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STONES

TNFRs mediate CaOx deposition in hyperoxaluria

> TNFR signalling is essential for CaOx crystal adhesion to the luminal membrane of renal tubules

Tumour necrosis factor receptors (TNFRs) have an essential role in calcium oxalate (CaOx) crystal deposition in renal tubules, according to new data from Hans-Joachim Anders and colleagues. These researchers previously found that TNFRs contribute to the induction of tubular epithelial cell necroptosis in oxalate crystal-induced acute kidney injury. Now they have investigated the role of these receptors in hyperoxaluria-related chronic kidney disease (CKD).

In their new study, Anders and colleagues analysed TNFR expression in kidney tissue from patients with primary hyperoxaluria type 1 and associated CKD, and from a control individual without kidney stones. They report that the tubular expression of TNFR1 and TNFR2 was upregulated in the patient samples. Similarly, expression of these receptors was increased in the renal tubules of mice with CaOx monohydrate-related nephrocalcinosis compared with those of healthy controls.

Next, the researchers showed that in contrast to wild-type controls, mice deficient in *Tnfr1*, *Tnfr2* or both, did not develop progressive CKD (characterized by diffuse tubular atrophy, interstitial fibrosis and interstitial infiltrates of phagocytes and T cells) when fed an oxalate-rich diet. Moreover, oxalate-fed wild-type mice showed diffuse bilateral nephrocalcinosis, whereas no intrarenal CaOx deposits were found in oxalate-fed *Tnfr*-deficient mice despite similar levels of hyperoxaluria. "The lack of crystal deposits in the knockout mice puzzled us and it took us a while to find the explanation," comments Anders.

Further investigations using isolated murine tubular epithelial cells indicated that *Tnfr* expression was required for the induction of annexin II and CD44 expression in response to CaOx crystals. These crystal-binding proteins were not expressed in the kidneys of hyperoxaluric *Tnfr*-deficient mice, but their mRNA and protein expression was increased in wild-type mice in response to an oxalate-rich diet.

Finally, the researchers report that TNFR blockade using the small molecule inhibitor R-7050 reduced intrarenal CD44 and annexin II expression; CaOx crystal deposition; and markers of renal fibrosis, tubular injury and intrarenal inflammation in mice with hyperoxaluria. They suggest that the lack of expression of intrarenal crystal adhesion molecules likely accounts for the absence of nephrocalcinosis in hyperoxaluric *Tnfr*-deficient mice.

The researchers conclude that "TNFR signalling is essential for CaOx crystal adhesion to the luminal membrane of renal tubules, which is a fundamental mechanism for the initiation of nephrocalcinosis". In addition, Anders suggests that TNFRs might represent "bottleneck molecular targets" for numerous crystal adhesion molecules, so could potentially be clinically important.

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ORIGINAL ARTICLE Mulay, S. R. *et al.* Hyperoxaluria requires TNF receptors to initiate crystal adhesion and kidney stone disease. *J. Am. Soc. Nephrol.* http://dx.doi.org/10.1681/ASN.2016040486 (2016)
FURTHER READING Mulay, S. R. *et al.* Cytotoxicity of crystals involves RIPK3-MLKL-mediated necroptosis. *Nat. Commun.* **7**, 10274 (2016)