EVOLVING CONCEPTS IN UROMODULIN BIOLOGY, PHYSIOLOGY, AND ITS ROLE IN DISEASE: A TALE OF TWO FORMS

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SUPPLEMENTARY MATERIALS

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Uromodulin Biology

Structure of Uromodulin

The UMOD gene is transcribed and translated into a precursor protein composed of 640 amino acids (AA) (**Figure 1A**). Motifs identified in the Uromodulin primary sequence include a signal peptide (AA 1–24), one epidermal growth factor-like (EGF-like) domain (AA 31–64), two calcium-binding EGF-like domains (AA 65–107 and 108–149), a D8C domain containing eight conserved cysteines (AA 199–287), a fourth EGF-like domain (AA 295–319), one bipartite zona pellucida (ZP)-like domain (AA 334–585), a stretch of mostly hydrophobic amino acids (586-640) that include a consensus cleavage site (AA 587, cleavage at this site by hepsin is essential for polymerization), an external hydrophobic patch (EHP, AA 598–607), and a signal for a glycosylphosphatidylinositol (GPI) anchor (AA 614). The ZP-like domain is essential for assembly into extracellular urinary polymers of supramolecular structure and is composed of the ZP-N (AA 334-426) and ZP-C (AA 505-585) subdomains, separated by 2 small internal hydrophobic patch (IHP) domains at AA 430–436 and 456–462. The 3D structure of a single uromodulin molecule is predicted using AlphaFold[1] and shown in **Figure 1B**. AlphaFold predictions for uromodulin appear to be highly correlative for specific domains, as discussed recently by Jovine[2,3]. The structure of polymerized uromodulin will be discussed more below. There are 48 cysteine residues involved in the formation of 24 intramolecular disulfide bonds[4].

Biosynthesis

Uromodulin maturation along the secretory pathway of polarized tubular cells involves extensive glycosylation that accounts for about 30% of the molecular weight of the protein. N-linked glycans are identified on 8 asparagine AA residues at the following locations: 38, 76, 80, 232, 275, 322, 396 and 513[5]. During post-translational processing in the Golgi apparatus, all high mannose glycans are matured to complex carbohydrates and modified by sialyation, fucosylation or sulfation, except at position N275[6]. Due to the preponderance of acidic amino acid residues and high content of sialic acid, uromodulin is a very acidic protein with an isoelectric point of about 3.5[7]. In addition to N-linked glycans, uromodulin also contains O-linked glycans[8]. The significance of these post-translational modifications for protein function is only partially known and is under investigation.

Cellular trafficking, polarized secretion, and uromodulin forms

The kidney produces and secretes two distinct forms of uromodulin (**Figure 2**): polymerizing uromodulin, lacking the polymerization inhibitory EHP sequence, released by hepsin proteolysis into the urine and non-polymerizing uromodulin with retained EHP sequence, released in the urine and as the major form in the circulation (serum). This is discussed in detail in the main text.

Polymerization of uromodulin is a highly regulated process

The three-dimensional structure of native uromodulin polymers has been recently described by cryo-electron tomography[4,9]. The human uromodulin filament core has a zig-zag shaped backbone formed by polymerized ZP domains and protruding arms (branches) composed of the EGF and D8C domains. The dissociation of EHP upon hepsin cleavage induces a conformational change in the ZP-N/ZP-C linker region that wraps two monomers interacting head-to-tail (ZP-N-to ZP-C), thereby linking three consecutive monomers. EHP dissociation and head-to tail incorporation of uromodulin monomers into a growing filament are coupled processes that occur in synchrony at the plasma membrane[9]. It is believed that N-glycans likely play a role in polarized sorting to the apical membrane[10]. These novel developments indicate the production of polymerizing uromodulin is a highly regulated process, which is important to consider when studying its physiology and role in disease.

