



# What Does Uromodulin Do?

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## Introduction

CKD represents a major health burden linked with higher risk for cardiovascular disease and premature mortality. *UMOD*, encoding uromodulin, is implicated in a spectrum from rare to common kidney diseases. Rare mutations lead to autosomal dominant tubulointerstitial kidney disease, an infrequent cause of CKD. Genome-wide association studies (GWAS) established *UMOD* as the top locus associated with CKD and eGFR<sub>Cre</sub> (1), with the “risk” allele being common (approximately 80% in European) and associated with higher urinary uromodulin levels (2). In this short perspective, we highlight recent research on the multifaceted roles of uromodulin in regulating tubular functions and beyond and identify future areas of research. For a more complete overview of uromodulin’s roles and implications in disease, we refer to previous reviews (3).

Uromodulin was cloned from kidney mRNA in 1987, and its cDNA was shown to be identical to the cDNA of previously described Tamm–Horsfall protein. The expression of *UMOD* is restricted to the thick ascending limb and the early distal convoluted tubule, and yet, it is the most abundant kidney-enriched transcript (3,4). Cellular maturation of uromodulin comprises the formation of 24 intramolecular disulfide bonds inside the endoplasmic reticulum and assembly of complex *N*-glycosylation in the endoplasmic reticulum and Golgi. Uromodulin is then released in urine after cleavage at the apical membrane by the serine protease hepsin (3) (Figure 1).

## Role in the Distal Tubule: Regulation of Salt Transport and Blood Pressure

The water-impermeable thick ascending limb of Henle’s loop reabsorbs approximately 30% of filtered NaCl, thereby diluting the tubular fluid and fueling the countercurrent multiplication critical for water conservation. Salt-losing tubulopathies (Bartter syndromes) and loop diuretics illustrate the importance of this segment in electrolyte, fluid, and BP homeostasis.

Phylo- and ontogenetic observations (coincidence of uromodulin immunodetection and emergence/development of the loop of Henle) and murine models suggest a functional link between uromodulin and loop of Henle activity (2,3). This nexus is at least partially explained by a positive regulation of Na<sup>+</sup>, K<sup>+</sup>, 2Cl<sup>−</sup> cotransporter (NKCC2) by uromodulin (2).

Furthermore, uromodulin overexpression drives salt-sensitive hypertension in mice, and there is mounting evidence for the importance of this regulatory pathway in humans (2). A case-control GWAS showed that the minor (“protective”) *UMOD* allele was associated with lower risk for hypertension and cardiovascular disease while also being associated with lower urinary uromodulin excretion (5), with most recent BP GWAS confirming the *UMOD* locus. The clinical effect of furosemide in hypertensive patients is influenced by the *UMOD* allelic status, suggestively linking uromodulin expression with NKCC2 activity and BP control (2). Recently, uromodulin was found to activate Na<sup>+</sup>, Cl<sup>−</sup> cotransporter (NCC) in the early distal convoluted tubule, highlighting its broader importance in distal NaCl handling (4), even if details of the molecular regulation of NKCC2 and NCC are unsolved (Figure 1C). Clinical studies assessing whether therapeutic responses to loop diuretics are influenced by *UMOD* allelic status are ongoing (<https://www.bhfumod.co.uk/>; ClinicalTrials.gov Identifier: NCT03354897) and will hopefully guide personalized pharmacotherapy in the future.

In addition to modulating NaCl uptake, uromodulin has been shown to regulate apical Ca<sup>2+</sup> and Mg<sup>2+</sup> channels in the distal convoluted tubule (3). Nonetheless, it seems counterintuitive that such a massively excreted glycoprotein carries the sole purpose of regulating tubular transporters and channels. Indeed, correlation studies suggest that the ancestral (“risk”) *UMOD* allele, driving higher urinary uromodulin excretion, has been kept at high population frequency not because it favors salt retention, but likely because it protects against urinary tract infections (UTIs) (6).

