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PROTEINURIA

New therapeutic strategy for proteinuria

4-Phenylbutyric acid (PBA) — a molecular chaperone known to modulate endoplasmic reticulum (ER) function — might be a suitable therapeutic to ameliorate the toxic effects of proteinuria, according to new research. Fabiola Terzi and colleagues report that PBA can inhibit ER stress-induced apoptosis and the unfolded protein response in proteinuric mice, markedly improving kidney function and reducing the severity of tubulointerstitial lesions.

"Using *in vitro* and *in vivo* molecular and pharmacological approaches, we uncovered a novel molecular pathway of chronic kidney disease (CKD) progression whereby proteinuria stimulates ATF4-induced LCN2 overexpression via a calcium release-induced ER stress response. This in turn leads to tubular apoptosis and renal lesions," explains Terzi. "Notably, we showed that this pathway is easily druggable with PBA."

In proof-of-principle studies, the researchers then showed that these experimental observations were relevant to human disease. LCN2 was overexpressed in the kidneys of patients with proteinuric nephropathies, and a decrease in urinary LCN2 was observed in a proteinuric patient exposed to PBA. Based on these findings, the researchers suggest that molecular chaperones, such as PBA, might improve the efficacy of renin–angiotensin system inhibitors in delaying CKD progression.

"Our previous studies found that LCN2 has a crucial role in CKD progression during nephron reduction and cystogenesis by mediating the mitogenic effects of EGFR receptor activation," says Terzi. "Here, we demonstrate that LCN2 also acts by triggering apoptosis in protein-overloaded tubular cells." Terzi proposes that LCN2 acts as a central integrator of multiple signalling pathways that can lead to CKD progression, but says that the signalling pathways triggered by LCN2 are unknown.

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ORIGINAL ARTICLE El Karoui, K. *et al.* Endoplasmic reticulum stress drives proteinuria-induced kidney lesions via Lipocalin 2. *Nat. Commun.* http://dx.doi.org/10.1038/ncomms10330