Uromodulin expression and production

How to report uromodulin expression and production by the kidney

As the studies on uromodulin have significantly increased in the last few decades, the nomenclature of how to report uromodulin has become blurred. Uromodulin expression is reported from kidney tissue specimens (human, rodents) and can be at the RNA or protein levels (**Table S1**). The heterogeneous distribution of TALs across various areas within the kidney could become a problem when reporting uromodulin expression because it introduces bias. For example, cortical tissue will have less TAL cells than medullary tissue. Accounting for such variability in the analysis is difficult. To address this problem, one could normalize the expression of uromodulin to NKCC2, the latter reflecting the abundance of TAL cells[11]. However, such an approach may introduce additional confounders, as NKCC2 expression is more abundant in the medullary TALs (mTAL) than cortical TALs (cTAL)[12]. Therefore, when using human kidney tissue specimens, it is important to use anatomically and histologically comparable areas to quantify expression at a bulk level, particularly in the cortex where the presence of TAL-rich medullary rays may shift the abundance of uromodulin expression (**Figure 3**). In rodent kidneys, this could be more controllable, by using equivalent areas in the cortex or medulla or include whole kidneys for analysis and adjust for weight. Newer imaging or spatial based RNA/protein approaches or single cell RNA analysis may circumvent these shortcomings since the expression can be normalized at the cell or regional level[13,14].

Because of complex regulatory mechanisms governing the expression of uromodulin, it is important to standardize the clinical and physiological variables when measurements of this protein are performed. We emphasize that the unadjusted urine concentration of uromodulin has a distinct relevance compared to the uromodulin adjusted to urine Cr. The latter is shown to correlate with timed secretion uromodulin and likely will reflect the rate of secretion[15,16], hence indicating the appropriateness of the tubular response and reserve. Unadjusted urine uromodulin, which is determined by the rate of secretion, is expected to be very relevant to the functions of uromodulin along the urinary tract, such as TAL impermeability and urinary defense, which may be dependent on specific concentrations of uromodulin in the urine. Of note that some have advocated the reporting of uromodulin adjusted to kidney function[16,17], and this is discussed further in the main text in the section on uromodulin and nephron mass.

Experimental interventions that regulate uromodulin expression

Several experimental interventions in humans and rodents that can alter the rate of uromodulin expression or production (reported as Cr adjusted concentration or amount released per time, such as 24 hours) have been reported (**Table S1**). Some of these interventions are not physiologic, such as inducing kidney injury or administration of pharmacological agents. Other interventions such as water or salt loading and administering of hormones such as DDAVP (known to act on TAL cells and regulate osmolarity) offer insights into uromodulin biology. For example, around 40 years ago, Lynn *et al*. studied 5 patients and showed that rate of urinary uromodulin secretion in 2-hour timed collections measured by radioimmunoassay correlated with increased urine volumes induced by water intake [18]. Although the effect of increased water intake and urine volume had variable results in rodents, the link between urine volume and uromodulin production was supported by a large observational study showing that 24-hour Uromodulin levels positively correlated with urine volumes [19]. Administration of AVP, which is known to activate and alter the expression NKCC2 and increase urinary concentration, decreases the expression and rate of secretion of uromodulin[20,21], but can also cause an initial acute release of uromodulin in the urine[22]. These observations support that the rate of uromodulin production is variable and likely highly regulated by multiple factors such as water intake, urine flow, salt intake and AVP.

Genetic factors determining uromodulin expression and secretion

The UMOD promoter is likely regulated by a large network of interacting transcription factors[23]. One of those transcription factors, hepatocyte nuclear factor 1 β has been shown to activate uromodulin expression[24]. Common SNPs around and within the UMOD gene area have been linked with uromodulin levels in the urine and in the serum, and these are summarized in **Table S4**. There is also a link between variants and uromodulin expression in the kidney, but this link may be context dependent as it is not consistently significant in healthy tissue but becomes significant in the setting of disease[25]. In addition, the regulation of uromodulin expression and/or secretion appears complex, as variants that are far from the UMOD gene even on separate chromosomes have been linked to levels in the urine or circulation (**Table S4**). It is also possible that the variants in the UMOD region regulate other genes. The reader is referred to other resources that discuss these in more details[26,27].

Overview of functions and sites of action of uromodulin

The functions of Uromodulin are summarized in **Figure 4**. In the main text, we discuss the role of uromodulin in hypertension and vascular biology. In the sections below, we discuss evolving concepts in other areas such as acute kidney injury (AKI), renal and systemic stress signaling, chronic kidney disease (CKD), AKI to CKD transition, systemic and kidney injury, urinary defense and immunomodulation.

