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GENETIC KIDNEY DISEASE

Uromodulin in ER stress and apoptosis

Mutations in *UMOD*, which encodes uromoulin, are associated with a form of tubulointerstitial kidney disease. Now findings demonstrate that misfolded uromodulin stimulates endoplasmic reticulum (ER) stress-mediated apoptosis of tubule epithelial cells.

To assess the mechanisms by which misfolded uromodulin triggers kidney disease, Bryce Johnson and colleagues used CRISPR–Cas9 to introduce the mouse equivalent of a human *UMOD* mutation into the mouse genome. Heterozygous *Umod*-mutant mice developed renal dysfunction with interstitial fibrosis and accumulation of uromodulin in the ER. Transcriptional analyses revealed marked upregulation of genes associated with innate immunity, ER stress and apoptosis. Genes involved in autophagy were not, however, transcriptionally upregulated, despite the known role of autophagy in clearing misfolded proteins. Further studies demonstrated that autophagy was in fact suppressed in mutant kidneys due to increased expression of the autophagy regulators AKT and mTOR. Interestingly, stimulation of autophagy induced clearance of aggregated mutant protein in cultured cells.

To investigate the effects of ER stress signalling the researchers stimulated mild, transient ER stress in cultured mutant uromodulin-producing cells by administering brefeldin A, which inhibits ER trafficking. Although brefeldin A treatment enhanced ER stress, susceptibility to caspase-mediated apoptosis was increased by the cytokines TNF and TRAIL — an effect that was suppressed by knocking down the proapoptotic gene *TRIB3*. The upregulation of proapoptotic genes in mutant kidneys and increased susceptibility of mutant cells to TNF and TRAIL-mediated apoptosis prompted the researchers to test the ability of TNF blockade to protect kidneys from cell death. Indeed, treatment of uromodulin-mutant mice with a soluble recombinant fusion protein, TNFR:Fc, reduced indices of renal apoptosis and fibrosis and improved renal function. The researchers conclude that an anti-TNF approach could potentially be used to prevent nephron loss in patients with uromodulin-associated kidney disease.

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“an anti-TNF approach could potentially be used to prevent nephron loss”

ORIGINAL ARTICLE Johnson, B.G. *et al.* Uromodulin p.Cys147Trp mutation drives kidney disease by activating ER stress and apoptosis. *J. Clin. Invest.* http://dx.doi.org/10.1172/JCI93817 (2017)