Researchers identify key regulators of urinary concentration in the kidney

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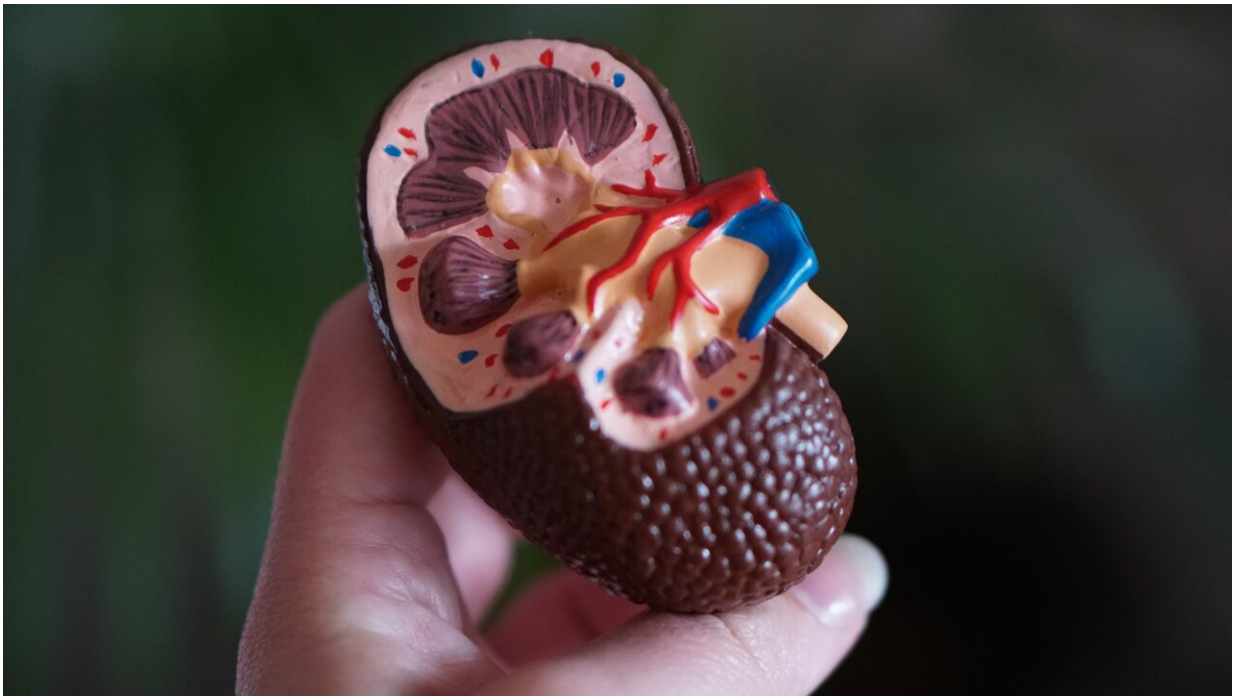

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Proper function of the kidney is critical for concentrating urine, regulating blood pressure, and for the tight control of electrolyte levels in the blood. The kidney achieves these important functions through many microscopic functional units, called nephrons. These nephrons consist of different segments with distinct functions. How these segments form during development and how their function is maintained in the adult is

only partially understood.

A team of MGH investigators has now investigated which factors control the formation and function of specific segments of the nephron, called the distal nephron.

The distal nephron is particularly important for the ability of the kidney to concentrate urine, regulate blood pressure, and control calcium and magnesium blood levels. Parts of the distal nephron have specific salt transporters, which are the main targets of medicine's most effective diuretics, used in the treatment of hypertension and chronic kidney disease. Thus, understanding how their function is regulated has important implications for these common diseases.

Alexander G. Marneros, MD, Ph.D., a physician-scientist at Mass General's Cutaneous Biology Research Center and an associate professor of Dermatology at Harvard Medical School, and colleagues set out to identify key regulators of distal nephron function. In a new research article published in the journal *Nature Communications,* he and his team show that two very similar proteins, the transcription factors AP-2α and AP-2β, regulate the function of two distinct segments of the distal nephron in mice.

Previously, Marneros showed in work published in *Developmental Cell* in 2020 that AP-2β is required for the formation of the segment of the distal nephron that is targeted by thiazide diuretics: the distal convoluted tubule. This prompted him to ask whether the closely related protein AP-2α also has a function in the kidney. His team found that while AP-2β function in the kidney is required for survival by regulating the development and function of distal convoluted tubules, AP-2α is important for the proper function of a different segment of the distal nephron, called the collecting duct, which is involved in the kidney's ability to concentrate urine. Notably, loss of even only half of AP-2β

levels causes progressive kidney disease, whereas complete loss of AP-2α resulted in less severe kidney abnormalities.

"These findings show that AP-2α and AP-2β are important regulators of distinct segments of the distal nephron. These new observations in genetic mouse models are important contributions to our understanding of how specific segments of the kidney are regulated on a molecular level," says Marneros.

"A detailed understanding of the mechanisms that not only lead to the formation of distal nephron segments but also that maintain the proper function of these segments in the adult is important for future novel therapeutic approaches in the management of various kidney diseases," he adds.

More information: Transcription factors AP-2α and AP-2β regulate distinct segments of the distal nephron in the mammalian kidney, *Nature Communications* (2022). DOI: 10.1038/s41467-022-29644-3

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