Role of uromodulin in AKI: a vicious cycle where AKI causes uromodulin deficiency and uromodulin deficiency increases the risk and severity of AKI

AKI causes acute uromodulin deficiency in the kidney and systemically:

A significant decrease in uromodulin mRNA and protein early after ischemia-reperfusion injury (IRI) has been consistently demonstrated by our group[28,29] and others[30-32]. We have shown that IRI suppresses the transcription and release of uromodulin towards the interstitium and circulation[28]. The magnitude and duration of uromodulin deficiency is proportional to the severity of injury [29] and occurs early. Of note, impaired uromodulin expression also occurs in forms of AKI other than IRI, such as cisplatin toxicity[33]. Therefore, the decrease in uromodulin is a cardinal feature of AKI. The mechanism of the decrease in uromodulin is likely complex and occurs despite relative preservation of TAL cell integrity during injury[34], which suggests a dynamic response, rather than loss of TAL cells, as a cause for uromodulin deficiency in AKI. This preservation was initially described by Sarfristein *et al.* in ischemic and nephrotoxic injury models[30]. We recently extended these findings to the bedside with specific relevance to non-polymerizing uromodulin, by showing that serum uromodulin levels drop significantly within 18 hours from post-surgical AKI[35]. Furthermore, in a cohort of kidney transplant donors with varying AKI etiologies, Mansour *et al.* that urinary uromodulin is significantly decreased in AKI and the drop is proportional to the severity by KDIGO scoring[36].

Uromodulin deficiency increases the severity of AKI:

We have demonstrated in multiple studies using $UMOD^{-/-}$ and $UMOD^{+/+}$ mice that uromodulin deficiency itself increases the severity of AKI through upregulation of chemokine signaling in proximal tubules that stimulates neutrophil infiltration and injury[28,34,37]. Specifically, uromodulin deficiency enhances RAC1/JNK/c-Jun signaling and proinflammatory cytokine (CXCL2, IL-23) expression in proximal epithelial cells[34,35,38]. Since basolaterally released uromodulin encounters the renal interstitium before reaching the circulation, the interaction between uromodulin and proximal tubule

stress signaling is likely to be a result of direct paracrine action. Uromodulin is also an important determinant of renal mononuclear phagocyte (MPC) abundance and polarization to M2 phenotype during AKI, with UMOD$^{-/-}$ mice showing increased M1 inflammatory signaling and decreased macrophage chemokine/growth factor signaling as well as a failure to upregulate M2 signaling during the repair phase of recovery. Furthermore, administration of a non-polymerizing form of uromodulin in mice improved recovery from AKI, and caused an increase in CD206^{+} MPCs, suggesting an important role of uromodulin in polarization of MPCs towards a healing phenotype[39]. These results also suggest that uromodulin could be developed as a biological therapeutic for use in clinical AKI. These findings are translating into clinical applications, since we recently showed that low admission plasma uromodulin was correlated with increased risk of in-hospital AKI, independently of kidney function and other co-morbidities[40]. This is in addition to the growing body of literature showing that low serum and urine uromodulin is associated with increased risk of incident kidney disease and progression[41-47] (**Table S5**).

AKI recovery is associated with overexpression of uromodulin and increase basolateral shift towards interstitium and serum:

During recovery from AKI, there is a significant increase in uromodulin expression in TAL cells and a shift towards the interstitium and circulation[28], where uromodulin particularly localizes at the basolateral domain of S3 segments. We showed previously that this increase is essential in terminating inflammatory signaling[28,34], and that uromodulin is playing an important role in shaping the response of renal MPCs and their potential role in kidney recovery[39]. Since interstitial/serum uromodulin is predominantly hepsin independent[48], this data suggests that recovery is marked by at least activation of the path to produce non-polymerizing uromodulin. Further studies are needed to define the role of injury on specific forms of uromodulin and better understand the cellular processes that are regulated, so that therapies to modulate production of uromodulin could be developed.

Novel molecular insights into the impact of uromodulin to limit stress signaling systemically and in proximal tubules

Using unbiased transcriptomics and proteomics, we recently showed that uromodulin deficiency induces oxidative stress in renal proximal tubules (measured by orthogonal methods: peroxide measurements, intravital reporters, redox molecules)[35] . We confirmed that the elevated reactive oxygen species burden caused cellular damage, because of increased lipid oxidation (targeted lipidomics) and by alterations in mitochondrial morphology[35]. These findings further explain the increased susceptibility of UMOD$^{-/-}$ mice to AKI, particularly by showing that proinflammatory cytokines such as IL-23 are downstream from oxidative injury. Since AKI itself induces uromodulin deficiency, it is possible that the oxidant injury typically seen with AKI is caused by acute uromodulin deficiency. Furthermore, CKD is a state of uromodulin deficiency and could in itself predispose individuals to oxidant injury independently of the level of kidney function.

