Uromodulin, an Emerging Novel Pathway for Blood Pressure Regulation and Hypertension

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Online Data Supplement

Uromodulin was discovered in 1950 by Igor Tamm and Frank Horsfall, using a salt precipitation procedure to isolate a potent inhibitor of viral hemagglutination from urine. Muchmore and Decker, in 1985, isolated a glycoprotein (calling it uromodulin) with in vitro immunosuppressive properties from urine of pregnant women. In 1987, Pennica et al confirmed by cDNA analysis that uromodulin and Tamm–Horsfall protein were identical proteins. Since the initial discovery and without any clear understanding of the function of uromodulin, it was only in 2002 when Hart et al identified causative uromodulin mutations in a subset of families having familial juvenile hyperuricemic nephropathy and medullary cystic kidney disease type 2 that interest in uromodulin biology and function was revived. Interest in uromodulin was further revitalized by genome-wide association studies (GWASs) in 2009/2010 showing an association between common single-nucleotide polymorphisms in the upstream region of the UMOD gene with renal function and hypertension. In 2013, 2 independent groups undertaking post-GWAS functional dissection of the UMOD loci provided molecular insights into a new pathway for hypertension and sodium homeostasis involving uromodulin and opening an exciting line of investigation that could enhance our understanding of renal tubule physiology, sodium homeostasis, blood pressure (BP) regulation, and potentially lead to novel therapies for hypertension.

Uromodulin is a protein exclusively expressed by epithelial cells of the thick ascending limb of Henle’s loop (TAL; Figure 1). The 640-amino-acid precursor is cotranslationally translocated into the endoplasmic reticulum (ER), extensively glycosylated, glypiated, and glycosylphosphatidylinositol anchored to the apical tubular cell membrane. From here it is released by a specific, but as yet unidentified, serine protease(s). The released protein is excreted in the urine at a rate of 20 to 100 mg/d and represents the most abundant urinary protein in the healthy individual and is the main constituent of hyaline urinary casts.

UMOD Gene and Biology

UMOD is located on the reverse strand of chromosome 16 (16p12.3) at position 20,344,374 to 20,367,623 bp (GRCh37/hg19 assembly). The gene is composed of 11 exons with several alternatively spliced transcripts. The transcription specificity of UMOD to the kidney is determined by its cis-acting promoter sequence—in humans, the 5.6 kbp of human genomic sequence, consisting of 3.7 kbp promoter, exon 1, intron 1, and the untranslated part of exon 2. Zhu et al reported the first 589 bp of the UMOD promoter as highly conserved across species (human, rat, mouse, and cow) and that the 3 Kb promoter region drives TAL-specific expression of UMOD.

From cDNA sequence, the uromodulin precursor is composed of 640 amino-acid residues, and motifs include signal sequence (residues 1–24) directing its entry in the secretory pathway; 1 epidermal growth factor–like and 2 calcium-binding epidermal growth factor–like domains (residues 31–64, 65–107, and 108–149) which have roles in adhesion, coagulation, and receptor–ligand interaction; 1 central domain of unknown function (named D8C containing eight conserved cysteines); 1 zona pellucida domain (residues 334–585) essential for protein polymerization; a glycosylphosphatidylinositol attachment site (residue 614); and 8 potential N-glycosylation sites. The molecular weight of uromodulin (105 kDa) is significantly contributed (30%) by N-glycosylation, and there are 48 cysteine residues involved in disulfide bond formation.

The uromodulin signal peptide is cleaved in the ER, the protein is glycosylated on 7 of its 8 potential N-glycosylation sites, disulphide bridges are formed, and glypination on its C terminus occurs. The Golgi apparatus further modifies the N-glycan moieties. The mature glycan moieties and the glycosylphosphatidylinositol modifications route the protein to the apical membrane of TAL epithelial cells, where uromodulin is finally glycosylphosphatidylinositol anchored facing the tubular lumen.