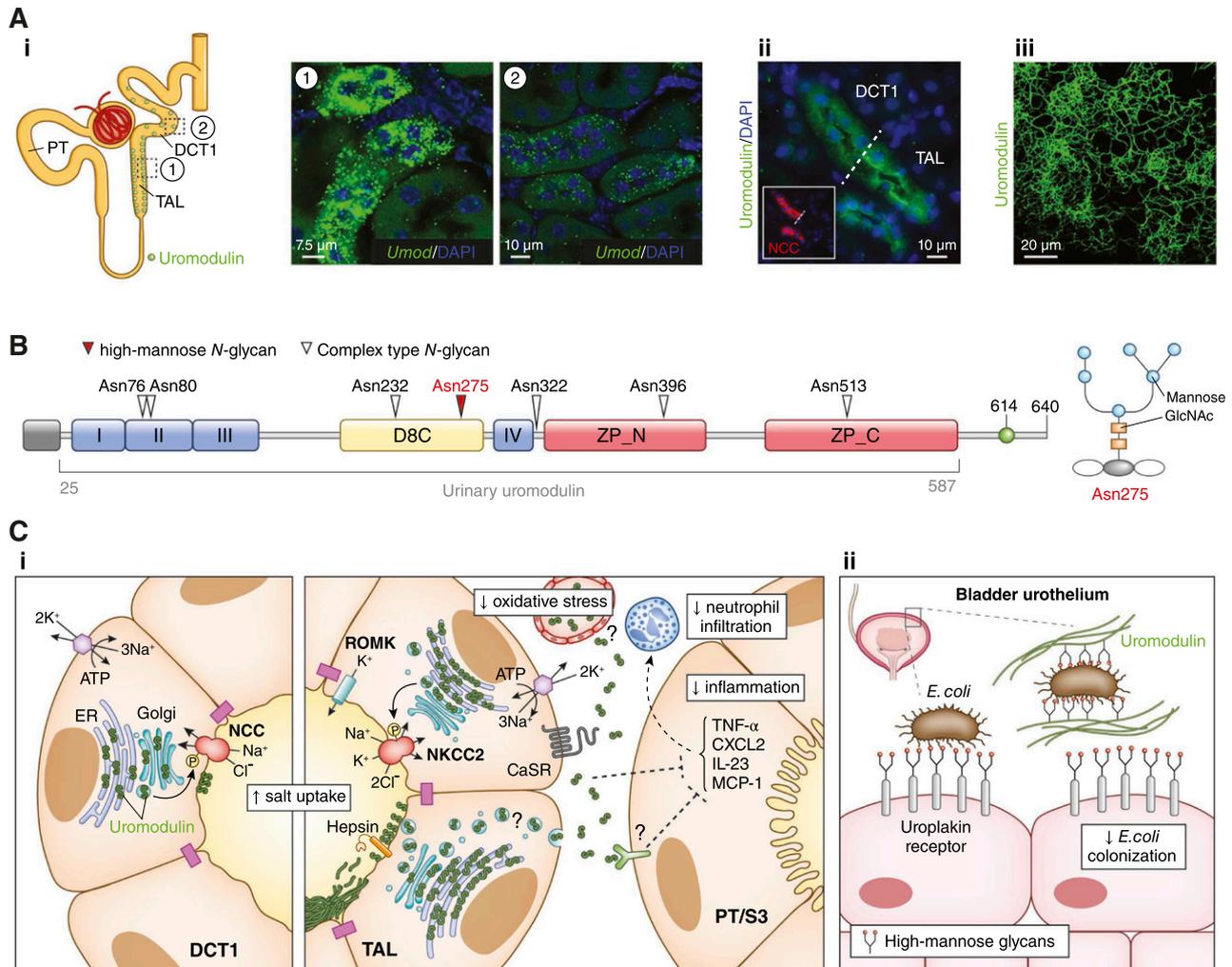
## Role in the Urine: Protection from Urinary Tract Infections

Pathogens exercise powerful selective pressure by affecting reproductive fitness. Antibacterial functions would therefore fit within an evolutionary framework explaining why most of us carry genetic determinants driving high uromodulin expression (6).

On the basis of the cryoelectron tomography–derived three-dimensional structure of native uromodulin filaments and biochemical data, a model has been proposed in which urinary uromodulin polymers act as multivalent ligands for uropathogens (*via* interaction between bacterial lectin and uromodulin high-mannose glycan Asn275), antagonizing uropathogen binding to

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**Figure 1. | An overview of uromodulin expression, structure, and functions.** (A) Uromodulin expression. (A, i) Uromodulin expression (green) in the thick ascending limb (TAL; ①) and the early distal convoluted tubule (DCT1; ②) as shown by *in situ* hybridization (RNAscope) for *Umod* mRNA in mouse kidney cortex. Nephron segments are identified through cohybridization for *Slc12a1* and *Slc12a3*, respectively (not shown). (A, ii) Immunofluorescence staining for uromodulin (green) in the mouse kidney showing apically enhanced signal in the TAL with abrupt transition to weaker staining in the DCT1 (identified by  $\text{Na}^+$ ,  $\text{Cl}^-$  cotransporter [NCC] serial section immunostaining in red; inset). DAPI, 4',6-diamidino-2-phenylindole. (A, iii) Uromodulin filaments (green) covering a monolayer of primary TAL cells obtained from microdissected mouse kidney. (A, i and ii) are modified from ref. 4, with permission. (B) Predicted structure of uromodulin containing a leader peptide directing nascent uromodulin into the endoplasmic reticulum (ER) (black), four EGF-like domains (blue), of which EGF-II and EGF-III are predicted to be  $\text{Ca}^{2+}$  binding, a cysteine-rich D8C domain (yellow), a bipartite Zona Pellucida (ZP) domain (ZP\_N and ZP\_C; red), and a glycosylphosphatidylinositol-anchoring site at position 614 (green). The seven *N*-glycosylation sites are indicated by triangles; the high-mannose chain on residue Asn275 is highlighted in red, and a possible high-mannose configuration is shown in more detail in the right panel. GlcNAc, *N*-acetylglucosamine. (C) Roles of uromodulin. (C, i) In the TAL and DCT1, uromodulin increases phosphorylation and activation of  $\text{Na}^+$ ,  $\text{K}^+$ ,  $2\text{Cl}^-$  cotransporter (NKCC2) and NCC, respectively, thus positively modulating  $\text{NaCl}$  reabsorption at these sites. Uromodulin matures in the ER and Golgi apparatus and traffics to the apical membrane within secretory vesicles. At the apical membrane, uromodulin undergoes proteolytic cleavage by serine protease hepsin to be released in urine and form high-molecular weight polymers. Through unknown mechanisms, a smaller amount of uromodulin is also trafficked to the basolateral cell pole to be released into the interstitium and the circulation, where it likely remains in the monomeric form. A modulatory role on neighboring S3 proximal tubule (PT) cytokine production and release (especially in AKI models) has been ascribed to basolaterally released uromodulin. Although the mechanisms of PT uromodulin sensing are currently unsolved, the overall effect of uromodulin is a negative modulation of local and systemic inflammation, of neutrophil infiltration, and of systemic oxidative stress (more details are in the text and ref. 10). (C, ii) High-mannose *N*-glycans from uromodulin are predicted to bind to FimH lectins expressed on *E. coli* type 1 fimbriae. Thereby, urinary uromodulin competes with bladder urothelial uroplakin receptors for the binding of *E. coli* and prevents *E. coli* from bladder colonization. CaSR, calcium-sensing receptor; CXCL2, C-X-C motif chemokine ligand 2; MCP-1, monocyte chemoattractant protein 1; ROMK, renal outer medullary potassium channel.