As discussed, we established that uromodulin inhibited the activation of Rac1/JNK/c-Jun in proximal epithelial cells in the kidney[35]. The transient receptor potential cation channel, subfamily M, member 2 (TRPM2) channel has been linked to activation of Rac1 and its role in oxidant injury within the kidney[49]. TRPM2 is activated by ROS and itself causes more downstream oxidative stress[50]. Therefore, during AKI, there will be a positive feedback loop between TRPM2 and ROS that needs to be interrupted. The plasma membrane presence of TRPM2 makes it an ideal target for interstitial/circulating uromodulin[49]. Indeed, we demonstrated that uromodulin inhibited TRPM2 activity using a HEK-293 recombinant cell line expressing an inducible copy of TRPM2, in which channel-specific activation can be monitored by measuring the kinetics of calcium influx[35]. We also treated UMOD$^{-/-}$ mice with the TRPM2 inhibitor 2-aminoethoxydiphenyl borate (2-APB) and found that 2-APB significantly lowered systemic oxidative DNA damage in these mice. To extend these findings to AKI,

we showed that pretreatment of both the UMOD$^{+/+}$ and UMOD$^{-/-}$ mice with 2-APB significantly reduced systemic oxidative damage after IRI. The difference in oxidative damage seen between these mice was lost upon treatment with 2-APB, implying that TRPM2 is a main target for the inhibitory effect of uromodulin on systemic oxidative stress. These developments provide evidence that uromodulin is an important inhibitor of systemic and renal oxidant injury, and its effect occurs through inhibiting the activation of TRPM2.

The implications of these findings have ramifications for CKD, which is a chronic state of uromodulin deficiency[43,51]. Findings from this research may imply that the observed uromodulin deficiency is a major contributor to the pro-inflammatory phenotype and maladaptive responses seen in advanced CKD by inducing systemic oxidative stress[52,53]. The effect of uromodulin deficiency on increased systemic oxidative stress may be a factor in the increased mortality and cardiovascular complications associated with low serum uromodulin levels[54-57] (**Table S5**).

The role of uromodulin in adaptive vs. maladaptive repair and AKI to CKD transition

AKI is a major cause of CKD[58-62], and mounting evidence suggests that the transition from AKI to CKD occurs through maladaptive repair[63-65]. After decreased expression of uromodulin during AKI, early recovery is characterized by a significant increase in uromodulin expression in TAL cells and a shift in trafficking towards the interstitium and circulation[28]. We showed previously that this increase is essential in terminating inflammatory signaling, and that recovery in the setting of uromodulin deficiency is significantly delayed[28]. Therefore, it is likely that uromodulin has a role in preventing progression of kidney injury towards fibrosis, and if uromodulin deficiency persists post AKI (examples include very severe AKI or AKI in existing CKD), the outcome will be deleterious. Maydan *et al.* demonstrated that uromodulin reduced KIM-1 levels in human renal adenocarcinoma cells and UMOD$^{-/-}$ mice had higher levels of KIM-1[66]. Since persistent KIM-1 expression is associated with maladaptive repair and progression to CKD[67], it is possible that failure of uromodulin upregulation post AKI could lead towards maladaptive repair. We propose that persistent uromodulin deficiency post AKI promotes fibrosis, possibly through activation of TRPM2 and persistent oxidant injury and activation of a maladaptive repair program. This paradigm is supported by a recent study by Puthumana *et al*, showing that higher uromodulin levels in the urine 3 months post-hospitalization are associated with decreased risk of incident CKD and CKD progression[68]. This was corroborated by experimental studies showing higher levels of uromodulin in models of repair after AKI[68].

