Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.1342-22
Intern Med 63: 17-23, 2024
http://internmed.jp

【 REVIEW ARTICLE 】

The Versatile Role of Uromodulin in Renal Homeostasis and Its Relevance in Chronic Kidney Disease

Tomoaki Takata and Hajime Isomoto

Abstract:

Uromodulin, also known as the Tamm-Horsfall protein, is predominantly expressed in epithelial cells of the kidney. It is secreted mainly in the urine, although small amounts are also found in serum. Uromodulin plays an important role in maintaining renal homeostasis, particularly in salt/water transport mechanisms and is associated with salt-sensitive hypertension. It also regulates urinary tract infections, kidney stones, and the immune response in the kidneys or extrarenal organs. Uromodulin has been shown to be associated with the renal function, age, nephron volume, and metabolic abnormalities and has been proposed as a novel biomarker for the tubular function or injury. These findings suggest that uromodulin is a key molecule underlying the mechanisms or therapeutic approaches of chronic kidney disease, particularly nephrosclerosis and diabetic nephropathy, which are causes of end-stage renal disease. This review focuses on the current understanding of the role of uromodulin from a biological, physiological, and pathological standpoint.

Key words: aging, biomarker, chronic kidney disease, hypertension, nephron mass, renal tubule

(Intern Med 63: 17-23, 2024)
(DOI: 10.2169/internalmedicine.1342-22)

Introduction

Chronic kidney disease (CKD) is a public health burden and an emerging risk factor for end-stage renal disease (ESRD), cardiovascular disease, and mortality (1-3). The prevalence of CKD increases with age and is significantly higher in hypertensive populations than in normotensive ones (4); therefore, with the increase in the elderly population of Japan, CKD is becoming a common disease. This epidemiological finding may partly underlie the recent changes in the etiology of ESRD.

Diabetic nephropathy has been the most common primary disease among incident dialysis patients in Japan since 1998 (5), but the percentage has remained nearly unchanged for the past few years. In contrast, the percentage of patients with nephrosclerosis has increased, becoming the second-most common cause of ESRD (6). Therefore, it is important to appropriately manage diabetes, hypertension, and other CKD-related conditions. Therapies targeting blood pressure, glucose, and other metabolic abnormalities can slow the progression of CKD (7); however, the detailed mechanisms underlying these therapeutic approaches are not fully understood. Furthermore, no biomarkers have been directly linked to the mechanism of CKD. These limitations highlight the need to elucidate the underlying mechanisms and identify causal biomarkers of CKD.

Uromodulin, also known as the Tamm-Horsfall protein, is a glycoprotein that is predominantly expressed in kidney epithelial cells. Rare mutations in the *UMOD*, a gene that encodes uromodulin, have been known to cause autosomal dominant tubulo-interstitial kidney disease (ADTKD) (8). Recent genome-wide association studies (GWASs) have revealed various genetic loci associated with the renal function and risk of CKD in European and Asian populations, including the Japanese population (9, 10). Among these, the locus *UMOD* shows a remarkable association with the renal function (9). The relevance of variation in the *UMOD* locus to CKD was also evident in another study, which showed its influence was stronger among older adults than younger ones (11). Furthermore, the *UMOD* locus is associated with hypertension (12). Recent advances in the investigation of uromodulin and its relevance to kidney diseases have changed our understanding of rare inherited diseases to

Division of Gastroenterology and Nephrology, Faculty of Medicine, Tottori University, Japan
Received: November 24, 2022; Accepted: December 6, 2022; Advance Publication by J-STAGE: January 15, 2023
Correspondence to Dr. Tomoaki Takata, t-takata@tottori-u.ac.jp

