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Expression of Lysyl Oxidase Related Protein and Effect of Lysyl Oxidase Inhibition in Cyclosporine Induced Nephropathy Mouse Model

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Background and Aims: Lysyl oxidase-like 2 (LOXL2), an amine oxidase, contributes to fibrotic scarring in the tissue by facilitating collagen cross-linking. Recent data demonstrated upregulation of lysyl oxidase and LOXL2 in the fibrotic kidneys after administration of cyclosporine A (CsA). Thus, inhibition of LOXL2 may render therapeutic effects against CsA-induced nephropathy by ameliorating tubulointerstitial fibrosis. Method: Low salt fed CD-1 mice were administered olive oil or CsA (15 mg/kg/day, intraperitoneally) for 8 weeks. At 4 weeks, CsA-treated animals were divided into 2 groups respectively and treated with: (1) vehicle, (2) LOXL2 inhibitor (10 mg/kg/day, gavage feeding) for another 4 weeks up to 8 weeks. We explored the reduction of tubulointerstitial fibrosis as well as albuminuria with administration of LOXL2 inhibitor in CsA nephropathy mouse model. Results: CsA administration significantly increased the levels of serum creatinine (9.0 ± 2.0 vs. 25.7 ± 9.2 $\mu\text{mol/L}$, $p=0.038$), tubulointerstitial fibrosis (Sirius red, 207.3 ± 49.8 vs. 2082.0 ± 453.2 positive pixels per mm^2 , $p<0.001$), F4/80 positive inflammatory cell infiltration in mouse kidney (1.8 ± 0.8 vs. 3.3 ± 2.0 positive cells/field, $p<0.001$). These changes were associated with upregulated mRNA expression of LOXL2, TGF- β 1, and monocyte chemoattractant protein-1 (MCP-1). Administration of LOXL2 inhibitor significantly suppressed the expression of alpha-SMA and collagen 1A, and intrarenal F4/80 positive inflammatory cell infiltrations (19.8 ± 5.5 vs. 13.8 ± 1.7 positive cells/field, $p=0.029$). Moreover, LOXL2 inhibitor effectively reduced albuminuria excretion (44.6 ± 3.3 vs. 27.4 ± 4.3 $\mu\text{g/mg}$, $p=0.007$). Conclusion: Our results suggest that LOXL2 inhibitor treatment can attenuate CsA nephropathy progression and LOXL2 inhibitor may be a potential therapeutic target in CsA nephropathy.



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