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CHRONIC KIDNEY DISEASE

Targeting connexin-43 reduces progression of CKD in mice

New research conducted by Christos Chadjichristos and co-workers suggests that blocking expression of connexin-43 (Cx43, also known as gap junction α1 protein) protects against the recruitment of inflammatory cells and activation of profibrotic pathways in injured mouse kidneys. "We were very excited to discover that targeting Cx43 results in reversal of the progression of experimental chronic kidney disease (CKD)," enthuses Chadjichristos.

The researchers previously reported that renal expression of Cx43 is increased in mice during the early stages of hypertension-induced and obstructive nephropathy. In their current study, they show that reduced expression of Cx43 in a transgenic mouse model of hypertension-induced CKD is associated with preservation of renal structure and significant reductions in glomerulosclerosis, tubular dilatation and microalbuminuria—effects that are independent of systolic blood pressure. The team also demonstrated ameliorative effects of Cx43 knockdown on immune-cell infiltration and activation of profibrotic pathways in wild-type mice with unilateral ureteral obstruction, a model of tubulointerstitial disease. In such mice, injection of an antisense Cx43 oligodeoxynucleotide improved long-term kidney disease outcomes, indicating that the protective effects of reduced Cx43 expression were not restricted to genetically manipulated models.

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In vitro experiments using mouse cortical collecting duct cells co-cultured with monocytes showed that treatment with a peptide that specifically blocks Cx43 gap junctions (by preventing docking of Cx43 hemichannels) inhibited monocyte adhesion and activation of profibrotic pathways. Importantly, the researchers also demonstrated that Cx43 is a clinically relevant target. Using immunohistochemistry, they detected higher Cx43 expression in kidney biopsy samples from patients with a variety of inflammatory conditions (including moderate to severe nephroangiosclerosis and obstructive nephritis) than in samples from healthy controls.

The researchers speculate that overexpression of Cx43 in response to renal injury might result in propagation of inflammatory and profibrotic signals throughout the entire kidney, ultimately leading to the development of CKD. "Our findings suggest that Cx43 might be an additional target to reduce inflammation and renal fibrosis during the progression of CKD," concludes Chadjichristos. He adds that development of specific Cx43 antagonists is of major interest.

Peter Sidaway

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