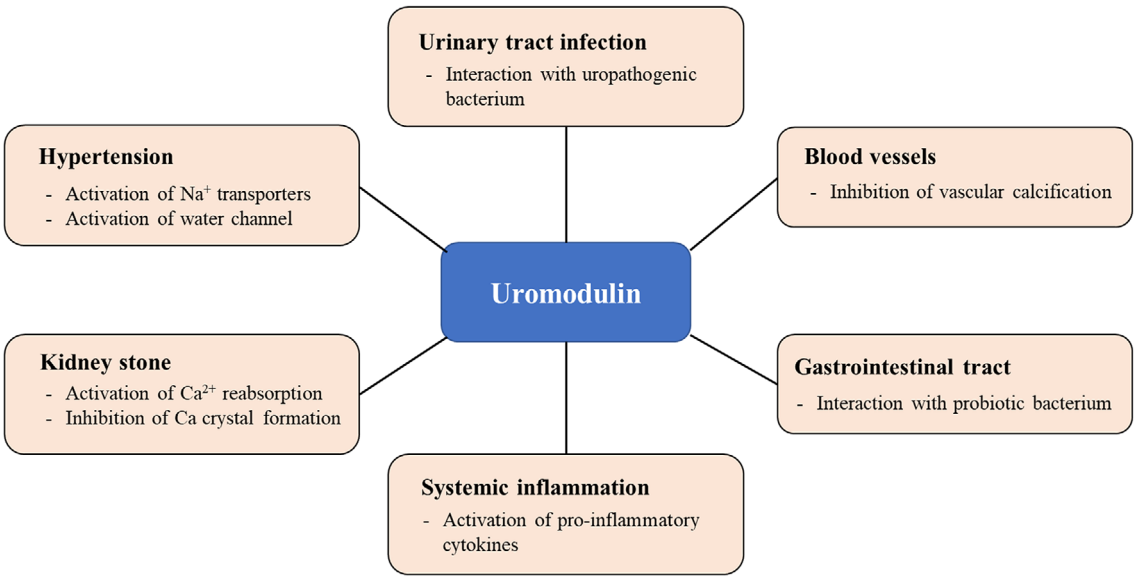

Figure 1. Local and systemic roles of uromodulin. Uromodulin is proposed to be involved in urinary tract infection, blood pressure regulation, kidney stone formation, and immunomodulation.

common CKD. These observations suggest that uromodulin may be a clue to understanding the underlying mechanism of CKD, particularly for age-related or hypertensive nephrosclerosis, thus providing a novel therapeutic target.

In this review, we will summarize the current understanding of the biology, function, and relevance of uromodulin in clinical practice.

Biology of Uromodulin

Uromodulin, or Tamm-Horsfall protein, is the most abundant protein in urine. Its structural components include a leader peptide, epidermal growth factor-like domains, cysteine-rich domain (D8C), and zona pellucida domain (13). The leader peptide directs its insertion to the endoplasmic reticulum (ER) (14). Because uromodulin has a complex structure with many cysteine residues involved in the formation of disulfide bonds, its processing in the ER is important for the maturation of uromodulin (15). Mature uromodulin is mainly accumulated in the apical membrane by polarized trafficking and is then secreted into the urine via proteolytic cleavage by the serin protease hepsin (16). Previous investigations evaluating ADTKD pathophysiology have revealed that mutant uromodulin alters membrane trafficking, resulting in decreased urinary uromodulin secretion (17-19). Defective transport of mutant uromodulin in turn causes its accumulation in the ER, leading to ER stress and inflammation (20-23). In addition to membrane trafficking, defective urinary secretion of uromodulin causes stress in the ER and renal injury. In a mouse model with mutant hepsin, deficient cleavage of uromodulin induced the intracellular accumulation of uromodulin and ER stress (24).