Role of uromodulin in CKD

We have discussed previously our interpretation of the data both from experimental models and human clinical studies[27]. Multiple experimental studies, including studies in in UMOD$^{-/-}$ mice and the recent work by Puthumana *et al*[68], have demonstrated a protective role for uromodulin in progressive kidney injury. This was corroborated by observational and prospective clinical studies, supporting that a higher level of uromodulin in the urine or circulation, independently of kidney function (**Table S5**). Based on these data, having higher uromodulin levels at any stage is associated with benefits, and this was also supported by histological data in kidney biopsies where uromodulin production rate was higher in patient with preserved tubules[16], and that was recently also shown in an experimental model[68]. Interestingly, studies investigating variants in the UMOD locus have suggested an opposite effect, where protective variants have been associated with low levels of urinary and serum uromodulin[11,69,70]. It is possible that the relation between UMOD locus and outcomes is mediated by uromodulin expression and hypertension[11,71], especially since the link between UMOD variants and expression may depend on disease context and is not very clear in healthy kidney tissue[25]. However, other factors should be considered, particularly with the strong preclinical models of uromodulin deletion[28,72] and the mounting clinical data (**Table S5**), including prospective studies showing that higher uromodulin levels in the urine and serum (independent of kidney function) are associated with

incident kidney disease[42,68], which argue against a reverse causation mechanism[70]. In fact, the UMOD locus may be independently associated with systemic and kidney outcomes[41,42]. The area around the UMOD loci and surrounding genes is likely a unique site affecting many genes within the kidney that are associated also with kidney function[73]. The independent association between UMOD loci and outcomes need to be further evaluated, and this will help better understand and interpret recent Mendelian randomization studies[69,70]

In summary, despite remaining areas of unclarity but of great importance pertaining to the role of the UMOD loci variants, there is a lot more evidence than not, that uromodulin has a protective role in kidney disease and progression (**Table S5**). Uromodulin is reactively increased in states of injury, and the inability to mount such a functional tubular response confers a bad prognosis. Uromodulin deficiency is more likely a state of high risk for renal and cardiovascular complications, and strategies to mitigate or enhance the abundance of uromodulin in specific settings, particularly as we know more about the differential functions of the polymerizing vs non-polymerizing forms. A better understanding of the role of uromodulin in CKD would then inform the development of therapeutics that could be guided by the level of this protein.

Uromodulin in infections and immunity

Since its discovery in the early 1950's by Tamm and Horsfall, uromodulin's identity as a modulator of the immune response to infectious disease has been well established. It was originally described as an inhibitor of viral hemagglutination[74,75]. Before it was known that the Tamm-Horsfall Protein was identical to uromodulin, it was discovered again in 1985 by Muchmore and Decker, who characterized its urinary form as an inhibitor of T-cell and monocyte activity *in vitro*[76].

Given its high abundance in the urine, early studies of uromodulin in infection and immunity focused on its potential role in urinary tract infections (UTIs). While early studies in patient populations found that patients with urinary tract infections and pyelonephritis developed autoantibodies to uromodulin[77,78], by the early 1990's there was growing evidence that levels of aggregated uromodulin were correlated with risk for UTIs[79,80]. This led to studies with purified urinary uromodulin, which was found to bind to type 1-fimbriated *E. coli*[81,82], likely through its highly conserved high mannose residues[83] which are capable of interacting with the FimH adhesions[84,85]. The development of a uromodulin knockout mouse in the early 2000's further supported a protective role for uromodulin in UTI, as $UMOD^{-/-}$ mice showed increased susceptibility to colonization of the bladder by type 1-fimbriated *E. coli*[86]. By 2005, uromodulin was well accepted as protective in the setting of urinary tract infection[87]. Recent studies have reinforced this role, with a prospective longitudinal cohort study demonstrating that higher urinary uromodulin was protective against UTI[88] and an observational cohort study finding that UTI patients with bacteremia were more likely to be unable to produce uromodulin[89]. This has led some to propose that the beneficial effect of higher urinary uromodulin granted a selective advantage to humans living in areas with high pathogen diversity or prevalence of antibiotic-resistant UTIs, which could explain the high allelic frequency of a UMOD promoter SNP variant that is positively correlated with urinary uromodulin levels, despite the identification of this SNP as a risk factor for CKD[90]. Recent cryo-electron tomography studies have conclusively demonstrated how polymerized uromodulin binds to urinary pathogens to prevent their adhesion to the urinary tract and promote their clearance by presenting specific epitopes able to bind bacterial type 1 pilus adhesins on regularly spaced protruding arms that extend from the uromodulin filament[5]. These findings suggest that devising strategies to enhance the release of polymeric uromodulin in patients with chronic or recurrent UTI could improve outcomes in these patients and further underscores the need to understand the physiological determinants of polymeric uromodulin expression.

