateral nephrectomy to induce a murine model of CKD. Animals were divided into 2 groups: vehicle (methylcelluose) or rosuvastatin (10mg/kg/day) by gavage. At sacrifice kidneys were harvested for morphology, mRNA, and protein analysis. Real time PCR was done to assess renal expression of TGF-beta1, LOXL2, and collagen I. Renal tissue was stained for aSMA, F4/80 and tubulointerstitial fibrosis was assessed by Sirius red stain.

Results: Our murine CKD model is characterized by increased BUN (47.8 ± 4.7 vs. normal 24.3 ± 3.6 mg/dL, $p<0.01$) and renal anemia (hemoglobin level: 11.0 ± 1.0 g/dL vs. normal 13.2 ± 0.4 g/dL, $p<0.01$) and overt proteinuria compared to age-matched control mice. F4/80-positive inflammatory cell (macrophage) infiltration in the renal interstitium was significantly reduced by rosuvastatin treatment (2.8 ± 1.2/HFP vs. 39.8 ± 8.3 /HPF, $p<0.01$). The mRNA expression of TGF beta1, LOXL2 and collagen 1 was increased in murine CKD kidney; rosuvastatin treatment significantly decreased TGF beta1 (2.91 ± 1.33 vs. 1.54 ± 0.42, $p<0.03$) and LOXL2 expression (2.85 ± 0.70 vs. 1.29 ± 0.24, $p<0.02$) as well as collagen I mRNA expression (7.72 ± 3.46 vs. 3.61 ± 1.21, $p<0.03$). Furthermore tubulointerstitial fibrosis assessed by Sirius red stain was significantly attenuated with ROS treatment (7.75 ± 3.16 % vs. 2.08 ± 0.49%, $p<0.03$).

Conclusion: In conclusion, rosuvastatin treatment demonstrated evident anti-fibrotic effect via significant down regulation of renal LOXL2 expression.

Keywords: Ischemia-reperfusion injury, lysyl oxidase-like 2, rosuvastatin, tubulointerstitial fibrosis