Hepsin also regulates the uromodulin structure in urine. Physiological cleavage by hepsin releases a zona pellucida domain that mediates the polymerization of uromodulin (16). Due to its ability to polymerize and form filaments, uromodulin can trap uropathogens or inhibit the interaction between the gallbladder epithelium and uropathogenic bacteria (13). Based on these biological and structural features, uromodulin is known to protect against urinary tract infections (UTIs). A protective role in UTIs is evident in the clinical setting. In a case-control study of UTI patients, patients with low urinary uromodulin levels were more common in the bacteremia group than those without bacteremia (25). The relevance of urinary uromodulin to UTIs was further demonstrated in a study of 953 subjects, in which elevated urinary uromodulin levels were associated with a decreased risk of UTIs (26). Recent investigations of the three-dimensional structure of urinary uromodulin by cryo-electron tomography have shown a polymerized zona pellucida domain with protruding arms of an epidermal growth factor-like domain and D8C (27). Most of the previously identified *UMOD* mutations in ADTKD were located in exon 4, which encodes D8C (28-30); however, the biological functions of D8C have not yet been elucidated.

Functions of Uromodulin

Overview

Uromodulin has been shown to have pleiotropic roles in renal homeostasis and systemic inflammation (Fig. 1). Among these, its regulatory roles in the tubular epithelial cell function have been extensively studied. The *UMOD* gene is evolutionally conserved in all vertebrates (31). Uromodulin is predominantly produced in epithelial cells in the thick ascending limb (TAL) of the loop of the Henle and is present in lesser amounts in epithelial cells in the early distal convoluted tubule (DCT) of the mammalian kidney (32). It has also been found on the skin and gills of fish and in

the distal tubules of some amphibians (33). Since tissues in which uromodulin is localized have a common function in handling sodium and chloride transport, it is suggested that uromodulin regulates the balance of salt and water (13). It should be noted that excessive sodium and water reabsorption in the kidney causes fluid overload and hypertension (34). The relevance of uromodulin in hypertension can be partially explained by the regulation of sodium and water balance, which is further discussed below.

Another aspect of uromodulin activity is immunomodulation. Uromodulin shows a distinct distribution in the kidney, mostly located in the inner stripe of the outer medulla. Because the outer medulla is vulnerable to changes in perfusion and is rich in immune cells, it has been suggested that UMOD regulates the immune response in the kidney (35).

Electrolytes and water transport

Urine concentration and dilution are among the most important functions of renal tubules. TAL, which is the primary uromodulin producing segment, is impermeable to water and contributes to the reabsorption of approximately 30% of filtered sodium and dilute tubular fluid. This water-impermeable reabsorption of sodium is critical for the countercurrent multiplier mechanism for free water conservation; the high interstitial osmolality produced by the reabsorption of sodium is the driving force of passive water transport at the collecting duct to concentrate urine (36).

Uromodulin has been shown to regulate sodium transporters in epithelial cells along with TAL and DCT, where the Na-K-2Cl cotransporter (NKCC2) and the Na-Cl cotransporter (NCC) are the main transporters responsible for sodium reabsorption (37). In mice lacking UMOD (*Umod*$^{-/-}$), NKCC2 was detected in subapical vesicles but was less strongly expressed in the apical membrane than in wild-type (WT) mice. Furthermore, NKCC2 phosphorylation was significantly decreased in *Umod*$^{-/-}$ mice (38). Because apical expression and phosphorylation are essential for the membrane protein function (39), the downregulation of apical expression and phosphorylation of NKCC2 in *Umod*$^{-/-}$ mice indicates defective transporter activation. The loss of function of NKCC2 generates a phenotype similar to Bartter syndrome, a salt-losing tubulopathy. Similar to NKCC2, uromodulin activates NCC in the early DCT (32), indicating its importance in the regulation of sodium. Recently, vasopressin has been shown to increase urinary secretion of uromodulin (40). Vasopressin plays an important role in determining the urine concentration by inducing the apical expression of the water channel aquaporin-2 (AQP2) (41, 42). Because vasopressin is a hormone secreted during dehydration or volume depletion, upregulated uromodulin secretion by vasopressin is considered a reasonable physiological response. Furthermore, urinary uromodulin secretion increases under dehydration condition and, conversely, activates AQP2 in collecting duct cells (43). These findings suggest that the TAL and collecting duct work cooperatively to retain sodium and water through cross-talk with uromodulin (Fig. 2).