Uromodulin's role in immunity and infection extends beyond the urinary tract. Many of the early *in vitro* studies characterizing uromodulin's immune regulatory properties were done with the polymerized urinary form, which appears to be differentially glycosylated in pregnant women[91]. This form acts as a pro-inflammatory molecule, activating the expression of pro-inflammatory cytokines[92] including that of Il-1β through the NLRP3 inflammasome[42] leading to its characterization as a Damage Associated Molecular Pattern (DAMP). Aggregated uromodulin can also bind to components of the complement cascade[93] as well as cytokines[94,95] and tumor necrosis factor[96], leading some to propose it may act as a cytokine sink. Treatment of neutrophils with urinary uromodulin shows that it can bind to and functionally inhibit neutrophils via Siglec-9, reducing their ability to generate reactive oxygen species, undergo chemotaxis and kill pathogens[97]. However, it is important to note that uromodulin in the serum is primarily not aggregated[39] and thus the extension of these findings beyond the urinary tract should be limited. Indeed, uromodulin knockout mice have multiple immune system defects. These mice have decreased mononuclear phagocyte levels (MPC) within the kidney, and the MPCs that are found in $UMOD^{-/-}$ mice have decreased plasticity and phagocytic activity[39], which inhibits their function in recovery from kidney injury. These mice also exhibit systemic neutrophilia[97] downstream of activation of the IL-23/IL-17 axis[38]. Consistent with these immune defects in mice, lower serum uromodulin is associated with an increased risk of fatal infections from any source in a cohort of coronary angiography patients[54]. Taken together, these results suggest that uromodulin confers protection against infection that extends beyond the urinary tract. Furthermore, systemic levels of uromodulin increase in humans and animal models of sepsis, and we recently showed that circulating uromodulin is protective in this setting[98].

Future challenges: a call to action

There are important roadblocks in the field that hinder more efficient translation and the application of uromodulin as an important theragnostic marker. In particular, it is imperative to develop standardized methods to measure and report uromodulin in the urine and circulation, which will also help define "normal" ranges and perform multicenter studies that allow application of uromodulin measurements to clinical use. Another area of need is to devise a common nomenclature that defines the significance of uromodulin measurements, particularly as indicator of the functional tubular response.

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Supplementary tables

Interventions	Kidney		Urine				Serum			
	Protein	RNA	Concentration	Western	Concentration /Cr	Secretion rate (mg/time)	Concentration	Species	Authors	Reference number (SR)
Water Handling and Diuresis										
Water Intake/loading						↑		H	Lynn	99
						↑		M	Catalano	100
						↔		R	Bachmann	20
	↔							R	Ecelbarger	21
						↑		R	Thulesen	101
Vasopressin	↓							R	Ecelbarger	21
Desmopressin	↓			↑				M	Nanamatsu	22
						↓		R	Bachmann	20
Furosemide						↑		H	Dulawa	102
						↔		R	Bachmann	20
Vasopressin + Furosemide	↑							R	Ecelbarger	21
Salt Handling and Cationic Ions										
Salt intake	↑	↑						R	Ying	103
						↑		H	Torffvit	104
						↓	↓	H	Du	105
Salt loading	↔			↑				M	Olinger	106
	↔	↓				↓		R	Mary	107
CasR Activation					↓			H	Tokonami	108
Injury										
High protein diet						↑		R	Bachmann	20
Streptozotocin	↓	↓	↑			↑		R	Rasch	109
						↑		R	Thulesen	101
IRI	↓	↓						M	Heitmeier	29
		↓						R	Safristein	32
		↓						R	Yoshida	31
							↓	M	LaFavers	35
IRI Recovery	↑						↑	M	El-Achkar	28
Ethylene Glycol			↔					R	Li	110
Sodium Oxalate	↓							R	de Araujo	111
hydroxyl-L-proline	↓							R	Huang	112
BP Lowering					↔			H	Malhotra	113

Table S1: Effect on experimental interventions on uromodulin expression and secretion rate and concentration in kidney urine and circulation. Colors reflect direction of uromodulin with intervention. Blue: Decease; Red: Increase; Grey: no change- Species: Human (H); Rat (R), Mouse (M). CasR - Calcium sensing receptor, IRI - ischemia reperfusion injury, BP - blood pressure, SR- supplemental references

