Murine Recombinant ACE2 Reduces Renal Fibrosis in Experimental Alport Syndrome (AS)

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ACE2 is a monocarboxypeptidase in the renin angiotensin system that catalyzes the breakdown of angiotensin II (AngII) to angiotensin-(1-7) (Ang1-7). We have reported that ACE2 expression and activity in kidney are reduced in experimental Alport Syndrom (AS) but the impact of this finding on disease progression has not been studied. Accordingly, we evaluated the effects of murine recombinant ACE2 (mrACE2) treatment in *Col4A3*$^{-/-}$ mice, a model of AS characterized by proteinuria and progressive renal injury. mrACE2 (0.5 mg/kg/day) was administered from 4 -7 weeks of age via osmotic mini-pump. Treatment with mrACE2 led to an increased urinary ACE2 excretion, reduced renal AngII level and a correspondingly increased Ang1-7 level in 7-week-old *Col4A3*$^{-/-}$ mice. Pathological structural changes and albuminuria in the mutant mice were both attenuated by mrACE2 administration. mrACE2 ameliorated kidney fibrosis in *Col4A3*$^{-/-}$ mice as shown by decreased expression of profibrotic genes, less accumulation of extracellular matrix proteins and inhibition of the TGF-β signaling activation. Further, the increases in proinflammatory cytokine expression, macrophage infiltration, inflammatory signaling pathway activation and heme oxygenase-1 (HO-1) level in *Col4A3*$^{-/-}$ mice were also reduced by mrACE2 treatment. Lastly, mrACE2

influenced the turnover of renal ACE2, as it suppressed the expression of TNF-α converting enzyme (TACE), a negative regulator of ACE2. In summary, treatment with mrACE2 alters angiotensin peptide metabolism in the kidneys of *Col4A3*$^{-/-}$ mice and attenuates the progression of AS nephropathy.

Key words: Alport syndrome, renin-angiotensin system, renal fibrosis, ACE2, TACE