bladder uroplakins and likely promoting clearance of aggregated bacteria by micturition (7) (Figure 1, B and C). In line, *Umod*-deficient mice display higher propensity for bladder

colonization by type 1 fimbriated *Escherichia coli*, the most common etiology in UTI (3). Is this relevant in humans, with a plethora of urinary antimicrobial peptides? Indirect

evidence stems from a population-based cohort study where urinary leukocyte counts were inversely correlated with urinary uromodulin concentrations, suggesting an “antiseptic” role (6). A prospective, longitudinal cohort study in older community-dwelling adults provided more direct proof by showing that persons in the highest urinary uromodulin concentration quartile had a significantly lower risk for UTI compared with those in the lowest quartile, independent of traditional UTI risk factors (8). These results suggest that uromodulin is an integral part of the urinary innate immune defense and hold promise for leveraging its biochemical and structural features or modulating its excretion rates to prevent or treat UTIs (3).

### Role in the Circulation: Modulating Inflammation

There is increasing interest in the value of uromodulin as a biomarker for kidney and systemic outcomes. Urinary levels of uromodulin reflect tubular mass and function and are positively correlated with eGFR. In at-risk cohorts, low urinary uromodulin levels likely reflect decreased tubular mass/function and are associated with a higher risk for AKI and cardiovascular disease. Large-scale urinary uromodulin measurements, however, bear considerable analytical and interpretative challenges (3).

A fraction of uromodulin is shuttled to the basolateral thick ascending limb membrane. ELISA consistently detects uromodulin in blood at levels approximately 100× lower than in urine, suggesting basolateral release of uromodulin. Serum uromodulin levels are positively correlated with eGFR<sub>crea</sub> and eGFR<sub>CysC</sub>, are negatively correlated with BUN, are undetectable in CKD stage 5, and surge after kidney transplantation, establishing their kidney source. Furthermore, higher serum uromodulin concentrations have been associated with a favorable metabolic profile, lower prevalence of cardiovascular comorbidities, and lower risk for 10-year mortality, independently of other cardiovascular risk factors including eGFR (3,9).

But what is the role of “nonurinary” uromodulin? In murine models of AKI, uromodulin translocates toward the basolateral pole and is likely released in the interstitium and systemic circulation. By crosstalking with adjacent proximal S3 tubules, uromodulin may modulate inflammatory response, accelerate recovery after AKI, and regulate bone marrow granulopoiesis *via* IL signaling, at least in mice (10). Recently, circulatory uromodulin was linked to systemic oxidative stress *via* its inhibition of TRPM2 channels. On the basis of murine and human data, the hypothesis put forward argues that AKI corresponds to a state of systemic uromodulin deficiency with correlating increase in systemic oxidative damage (11) (Figure 1C). These results provide potential clues why serum uromodulin might associate with cardiovascular outcomes. Further work will need to establish whether extrarenal outcomes associated with serum uromodulin are truly independent of kidney parameters. Indeed, serum uromodulin levels steeply drop already in CKD stage 1, not detected by conventional GFR biomarkers. Therefore, associations between serum uromodulin and cardiovascular disease should not only be adjusted for eGFR but also for additional indices of kidney and tubular damage such

as proteinuria (9). More basic questions regarding the mechanisms that direct, regulate, and mediate basolateral release and prevent uromodulin polymerization in the interstitium and blood need answers as well.

### Conclusion and Perspectives

Recent evidence obtained in mouse and man suggests multiple physiologic roles for uromodulin, in and outside the urine compartment, and the involvement of *UMOD* variants in a continuum of kidney diseases (3). Future studies should translate this knowledge on uromodulin into innovative therapies for conditions including salt-sensitive hypertension, UTI, CKD, and AKI.

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