Variables	Urine				Serum		
	Concentration	Concentration/Cr	secretion rate (mg/time)	Uromodulin per unit GFR	Concentration	Authors	Reference number (SR)
Demographics							
Sex	**Males higher**				**Females higher**	Steubl	114
					Females higher	Delgado	54
					Females higher	Then	56
		Females higher	**No difference**			Glauser	15
	No difference	**Females higher**	**No difference**			Pruijm	19
	No difference					Bakhoum	115
					Females higher	Scherberich	43
			No difference			Thornley	16
Age					**None, older adults**	van Donge	116
					- older adults	Leiherer	42
					- adults	Delgado	54
Body size		**+**				Glauser	15
			None			Thornley	16
Disease							
CKD			**-**			Lynn	18
		-	**-**	**+**	**-**	Thornely	16
					-	Leiherer	42
					-	Sjaarda	70
	+					Kottgen	117
	-		**-**			Nqebelele	118
					-	Fedak	119
ESKD				**-**	**-**	Lv	120
Early Diabetes			**+**			Zimmerhackl	121
			+			Torffvit	122
			+			Pfleiderer	**123**
Diabetes					**-**	Then	124
	-				**None**	Steubl	114
			None			Torffvit	125
					-	Delgado	54
Diabetic kidney disease					**-**	Bjornstad	126
			-			Torvffit	127
					-	Bjornstad	128
HTN	**-**				**None**	Steubl	114
					-	Delgado	54
					-	Leiherer	42
AKI					**-**	LaFavers	35
	-					Mansour	36
					-	Kusnierz-Cabala	129
	-					Bennet	130
	-					Askenazi	131
	-					Askenazi	132
	-					Zhang	133
	-					Sweetman	134

GN					-	Scherberich	43
SLE-nephritis	-					Bedair	135
					-	Scherberich	43
Stone unspecified			+			Jaggi	136
		None				Thornley	16
Stone-initial	-					Wai-Hoe	137
Stone – recurrent		-				Romero	138
	None					Wai-Hoe	137
		-				Glauser	15
			+			Singh	139
CAD					-	Delgado	54
Heart failure					-	Delgado	54
Metabolic syndrome					-	Then	140
Interstitial Cystitis	-					Canter	141

Table S2: Demographic and disease variable association with uromodulin expression and production. Colored boxes reflect reported associations between demographic or disease parameters and uromodulin levels. Blue color reflects negative correlation. Red represents positive correlation. Gray denotes no significant association. Older adults defined as all groups having a mean age greater than 60 years. Adults defined as all groups having a mean age greater than 40 years. CKD - chronic kidney disease, ESKD – end stage kidney disease, HTN – hypertension, AKI – acute kidney injury, GN – glomerulonephritis, SLE – systemic lupus erythematosus, CAD – coronary artery disease

Variables	Urine				Serum		
	Concentration	Concentration/ Cr	secretion rate (mg/time)	Uromodulin per unit GFR	Concentration	Authors	Reference number (SR)
Laboratory Parameters							
SBP	None					Bakhoum	115
					-	Delgado	54
Hypertension					-	Then	57
LDL					+	Delgado	54
HDL					+	Delgado	54
Triglycerides					-	Delgado	54
Fasting glucose					-	Delgado	54
HbA1c					-	Delgado	54
WBC Count					-	Then	142
CRP					-	Then	142
					-	Leiherer	42
					-	Steubl	114
					-	Delgado	54
Adipokines					-	Then	143
eGFR					+	Risch	144
					+	Then	145
					+	Leiherer	42
	+				+	Steubl	114
					+	Steubl	44
			+		+	Thornley	16
		+				Troyanov	146
					+	Delgado	54
					+	Usui	147
					+	Fedak	119
					None	Enko	148
	+	+				Ponte	69
	+				None	Prajczer	149
					+	Scherberich	43
					+	Kusnierz-Cabala	129
Cystatin C					-	Delgado	54
Renin					-	Delgado	54
Uric acid					-	Delgado	54
PTH					-	Delgado	54
Vitamin D					+	Delgado	54
Gestational Age	+					Saeidi	150
	+					DeFreitas	151
Birth weight			+			Pivin	152
Citrate excretion		+				Glauser	15
Coronary Calcification					-	Bjornstad	126
NT-proBNP					-	Delgado	54
Kidney Histology							
Tubular atrophy	-				-	Prajczer	149
				-		Thornley	16

Table S3: Association of laboratory parameters with uromodulin levels. Colored boxes reflect reported associations between laboratory parameters and uromodulin levels. Blue color reflects negative correlation.