As mentioned above, excess sodium and water retention cause fluid overload, leading to hypertension. Mice overexpressing WT uromodulin (Tg^{Umodwt}) showed increased levels of phosphorylated NKCC2 along with an increased blood pressure on a high-salt diet, and their blood pressure decreased on a low-salt diet (44). The relevance of uromodulin and its regulatory effect on sodium homeostasis are consistent with those of GWAS in humans. Single nucleotide polymorphisms in the *UMOD* gene are associated with hypertension. Conversely, variants with low urinary uromodulin are associated with a lower risk of hypertension (12). In a cohort study of the general population, subjects with high urinary uromodulin expression showed a trend for higher blood pressure with high salt intake, while subjects with low urinary uromodulin expression did not show an association between blood pressure and the sodium intake (45). These findings indicated that uromodulin is associated with salt-sensitive hypertension. Uromodulin upregulates NKCC2 and NCC through SPS1-related proline-alanine-rich kinase (SPAK) and oxidative stress response 1 (OSR1) kinase (32, 46), which are involved in the pathogenesis of salt-sensitive hypertension (47-49).

In addition to its key roles in modulating sodium and water reabsorption, uromodulin is involved in the regulation of calcium and magnesium. *Umod*$^{-/-}$ mice show supersaturation of urine with calcium oxalate or calcium phosphate and are prone to the formation of calcium crystals in the kidney (50). It has been suggested that osteopontin, an inhibitor of calcium crystal formation, cooperatively prevents crystal formation (51). A proposed mechanism of protection against urinary stone formation is increased Ca^{2+} reabsorption in the DCT through transient receptor potential vanilloid (TRPV) 5. Uromodulin stimulates the expression of apical TRPV5 by inhibiting endocytosis (52). Uromodulin upregulates membrane proteins, such as TRPV5 and AQP2, by inhibiting endocytosis (43, 52). Interestingly, the regulatory effect of uromodulin on apical membrane proteins is executed in a segment distant from its production, suggesting an autocrine-like function of uromodulin.

Immunomodulation

The role of uromodulin is not limited to the TAL, DCT, or the distal parts of the nephrons. Although its concentration is much lower than in urine, it is also secreted from the basolateral side and can be detected in serum (35, 53, 54). Serum and urinary uromodulin secretion are independently regulated and are suggested to have different functions. Immunomodulation is considered a distinct function of circulating uromodulin and protects against systemic inflammation and oxidative stress. Uromodulin activates interleukin (IL)-23/IL-17 and pro-inflammatory cytokines and induces granulopoiesis (55). In fact, *Umod*$^{-/-}$ mice show higher levels of pro-inflammatory cytokines/chemokines and neutrophilia than WT mice (56). These regulatory effects contribute to protection against ischemic reperfusion-induced proximal tubular injury (57, 58), sepsis (59, 60), and vascular calcifica-