ER processing is the rate-limiting step in uromodulin maturation (Figure 1). From the luminal side of the membrane, the protein is actively released by proteolytic cleavage at residue F587 (Figure 1). This implies that urinary uromodulin is composed of 563 amino acids...
and, depending on its glycosylation status, migrates as an 80- to 90-kDa band on SDS-PAGE. Cleavage is necessary for protein polymerization as it releases an inhibitory motif that prevents premature protein assembly. In addition to this classical apical targeting, to a minor degree, uromodulin also sorts to the basolateral pole of tubular epithelial cells.18

Uromodulin Pathophysiology

Urine uromodulin excretion increases from birth to adulthood and then remains stable until a decline after 60 years of age,19,20 whereas the urinary uromodulin/creatinine ratio seems to be relatively stable from 4 years of age through the seventh decade of life. It is positively correlated with estimated glomerular filtration rate (eGFR), urine volume, dietary salt, and protein intake.21–24 The urinary uromodulin–dietary salt correlation is more prominent in salt-sensitive hypertensive patients.25 Increased dietary salt in male Sprague-Dawley rats results in increases in relative steady-state mRNA and protein levels of uromodulin in the kidney, suggesting that a sodium-induced increase in urinary uromodulin reflects increased intrarenal synthesis rather than increased urinary shedding.23 Factors that may decrease uromodulin expression or excretion are angiotensin-converting enzyme inhibitors,26 hypothyroidism,27 and urinary tract obstruction.28 Uromodulin half-life was estimated to be 9 hours in rabbits and 16 hours in humans.29 and urinary uromodulin excretion is used as an indicator for renal tubular function.30 Indeed, reduced urinary uromodulin is evident in acute tubular necrosis, diabetic nephropathy, hyperprostaglandin E syndrome triggered by inflammatory cytokines, and active lupus nephritis.31–34

Studies of human UMOD mutations in polarized Madin Darby canine kidney cells showed that a cysteine-altering mutation in the evolutionary conserved cysteine-rich domain had more severe deficits in ER exit and surface translocation, triggering increased apoptosis than a cysteine-altering mutation outside of the domain. Both mutants were able to specifically bind and trap uromodulin preventing it from exiting the ER and translocating to the cell surface, partially accounting for the reduced urinary uromodulin in some diseases.35

The highly ordered organization of uromodulin on the apical membrane, because of the glycosylphosphatidylinositol anchor, can form a physical water barrier on the luminal plasma membrane of TAL cells. Such a barrier may play a role in ion transport to maintain countercurrent gradients in the interstitium.36

In the urine, uromodulin is mainly present as a high-molecular-weight polymer (M_r, 1–10×10^6 Da) that appears on electron microscopy analysis as a matrix of fibrils, with a width of ≈100 Å and an average length of 25 000 Å. Uromodulin is a polyanionic macromolecule attributable to extensive sialylation and sulfated N-linked glycans.37 In solution, uromodulin aggregates with gel-like properties when NaCl and CaCl_2 concentrations are ≈100 mmol/L and ≈1 mmol/L, respectively.38,39 The released protein forms a slowly moving polyanionic gel interacting or associating with plasma membrane–anchored uromodulin molecules. This potentially contributes to colloid osmotic pressure and retards passage of cations through the TAL, thus enhancing their active transport and reabsorption in this segment.11,12 In vivo evidence from knockout mice indicates that uromodulin reduces the risk of urinary tract infection40,41 and nephrolithiasis possibly by competing with the binding of Escherichia coli to uropelkins and by preventing the aggregation of calcium crystals respectively.42,43

Uromodulin can interact with and activate components of the immune system, including monocytes, neutrophils, and myeloid dendritic cells via toll-like receptor 4,7,37,44 and plays a role in inflammation and modulation of innate immune responses. Identification of glycosylphosphatidylinositol-anchored enriched endocytic compartments suggests that uromodulin’s immunosuppressive effects is through binding with tumor necrosis factor-α (TNF-α) and interleukin-1.45,46 Uromodulin from pregnant women increases the phagocytic activity of neutrophils by prostaglandin E2 release, suggesting specific interactions with neutrophil membranes.47 UMOD−/− mice show splenomegaly with prominent white pulp macrophage infiltration and elevated circulating TNF-α and interleukin-1.

