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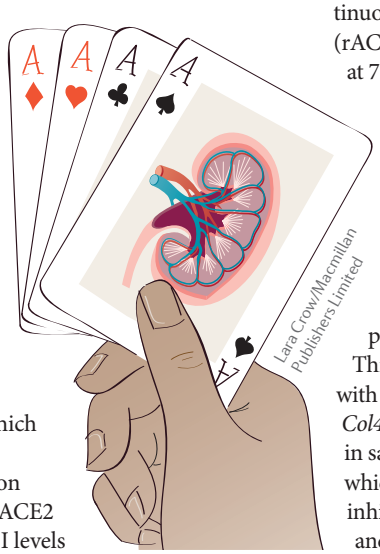
ALPORT SYNDROME

ACE2 administration slows kidney damage

A new study suggests that progression of kidney injury in Alport syndrome might be ameliorated by the administration of angiotensin-converting enzyme 2 (ACE2). This enzyme reduces the activity of the renin–angiotensin system (RAS) and counteracts some of its adverse effects by converting angiotensin II into angiotensin 1–7.



The rationale for ACE2 treatment was based on reduced levels of ACE2 in patients with renal disease and in experimental models, including in *Col4a3*$^{-/-}$ mice, which spontaneously develop Alport syndrome. "This study builds on our previous observation that ACE2 treatment lowers angiotensin II levels while increasing angiotensin 1–7 levels in *Col4a3*$^{-/-}$ mice," explains researcher Vanessa Williams. "We now sought to determine if ACE2 treatment could also attenuate the progression of kidney injury in these mice."

To address this question, 4 week old *Col4a3*$^{-/-}$ mice received osmotic pumps to achieve a steady and continuous release of recombinant ACE2 (rACE2); these mice were compared at 7 weeks of age with wild-type and *Col4a3*$^{-/-}$ mice receiving saline. "Our most significant finding was that rACE2 tended to improve kidney function as indicated by lowering of the urinary albumin excretion rate and a trend toward improved creatinine clearance and blood pressure," comments Williams. This improvement was associated with less severe renal fibrosis in *Col4a3*$^{-/-}$ mice receiving rACE2 than in saline-treated *Col4a3*$^{-/-}$ mice, which the researchers attributed to inhibition of excessive canonical and noncanonical transforming growth factor β signalling by ACE2. In addition, Williams explains that inflammation, as indicated by pro-inflammatory cytokine expression and macrophage infiltration, was attenuated by rACE2 and was associated with a decrease in mitogen-activated protein kinase signalling.

Thus, the study confirms that RAS activation has an important role in the pathological processes that contribute to kidney injury in Alport syndrome, and that inhibition of this pathway improves renal outcomes. "As ACE2 expression is altered in human kidney diseases, including in diabetic nephropathy, hypertensive nephrosclerosis, IgA nephropathy, and membranous nephropathy," says Williams, "rACE2 administration might have important therapeutic implications."

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ORIGINAL ARTICLE Bae, E. H. *et al.* Murine recombinant angiotensin-converting enzyme 2 attenuates kidney injury in experimental Alport syndrome. *Kidney Int.* http://dx.doi.org/10.1016/j.kint.2016.12.022 (2017)