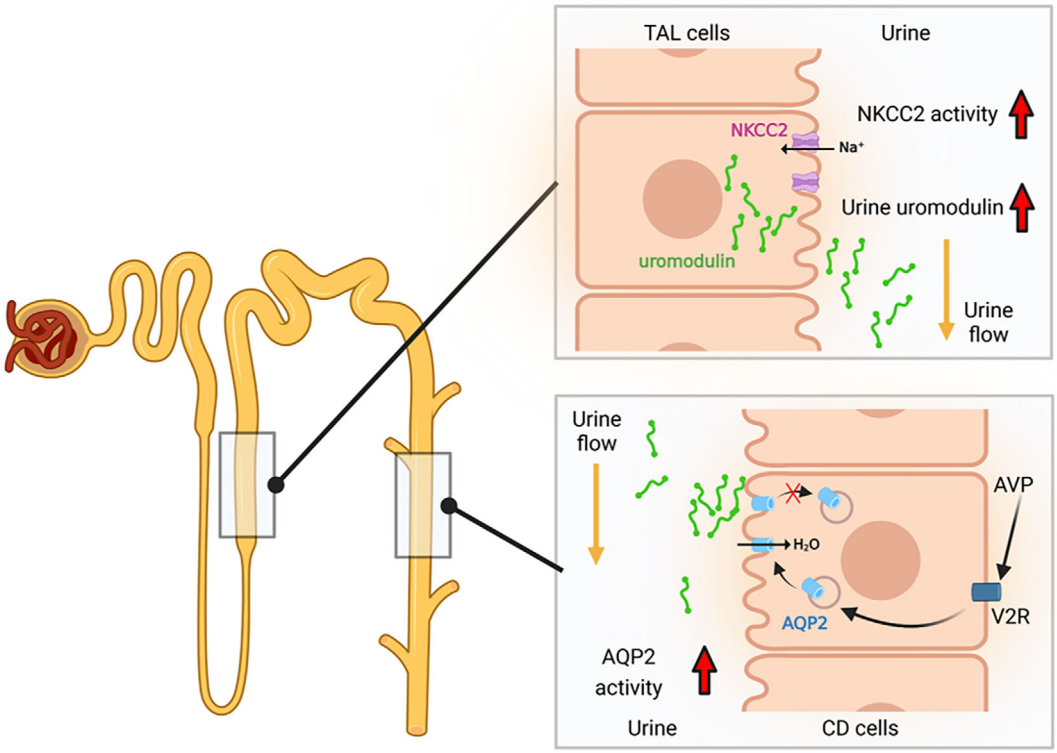

Figure 2. Physiological role of uromodulin on water retention. TAL and CD cooperatively work to retain free water through cross-talk via uromodulin. Vasopressin or water deprivation increase urinary secretion of uromodulin from the TAL. Urinary uromodulin at the epithelial surface of the CD cells induces the apical sorting of the water channel aquaporin-2. AQP2: aquaporin-2, AVP: arginine vasopressin, CD: collecting duct, NKCC2: Na-K-Cl cotransporter, TAL: thick ascending limb of loop of Henle, V2R: vasopressin-2 receptor

tion in CKD (61). Furthermore, uromodulin is involved in the binding of probiotic bacteria to the gastrointestinal epithelium and modulates the immune system (62). These findings indicate that uromodulin is a potential therapeutic target for systemic diseases; however, its relevance to extrarenal organs requires further research.

Uromodulin in Clinical Practice

Recently, uromodulin has been proposed as a novel biomarker for the diagnosis of CKD (63). Given that uromodulin is essentially generated in the kidney, primarily in the TAL, and is secreted in urine with lower levels in the serum, it would be expected that uromodulin is correlated with several renal properties, such as the nephron mass and renal function. The loss of functioning nephron causes hyperfiltration of the remaining nephrons, leading to glomerulosclerosis. Morphological parameters of the kidney or renal cortex, such as volume and length, which are proxies of the nephron mass, are well correlated with the renal function and predict the progression of CKD (64, 65). Urinary uromodulin has been shown to be associated with predictors of kidney mass, including the height, birth weight, and age in healthy subjects (66). Furthermore, urinary uromodulin was positively associated with an estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m^2 and urinary volume but negatively associated with age and diabetes (67). Similarly, serum uromodulin was associated with the eGFR calculated from cystatin C and was more sensitive than conventional markers, such as creatinine and cystatin C (68, 69). Serum uromodulin is also associated with the kidney function in transplanted kidneys and predicts a delayed graft function (70, 71).

The associations between uromodulin and the renal function or nephron mass indicate that uromodulin is a promising biomarker in CKD; however, several concerns have been raised about its feasibility. Urinary uromodulin secretion increased with diabetes mellitus and water diuresis (72, 73), and in turn, the serum level of uromodulin level was low in patients with diabetes (74, 75). Therefore, uromodulin secretion varies with physiological stimuli or pathological conditions underlying kidney injury. Uromodulin production per functioning nephron unit is thought to increase under conditions of kidney injury (35). These characteristics may shed light on uromodulin as a new biomarker of the tubular function, in contrast to creatinine reflecting glomerular filtration.

