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Characterization of the Intrarenal Renin Angiotensin System in Experimental Alport's Syndrome

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Background: Blockade of the renin angiotensin system (RAS) attenuates progression of experimental and clinical Alport Syndrome (AS). However, the mechanism(s) linking AS and activation of the RAS have not been fully elucidated.
Methods: We evaluated the RAS in 4 and 7-week-old Col4A3-/- and wild-type (WT) mice, a model of AS characterized by proteinuria and progressive renal injury.
Results: Renal angiotensin II (AngII) levels were significantly increased, while renal Ang-(1-7) levels decreased in 7-week-old Col4A3-/- mice compared to age-matched controls, and these changes were partially reversed by recombinant-ACE2 treatment (rACE2). Both angiotensinogen and renin protein expression increased in Col4A3-/- compared to WT mice. In agreement with the Ang-(1-7) levels, kidney ACE2 expression and activity were decreased in 7-week-old Col4A3-/- mice. The urinary excretion rate of ACE2 paralleled the decline in tissue expression. Expression of an AngII-induced gene set, that included heme oxygenase-1 (HO-1) and was defined in our prior study, was significantly up-regulated in the kidneys of 7-week-old Col4A3-/- mice compared to WT mice by microarray analysis. HO-1 protein expression was increased in kidneys of Col4A3-/- mice, and normalized by ACE inhibitor treatment. Urinary HO-1 excretion rate paralleled the renal HO-1 expression.
Conclusion: Progressive kidney injury in AS is associated with marked changes in expression of intrarenal RAS components and angiotensin peptides. HO-1 and ACE2 may represent novel markers of AS-associated kidney injury, while administration of rACE2 and/or Ang-(1-7) may represent novel therapeutic approaches in AS.

Key Words: Renin, Angiotensin, Alport