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PHARMACOLOGY

NHERF3 regulates MRP4-mediated efflux of drug molecules in the kidneys

The adaptor protein NHERF3 has been reported to regulate epithelial transporters and ion channels, but its physiological roles are not well understood. Now, new data suggest that NHERF3 regulates levels of the ATP-binding cassette transporter MRP4 and MRP4-mediated drug efflux in the kidneys.

To investigate the role of NHERF3 in transepithelial transport, Min Goo Lee and colleagues used human embryonic kidney (HEK) 293 cells and *Nherf3*-knockout mice. They report that NHERF3 and MRP4 interact directly in HEK 293 cells; in mice, the proteins co-localize in the apical regions of kidney tubules. Transfection of HEK 293 cells with NHERF3 increased the total and cell surface expression of MRP4 as well as MRP4-mediated efflux of the antiviral drug adefovir, whereas in *Nherf3*-knockout mice (which show mild hypercholesterolaemia under normal dietary and environmental conditions) renal Mrp4 expression was substantially lower and kidney and plasma concentrations of adefovir were significantly higher than in wild type controls.

"Our findings suggest that a major physiological role of NHERF3 is the regulation of organic transporters in kidney epithelia, especially those involved in the disposition and/or elimination of xenobiotic substrates," explains Lee. "A future pharmacogenomics study investigating the relationship between the nephrotoxicity of MRP4 substrate drugs and mutations in the NHERF3 and MRP4 genes might produce important outcomes."

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Original article Park, J. *et al.* Na^+/H^+ exchanger regulatory factor 3 is critical for multidrug resistance protein 4-mediated drug efflux in the kidney. *J. Am. Soc. Nephrol.* doi:10.1681/ASN.2013040438