Based on its biological aspects, it is likely that uromodulin protects kidneys against CKD. In fact, a high serum uromodulin level at baseline was protective against a decline in the renal function and urinary albumin secretion in patients at high risk for cardiovascular disease during four years of follow-up (76). A similar link has been observed

between urinary uromodulin and the onset of CKD (77). Low serum uromodulin concentrations can be used to detect early kidney injury, even when serum creatinine levels are within the normal range (76), indicating that uromodulin is useful for detecting early CKD. In light of these predictive abilities and its potency as a biomarker for hypertension, metabolic abnormalities and tubular injury, measurement of uromodulin seems to be useful in stratifying patients at risk for CKD and comorbid conditions or in detecting alterations in the renal function at an early stage.

Conclusions and Perspectives

In this review, we summarized the current knowledge on uromodulin and its relevance in CKD. Our understanding of uromodulin has changed from its role in rare inherited diseases to a common public health problem. The biology and functions of uromodulin under physiological conditions have been widely investigated. Uromodulin upregulates tubular epithelial sodium transporters and water channels, and the inappropriate reabsorption of sodium and water leads to hypertension. It is reasonable to expect that suppression of uromodulin would modify hypertension or volume overload via natriuresis and water diuresis. It is also reasonable to propose that uromodulin regulates the tubulo-glomerular feedback (TGF) system. The macula densa, located in between the TAL and DCT, lacks uromodulin expression. Because the macula densa acts as the sensor of the luminal fluid by apical NKCC2 and regulates the TGF, urinary uromodulin may affect the TGF, thereby leading to a reduction in the intraglomerular pressure. This hypothesis potentiates uromodulin as a novel reno-protective agents. The regulatory roles of uromodulin in ion transport, especially sodium transport, require further studies to establish novel therapeutic approaches.

Although evidence is still scarce at present, basolateral secretion and the immunomodulatory effects are also important characteristics of uromodulin. Renal tubular inflammation and oxidative stress are closely related to the progression of kidney disease caused by various etiologies, including diabetic kidney disease. Understanding the precise function of circulating uromodulin may open new avenues of research and advances in therapeutic strategies for CKD.

In addition, whether or not uromodulin is associated with age-related kidney disease is also unclear. The evaluation of the GFR based on the serum creatinine or cystatin C levels has long been the primary index of CKD. Based on its derivation, uromodulin highlights the roles of renal tubules and the importance of assessing the tubular function, which is another aspect of kidney health. Combining conventional markers of the glomerular function and new tubular function biomarkers will improve the assessment of CKD and its complications. Further research on uromodulin will surely benefit the clinical practice of CKD.

The authors state that they have no Conflict of Interest (COI).

