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DIABETIC NEPHROPATHY

Netrin-1 expression in proximal tubular epithelial cells protects against kidney inflammation and injury

A recent paper published in *The American Journal of Pathology* reports a protective role of the anti-inflammatory molecule netrin-1 in diabetic kidney disease. The authors previously found an association between increasing netrin-1 levels in the urine of patients with diabetes and increasing albuminuria. "Nature is smart; it does not waste energy producing something that is damaging" says researcher Ganesan Ramesh, "so we proposed that netrin-1 expression may be induced as a protective mechanism." The researchers hypothesized that overexpression of netrin-1 in mouse proximal tubular epithelial cells before the induction of diabetes might suppress the disease process.

In wild-type mice, streptozotocin-induced diabetes was associated with deterioration in renal function and an increase in albuminuria, as well as increases in fibrosis, neutrophil and

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macrophage infiltration, chemokine expression and apoptosis in the kidney. However, specific overexpression of netrin-1 in proximal tubular epithelial cells suppressed these effects. Interestingly, epithelial-cell-specific netrin-1 overexpression also abrogated the diabetes-induced expression of cyclooxygenase-2 (COX-2) in cortical tubules and suppressed prostaglandin E2 (PGE2) excretion in urine. These data suggest that netrin-1 suppresses diabetes-induced kidney inflammation by inhibiting the COX-2-mediated production of PGE2.

In vitro, netrin-1 dose-dependently increased the uptake of albumin by mouse proximal tubular epithelial cells but did not affect glucose uptake. PI3-kinase and ERK-kinase inhibitors suppressed netrin-1-induced albumin uptake, suggesting that netrin-1 increases albumin uptake by proximal tubular epithelial cells—and, therefore, reduces albuminuria—through activation of PI3 kinase and ERK signalling pathways.

"Tubular epithelial cells may be critical players in the development of nephropathy, and inflammation plays an important role in this disease", concludes Ramesh. "We should look beyond the glomerular basement membrane to move forward and develop effective therapies for nephropathy."

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Original article Mohamed, R. *et al*. Kidney proximal tubular epithelial-specific overexpression of netrin-1 suppresses inflammation and albuminuria through suppression of COX-2-mediated PGE2 production in streptozotocin-induced diabetic mice. *Am. J. Pathol.* doi:10.1016/j.ajpath.2012.08.014