Uromodulin-Associated Kidney Diseases

Mutations in the UMOD gene cause medullary cystic kidney disease type 2 (MIM 603860) and familial juvenile hyperuricemic nephropathy (MIM 162000) that are autosomal dominant diseases characterized by tubulointerstitial nephritis and hyperuricemia (prevalence 1 per 100 000). About 58 mutations have been reported to date, and most of them occur in exons 3 and 4 encoding for the N-terminal half of the protein and 3 mutations in exon 5 affecting residues in the Zona Pellucida domain. The pathological basis of uromodulin-associated
kidney disease seems to be protein misfolding, abnormal trafficking, and ER stress (See online-only Data Supplement).

**Further Insights From UMOD Knockout Mice**

Uromodulin has extra- and intracellular functions, the latter related to urinary concentrating mechanisms which disturb transcellular electrolyte transport, and the former linked with anti-inflammatory properties of the glycoprotein. UMOD−/− mice show few, if any, signs of uromodulin-associated kidney disease, no abnormalities of steady-state electrolyte handling, but significantly reduced creatinine clearance and impaired urine concentrating ability. If uromodulin participates in the water impermeability at the TAL, then a failure of this feature in UMOD−/− mice would reduce NaCl reabsorption, decrease the interstitial osmolality, and impair the urine concentrating ability. Intracellular examination of UMOD-deficient mice did indeed show impaired urinary concentrating ability with increased expression of the thiazide-sensitive NaCl channel in the distal convoluted tubule, suggesting a compensatory adaptation for putatively insufficient Na+/K+-ATPase, NKCC2, chloride channel protein class K2, sodium-hydrogen exchanger 3, renal outer medullary potassium channel activity was reduced at the apical surface because of the potassium channel remaining intracellular and inactive. In vitro studies more recently indicate that NKCC2 phosphorylation and activity is mediated by membrane-anchored uromodulin.

Renal ischemia–reperfusion in UMOD−/− mice is significantly worse than in wild-type animals and is associated with increased inflammatory response and increased neutrophil infiltration in the outer medulla. The phenotype of injury predominantly is that of tubular necrosis affecting the S3 segments, but not the uromodulin-deficient TAL. That uromodulin produced in TAL affects the susceptibility of neighboring proximal tubules to injury suggests a uromodulin-dependent TAL-S3 tubular cross-talk.

**UMOD Promoter Variation and Insights From GWASs**

Common variants in the UMOD gene have been associated with renal function and hypertension in separate GWASs. Two single-nucleotide polymorphisms (the T allele of rs12917707 and C allele of rs4293393) within the promoter region of the UMOD gene are associated with higher eGFR, decreased risk of chronic kidney disease (CKD), and a lower level of urinary uromodulin excretion. Furthermore, higher uromodulin levels have been shown to precede future development of CKD. The minor G allele of rs13333226 (ancestral and in perfect linkage disequilibrium with rs12917707 and rs4293393) is associated with a lower risk of hypertension (odds ratio [95% confidence interval], 0.87 [0.84–0.91]), reduced urinary uromodulin excretion, and increased eGFR (3.6 mL/min per lower allele) in a large GWAS of BP extremes. Each copy of the G allele of rs13333226 is associated with 0.49 mm Hg lower systolic BP and 0.30 mm Hg lower diastolic BP.