References

1. Anavekar NS, McMurray JJV, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med **351**: 1285-1295, 2004.
2. Hallan SI, Matsushita K, Sang Y, et al. Age and association of kidney measures with mortality and end-stage renal disease. JAMA **308**: 2349-2360, 2012.
3. Kon S, Konta T, Ichikawa K, et al. Association between renal function and cardiovascular and all-cause mortality in the community-based elderly population: results from the Specific Health Check and Guidance Program in Japan. Clin Exp Nephrol **22**: 346-352, 2018.
4. Imai E, Horio M, Watanabe T, et al. Prevalence of chronic kidney disease in the Japanese general population. Clin Exp Nephrol **13**: 621-630, 2009.
5. Nakai S, Watanabe Y, Masakane I, et al. Overview of regular dialysis treatment in Japan (as of 31 December 2011). Ther Apher Dial **17**: 567-611, 2013.
6. Nitta K, Goto S, Masakane I, et al. Annual dialysis data report for 2018, JSDT Renal Data Registry: survey methods, facility data, incidence, prevalence, and mortality. Ren Replace Ther **6**: 41, 2020.
7. Takata T, Isomoto H. Pleiotropic effects of sodium-glucose cotransporter-2 inhibitors: renoprotective mechanisms beyond glycemic control. Int J Mol Sci **22**: 4374, 2021.
8. Eckardt KU, Alper SL, Antignac C, et al. Autosomal dominant tubulointerstitial kidney disease: diagnosis, classification, and management - A KDIGO consensus report. Kidney Int **88**: 676-683, 2015.
9. Wuttke M, Li Y, Li M, et al. A catalog of genetic loci associated with kidney function from analyses of a million individuals. Nat Genet **51**: 957-972, 2019.
10. Okada Y, Sim X, Go MJ, et al. Meta-analysis identifies multiple loci associated with kidney function-related traits in east Asian populations. Nat Genet **44**: 904-909, 2012.
11. Gudbjartsson DF, Holm H, Indridason OS, et al. Association of variants at UMOD with chronic kidney disease and kidney stones-role of age and comorbid diseases. PLOS Genet **6**: e1001039, 2010.
12. Padmanabhan S, Melander O, Johnson T, et al. Genome-wide association study of blood pressure extremes identifies variant near UMOD associated with hypertension. PLOS Genet **6**: e1001177, 2010.
13. Schaeffer C, Devuyst O, Rampoldi L. Uromodulin: roles in health and disease. Annu Rev Physiol **83**: 477-501, 2021.
14. Oman TJ, van der Donk WA. Follow the leader: the use of leader peptides to guide natural product biosynthesis. Nat Chem Biol **6**: 9-18, 2010.
15. Serafini-Cessi F, Malagolini N, Hoops TC, Rindler MJ. Biosynthesis and oligosaccharide processing of human Tamm-Horsfall glycoprotein permanently expressed in HeLa cells. Biochem Biophys Res Commun **194**: 784-790, 1993.
16. Brunati M, Perucca S, Han L, et al. The serine protease hepsin mediates urinary secretion and polymerisation of zona pellucida domain protein uromodulin. eLife **4**: e08887, 2015.
17. Utami SB, Mahati E, Li P, et al. Apoptosis induced by an uromodulin mutant C112Y and its suppression by topiroxostat. Clin Exp Nephrol **19**: 576-584, 2015.
18. Vylet'al P, Kublová M, Kalbácová M, et al. Alterations of uromodulin biology: a common denominator of the genetically heterogeneous FJHN/MCKD syndrome. Kidney Int **70**: 1155-1169, 2006.
19. Rampoldi L, Scolari F, Amoroso A, Ghiggeri G, Devuyst O. The rediscovery of uromodulin (Tamm-Horsfall protein): from tubulointerstitial nephropathy to chronic kidney disease. Kidney Int **80**: 338-347, 2011.

20. Williams SE, Reed AAC, Galvanovskis J, et al. Uromodulin mutations causing familial juvenile hyperuricaemic nephropathy lead to protein maturation defects and retention in the endoplasmic reticulum. Hum Mol Genet **18**: 2963-2974, 2009.

21. Kemter E, Fröhlich T, Arnold GJ, Wolf E, Wanke R. Mitochondrial dysregulation secondary to endoplasmic reticulum stress in autosomal dominant tubulointerstitial kidney disease - UMOD (ADTKD-UMOD). Sci Rep **7**: 42970, 2017.

22. Schaeffer C, Merella S, Pasqualetto E, Lazarevic D, Rampoldi L. Mutant uromodulin expression leads to altered homeostasis of the endoplasmic reticulum and activates the unfolded protein response. PLOS ONE **12**: e0175970, 2017.

23. Trudu M, Schaeffer C, Riba M, et al. Early involvement of cellular stress and inflammatory signals in the pathogenesis of tubulointerstitial kidney disease due to UMOD mutations. Sci Rep **7**: 7383, 2017.

