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Murine Recombinant ACE2 Attenuates Kidney Injury in Experimental Alport's Syndrome

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Background: ACE2 is a monocarboxypeptidase in the renin angiotensin system that catalyzes the breakdown of Angiotensin II (AngII) to Ang1-7. We have reported that ACE2 expression and activity in the kidney are reduced in experimental AS but the impact of this finding on kidney disease progression has not been studied.
Methods: we evaluated the effects of treatment with murine recombinant ACE2 (mrACE2) in Col4A3-/- mice, a model of AS characterized by proteinuria and progressive renal injury. mrACE2 was administered from 4-7 weeks of age via osmotic mini-pump.
Results: Treatment with mrACE2 led to an increase in both kidney renal ACE2 expression and the urinary ACE2 excretion rate in 7-week-old Col4A3-/- mice compared to untreated group. Kidney AngII levels declined and kidney Ang1-7 levels increased. These effects were associated with a significant decrease in proteinuria in the treated 7-week-old Col4A3-/- mice compared to the untreated group. Ang II infusion induced Tumor necrosis factor α (TNF-α) converting enzyme (TACE) expression and activity and decreased ACE2 expression and activity which were counter-regulated by mrACE2 treatment. The inflammatory cytokine IL-6 and F4/80, a macrophage marker, were also reduced by treatment with mrACE2. Transforming growth factor-β1 (TGF-β1), col1α1, and alpha smooth muscle actin levels were increased in the kidneys of 7-week-old Col4A3-/- mice and all were reduced by mrACE2.
Conclusion: Treatment with mrACE2 alters angiotensin peptide metabolism in the kidneys of Col4A3-/- mice and attenuates the progression of AS nephropathy.

Key Words: Alport, ACE2, RAS