The human GWASs all consistently show the uromodulin decreasing alleles (of rs12917707, rs4293393, rs13333226) to be associated with higher GFR. Although lower GFR may indicate renal damage and reduced functioning tubular mass resulting in lower urinary uromodulin as seen in clinical studies, the single-nucleotide polymorphism–GFR association implies a possible causal association between UMOD variation on GFR. If this were the case, then absence of UMOD in UMOD−/− mice should also show high GFR, but surprisingly, UMOD−/− mice show significantly decreased urinary GFR compared with wild-type mice. One suggested explanation is related to the finding that adjusted 24-hour uromodulin excretion increases in diabetic patients with early kidney disease but without a significantly decreased GFR. Therefore, absolute uromodulin excretion decreases with the reduction in total nephron mass seen with CKD, but the amount of uromodulin secreted by each single functioning nephron unit is increased. Consequently, in patients with early CKD and preserved GFR, uromodulin excretion per 24 hours may be increased. A second explanation comes from data from our laboratory comparing creatinine clearance changes in wild-type and UMOD−/− mice after salt loading. We showed that creatinine clearance was significantly decreased in UMOD−/− mice at baseline but increased significantly after salt loading. This suggests that the association between high eGFR and the uromodulin decreasing allele may be confounded by an interaction with the high background salt intake in humans. Finally, in contrast to uromodulin-associated kidney disease, UMOD promoter single-nucleotide polymorphisms from large GWASs were not (or only weakly) associated with hyperuricemia and gout. In summary, a causal role for uromodulin on renal function may be counterfactual from available data, and a search for causal variants underlying the GWAS signal for eGFR was unsuccessful. On the contrary, the exploration of the uromodulin–hypertension association has been more successful opening up new insights into TAL function and BP regulation.
A New Pathway for Hypertension

There is consistent and accruing evidence that implicates uromodulin in sodium homeostasis and hence BP regulation.5–10 The rs13333226 G allele (low uromodulin) is associated with lower fractional excretion of sodium during conditions of liberal sodium intake and lower fractional excretion of endogenous lithium, pointing to increased sodium reabsorption at the proximal tubular level.8 The genotype association of rs13333226 and urinary uromodulin excretion is more pronounced with low salt intake and blunted with high salt intake.8 These data suggest that the GWAS association for hypertension at rs1333226 is mediated through uromodulin and possibly through an effect on sodium homeostasis.

Trudu et al10 and Graham et al9 in a set of complementary experiments provide further evidence for the critical role of uromodulin in sodium balance and hypertension. Graham et al9 showed that UMOD−/− mice had significantly lower systolic BP than the wild-type mice, they were resistant to salt-induced changes of BP, and they demonstrated a shift to the left of the pressure–natriuresis curve.9 Trudu et al10 in contrast showed that UMOD overexpression caused a dose-dependent increase in UMOD expression and excretion associated with increased BP. They also demonstrated that furosemide treatment significantly enhanced natriuresis and reduced BP levels both in the transgenic mouse and in hypertensive individuals homozygous for the uromodulin increasing allele.10 These studies indicate that the link between uromodulin and hypertension is sodium transport in the TAL (Figure 2). Interestingly, TNF-α is also produced by the TAL and acts in an autocrine manner to downregulate NKCC2 expression,61 providing a potential link between the intracellular and extracellular roles of uromodulin in BP control. TNF-α administration has proven to be a potent inhibitor to sodium reabsorption causing exaggerated natriuretic responses and BP-lowering effects.62,63 The notion that TNF exhibits natriuretic effects by direct effects on tubular sodium reabsorption also is supported by the increase in fractional excretion of sodium during TNF infusion in mice and with in vitro studies showing that TNF inhibits epithelial sodium channel activity in distal tubule cells.64,65 The macula densa expresses NKCC2 but not uromodulin. Luminal chloride sensed by the macula densa by NKCC2 enables modulation of GFR through tubuloglomerular feedback.66 Detection of elevated luminal chloride levels triggers the release of signaling molecules from the macula densa, causing constriction of the afferent arteriole and a drop in GFR.66 Two interesting observations may shed some insight into the complex intra- and extracellular role of uromodulin in salt balance. If NKCC2 activity modulated by intracellular uromodulin is the cause of BP variation, then in UMOD−/− mice or humans carrying the low uromodulin genetic variant, low BP should be associated with an activation of the renin–angiotensin system, but evidence for this is lacking.5,68 Furthermore, in humans and salt-loaded UMOD−/− mice, GFR is increased with reduced uromodulin, which is unexpected. This is because the increased sodium chloride in the luminal fluid should lead to the macula densa reducing GFR through tubuloglomerular feedback. This raises the possibility that extracellular luminal uromodulin may interact with NKCC2 in the macula densa to interfere with tubuloglomerular feedback. Although these observations are preliminary, if validated it enlarges the scope of targeting uromodulin both intracellularly and within the tubular lumen (Figure 2).