Red represents positive correlation. Gray denotes no significant association. SBP – systolic blood pressure, LDL – low density lipoprotein, HDL – high density lipoprotein, HbA1c – Hemoglobin A1C, WBC – white blood cell, CRP – c-reactive protein, eGFR – estimated glomerular filtration rate, PTH – parathyroid hormone, NT-proBNP – N-terminal pro-brain natriuretic peptide

Chromosome	SNP	Gene	Urine			Kidney	Serum		
			Concentration	Concentration /Cr	secretion rate (mg/time)	RNA	Concentration	Authors	Reference number (SR)
2	rs2438298	CAB39						Olden	153
7	rs55791829 (C)	PRAKG2					-	Li	154
	rs55791829 (G)						+	Li	154
11	rs1532763	SORL1						Olden	153
	rs2855800	KCNJ1						Olden	153
15	rs9672398 (G)	WDR72		-				Joseph	155
	rs9672398 (T)			+				Joseph	155
16	rs12446492 (A)	PDILT		-				Troyanov	146
	rs12446492 (T)			+				Troyanov	146
	rs12917707 (T)	UMOD		-				Olden	153
				-				Shlipak	156
							-	Delgado	54
			-	-				Ponte	69
					-			Ponte	157
	rs12917707 (G)			+				Olden	153
				+				Shlipak	156
							+	Delgado	54
			+	+				Ponte	69
					+			Ponte	157
	rs12934455 (T)	UMOD	-					Joseph	155
	rs12934455 (C)		+					Joseph	155
	rs13333226 (G)	UMOD		-				Padmanabhan	158
			None	None				Nqebelele	118
	rs13333226 (A)			-				Padmanabhan	158
			None	None				Nqebelele	118
	rs13335818 (T)	UMOD					-	Leiherer	42
				-				Joseph	155
	rs13335818 (C)						+	Leiherer	42
				+				Joseph	155
	rs34882080 (G)	UMOD				-		Stanzick	159
	rs34882080 (A)					+		Stanzick	159
	rs4293393 (C)	UMOD		-				Troyanov	146
			-					Kottgen	117
	rs4293393 (T)			+				Troyanov	146
			+					Kottgen	117
	rs77924615 (A)	PDILT	-	-				Joseph	155
						-		Stanzick	159
							-	Li	154
	rs77924615 (G)		+	+				Joseph	155
						+		Stanzick	159
							+	Li	154
17	rs8067385 (C)	KRT40	-					Joseph	155
	rs8067385 (G)		+					Joseph	155
	rs7224888 (T)	B4GALNT2					-	Li	154
	rs7224888 (C)						+	Li	154

Table S4: Association of single nucleotide polymorphism (SNP) variants with uromodulin expression and levels. Blue and red boxes represent negative and positive correlations, respectively. Grey boxes show no association. Black box color indicates specific nucleotide variant not specified.

Outcomes	Urine		Serum		
	Concentration	Concentration/Cr	Concentration	Authors	Reference number (SR)
Incident CKD	↔			Shlipak	156
			↓	Leiherer	42
	↓			Garimella	160
	↓			Puthumana	68
CKD progression	↓			Garimella	161
	↓			Jotwani	162
	↓			Steubl	163
	↓			Garimella	160
	↓			Puthumana	68
			↓	Steubl	47
			↓	Then	145
		MR study, ↑		Ponte	69
			MR study, ↑	Sjaarda	70
Incident AKI			↓	Patidar	40
	↓			Bullen	164
		↓		Garimella	165
Death	↓			Garimella	161
	↓			Garimella	160
			↓	Steubl	47
			↓	Steubl	55
			↓	Delgado	54
			↓	Then	56
CVD	↓			Garimella	166
			↓	Steubl	47
			↓	Steubl	55
			↓	Then	56
			↓	Leiherer	167
Allograft failure			↓	Bostom	168
DGF			↓	Scherberich	43
UTI	↓			Garimella	88

Table S5: Association of uromodulin levels with outcomes. Blue and red boxes represent decreased and increase risk (adjusted for confounders). Grey box indicates no association. CKD – chronic kidney disease, AKI – acute kidney injury, CVD – cardiovascular disease, DGF – delayed graft function, UTI – urinary tract infection, MR – Mendelian randomization