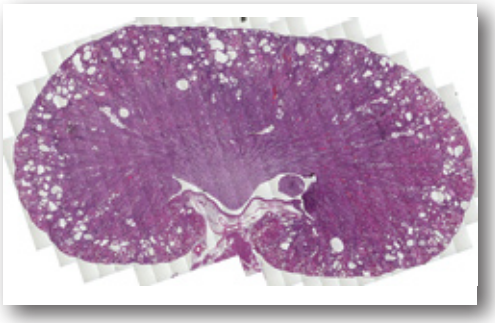
A tiny defect, a terrible disease, a new approach

A hormone that dilates blood vessels during pregnancy opens an indirect pathway for treating polycystic kidney disease

For something so seemingly inconsequential, primary cilia seemed an unlikely cause for something so devastating. Primary cilia are microscopic hairlike structures that stick out like antennae from virtually every cell in the human body, including the epithelial cells lining the kidneys. These nonmoving primary cilia were thought to be little more than evolutionary leftovers until 2000, when research first linked cilia defects to polycystic kidney disease (PKD), a life-threatening genetic disorder that affects 600,000 Americans, according to the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) and the Polycystic Kidney Disease Foundation. Half of those diagnosed with PKD will progress to end-stage renal disease by age 60.

A decade after the discovery, we know a tremendous amount about ciliopathies, a raft of diseases or conditions now associated with defects in primary cilia. Yet there is still no effective treatment for PKD. Researchers have concentrated on halting or reversing the formation of the characteristic large fluid-filled cysts that gradually encroach on kidney function, but Heather Ward, Angela Wandinger-Ness, and others at the University of New Mexico, plus collaborators elsewhere, took another approach. They examined the noncystic aspects of PKD progression, particularly the poor blood flow and extensive internal scarring, called fibrosis, that encroaches on the glomeruli, the vital clusters of looping blood vessels that filter wastes and excess water from the blood. The group looked at a hormone called relaxin, first identified in pregnant women (but also present in men) that works (among other things) as a powerful vasodilator. What would be relaxin's effect on a cystic kidney?

Ward turned to special lab rats genetically altered to model PKD and saw an immediate improvement in renal function and blood flow after a course of relaxin. During human pregnancies, the relaxin hormone also regulates nitric oxide production, controls several signaling pathways, and stimulates the degradation of extracellular matrix around organ tissues by dissolving collagen. After four weeks on relaxin, the PKD model rats had lower collagen scores in their kidneys, indications that either scar formation was slowing down or the old fibroid tissue was breaking up. Most surprisingly, cysts seemed smaller in treated animals.



The kidneys of special lab rats genetically altered to model PKD show the characteristic large fluid-filled cysts that gradually encroach on kidney function.

That finding sent Ward and colleagues exploring the differences in kidney gene expression between relaxin- and control-treated rats. The researchers now believe that relaxin, in part, affects genes associated with epithelial trafficking. Their hypothesis is that relaxin's direct effect on signaling pathways of kidney fibroblasts and vascular cells is improving the renal environment, indirectly affecting cystic epithelia and slowing cyst growth.

In any case, Ward and colleagues say that the dramatic improvement in renal function and decreased fibrosis they have seen in the rat models make relaxin a promising candidate for treating PKD, the first ciliopathy and a condition that still exacts a heavy toll in health costs and in human lives.

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Relaxin Improves Cystic Kidney Disease in Rats and Alters Transcription of Ciliary Trafficking Genes

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