Future Perspectives

GWAS discovery followed by functional validation has resulted in renewed interest in UMOD and its role in BP regulation. These early functional data while promising highlights the importance of further work that needs to be prioritized to elucidate the underpinning molecular mechanisms. Some of the crucial questions that need to be investigated include the role of uromodulin in maintaining water impermeability in TAL; the effect of uromodulin on NKCC2, macula densa, tubuloglomerular feedback, distal sodium transporters, renin–angiotensin–aldosterone system; and whether immune mechanisms play a role in BP regulation by uromodulin. More importantly, further research in these areas will enable development of a therapeutic application (either novel drug or repurposing an existing drug or a screening diagnostic) for targeted treatment. This is crucial because despite major advances in cardiovascular health, hypertension remains the risk factor contributing most to the overall burden of disease globally and there is a paucity of novel antihypertensive drugs in clinical trials or pharmaceutical development pipeline. More fundamentally, the uromodulin story highlights the power of GWAS in identifying novel pathways of disease.
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Disclosures

None.

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Supplementary Material

Uromodulin, an emerging novel pathway for BP regulation and hypertension
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Insights into uromodulin function from UAKD

Most of the mutations (55) are missense and 3 are in-frame deletions. \(^1\) \(^2\) \(^3\) Mutations reducing either UMOD transcript or encoding for completely truncated protein have not been identified as a cause of UAKD. Similar clinical findings of tubulointerstitial nephritis and hyperuricemia can be associated with mutations in the gene encoding the transcription factor hepatocyte nuclear factor-1b (HNFI\(\beta\)) (TCF2; MIM 137920)\(^4\) and in the REN gene encoding renin (MIM 613093). \(^5\) It is known that the HNFI\(\beta\) positively regulates UMOD expression and binds to the promoter elements of the gene and inactivation of HNFI\(\beta\) in vivo is associated with decreased UMOD transcription. \(^6\) The identified mutations in UMOD cause protein misfolding, which leads to its aberrant intracellular trafficking, retention in ER, altered formation of supramolecular domains on the apical plasma membrane of TAL cells, abnormal UMOD expression in the kidney and decreased urinary uromodulin excretion. The decrease in uromodulin excretion reflects intracellular accumulation of uromodulin in tubular cells, leading to tubulointerstitial injury probably facilitated by ER stress, and lead to progressive renal damage eventually requiring dialysis and renal transplantation. \(^1\) \(^2\) \(^2\) \(^9\) The earliest symptom in UAKD patients is often hyperuricemia that results from reduced fractional excretion of uric acid, is present in \(~80\%\) of patients, and is frequently associated with gout. \(^1\) \(^3\) \(^7\) \(^8\) Mild urine-concentrating ability is an almost constant finding, sometimes resulting in polyuria and polydipsia. It is likely that the primary event is ER accumulation of mutant uromodulin in TAL cells that reduces the amount of uromodulin entering the secretory pathway and affecting a) the trafficking of the wild-type protein and the b) efficient delivery of other transporters in the TAL. Uromodulin is important in keeping the TAL water-tight, and loss of the functional TAL segment would decrease the concentrating ability of the loop of Henle and result in decreased urinary concentration. The urinary concentrating defect precedes the development of renal impairment. The decreased ability to reabsorb sodium in the thick ascending limb would be balanced by an increase in proximal tubular reabsorption of sodium and secondarily of uric acid, resulting in hyperuricemia. \(^2\) Renal cysts in UAKD could be a consequence of progressive TAL cellular damage and secondary proliferation or ciliary dysfunction. \(^9\)

The Umod\(^{A227T}\) mouse revealed some features of that reported in UAKD, such as urine concentration ability defects, reduced fractional excretion of uric acid, and increased accumulation of uromodulin in TAL cells but lacked any inflammation or renal fibrosis. \(^10\) Rampoldi et al generated and characterised the C148W mouse and reported tubulointerstitial fibrosis, inflammatory cell infiltration, tubule dilation, and necrotic distal tubule cells. \(^11\) Furthermore, these mice displayed similar phenotype to UAKD’s in that they show urinary concentration deficits, ER retention of mutant uromodulin, and hyperplasia of the ER membranes.

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