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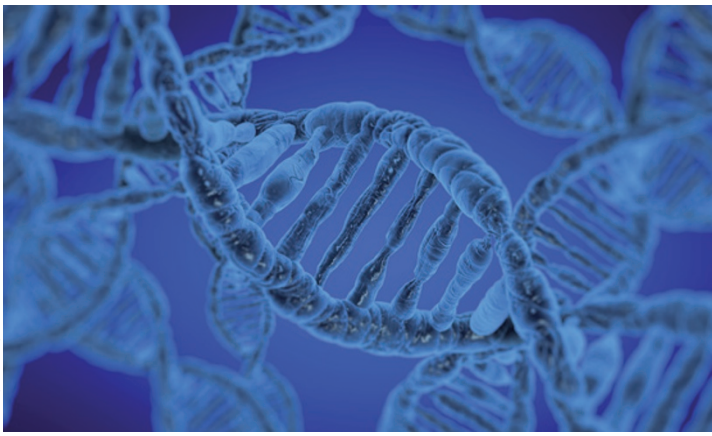
RENIN–ANGIOTENSIN SYSTEM

Targeting multiple RAS genes



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All renin–angiotensin system (RAS) genes are targets of Wnt/β-catenin signalling—and blockade of this pathway abolishes RAS induction—according to new data from Youhua Liu and colleagues. "The clinical implications of these findings are potentially very significant; they may lead to changes in the management of patients with chronic kidney disease (CKD)," says Liu.

RAS activation has a key role in the pathogenesis and progression of CKD and cardiovascular disease. However, the efficacy of RAS blockade using angiotensin-converting-enzyme (ACE) inhibitors or angiotensin II-receptor blockers (ARBs) is limited. "Treatment with ACE inhibitors or ARBs usually causes compensatory upregulation of RAS components, such as renin, leading to decreased effectiveness in the long term," explains Liu. "Therefore, a strategy that inhibits expression of RAS components, rather than RAS activity, could be an important and potentially more effective therapy."

Using bioinformatics analysis, the researchers identified putative T-cell factor/lymphoid enhancer factor (LEF)-binding sites in the promoter regions of all RAS genes. In a human kidney proximal tubular epithelial cell line (HKC-8), constitutively activated β-catenin promoted binding of LEF-1 to these sites, and overexpression of β-catenin or various Wnt ligands induced expression of all RAS genes.

Consistent with these findings, blockade of Wnt/β-catenin signalling using the β-catenin inhibitor ICG-001 suppressed the induction of multiple RAS genes and the expression of the RAS proteins angiotensinogen, renin, ACE and angiotensin II type I receptor, in HKC-8 cells and in the renal tissue of mice with adriamycin (ADR) nephropathy—a model of focal segmental glomerulosclerosis. "As all RAS genes are downstream targets of Wnt/β-catenin signalling, targeting Wnt/β-catenin—the master regulator of RAS—completely eradicates RAS activation," explains Liu.

Finally, the researchers assessed the efficacy of ICG-001 in the ADR nephropathy model. Late administration of ICG-001 (3 weeks after ADR injection) or transient treatment (from day 7 after ADR injection with treatment withdrawal after 2 weeks) restored expression of podocyte proteins and reduced albuminuria, renal fibrosis and inflammation at 5 weeks after ADR injection.

"The withdrawal protocol was designed to imitate a clinical scenario in which patients diagnosed with CKD will no longer be treated for their lifetimes," comments Liu. "Our data suggest that after a short duration of treatment with ICG-001, CKD can be reversed. This finding implies that kidneys have a tremendous capacity for repair and/or recovery after injury."

Next, the researchers plan to test whether blockade of Wnt/β-catenin signalling affects blood pressure. They also hope to carry out a head-to-head comparison of the efficacy of ICG-001 versus ACE inhibitor or ARB in CKD. "In theory, inhibition of Wnt/β-catenin signalling using ICG-001 should be superior to current anti-RAS therapy," says Liu.

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