24. Olinger E, Lake J, Sheehan S, et al. Hepsin-mediated processing of uromodulin is crucial for salt-sensitivity and thick ascending limb homeostasis. Sci Rep **9**: 12287, 2019.

25. van der Starre WE, van Nieuwkoop C, Thomson U, et al. Urinary proteins, vitamin D and genetic polymorphisms as risk factors for febrile urinary tract infection and relation with bacteremia: a case control study. PLOS ONE **10**: e0121302, 2015.

26. Garimella PS, Bartz TM, Ix JH, et al. Urinary uromodulin and risk of urinary tract infections: the cardiovascular health study. Am J Kidney Dis **69**: 744-751, 2017.

27. Weiss GL, Stanisich JJ, Sauer MM, et al. Architecture and function of human uromodulin filaments in urinary tract infections. Science **369**: 1005-1010, 2020.

28. Iguchi A, Eino A, Yamazaki H, et al. A novel mutation in the uromodulin gene in a Japanese family with a mild phenotype of familial juvenile hyperuricemic nephropathy. CEN Case Rep **2**: 228-233, 2013.

29. Lin Z, Yang J, Liu H, et al. A novel uromodulin mutation in autosomal dominant tubulointerstitial kidney disease: a pedigree-based study and literature review. Ren Fail **40**: 146-151, 2018.

30. Ma L, Liu Y, Landry NK, El-Achkar TM, Lieske JC, Wu XR. Point mutation in D8C domain of Tamm-Horsfall protein/uromodulin in transgenic mice causes progressive renal damage and hyperuricemia. PLOS ONE **12**: e0186769, 2017.

31. Badgett A, Kumar S. Phylogeny of Tamm-Horsfall protein. Urol Int **61**: 72-75, 1998.

32. Tokonami N, Takata T, Beyeler J, et al. Uromodulin is expressed in the distal convoluted tubule, where it is critical for regulation of the sodium chloride cotransporter NCC. Kidney Int **94**: 701-715, 2018.

33. Howie AJ, Lote CJ, Cunningham AA, Zaccone G, Fasulo S. Distribution of immunoreactive Tamm-Horsfall protein in various species in the vertebrate classes. Cell Tissue Res **274**: 15-19, 1993.

34. Guyton AC. Blood pressure control - special role of the kidneys and body fluids. Science **252**: 1813-1816, 1991.

35. LaFavers KA, Micanovic R, Sabo AR, Maghak LA, El-Achkar TM. Evolving concepts in uromodulin biology, physiology, and its role in disease: a tale of two forms. Hypertension **79**: 2409-2418, 2022.

36. Burg MB. Thick ascending limb of Henle's loop. Kidney Int **22**: 454-464, 1982.

37. Kipp A, Olinger E. What does uromodulin do? Clin J Am Soc Nephrol **16**: 150-153, 2020.

38. Mutig K, Kahl T, Saritas T, et al. Activation of the bumetanide-sensitive Na^+,K^+,$2Cl^-$ Cotransporter (NKCC2) is facilitated by Tamm-Horsfall protein in a chloride-sensitive manner. J Biol Chem **286**: 30200-30210, 2011.

39. Rust K, Wodarz A. Transcriptional control of apical-basal polarity regulators. Int J Mol Sci **22**: 1-13, 2021.

40. Nanamatsu A, Mori T, Ando F, et al. Vasopressin induces urinary uromodulin secretion by activating PKA (protein kinase A). Hypertension **77**: 1953-1963, 2021.

41. Sandoval PC, Claxton JS, Lee JW, Saeed F, Hoffert JD, Knepper MA. Systems-level analysis reveals selective regulation of *Aqp2* gene expression by vasopressin. Sci Rep **6**: 34863, 2016.

42. Roche JV, Törnroth-Horsefield S. Aquaporin protein-protein interactions. Int J Mol Sci **18**: 1-23, 2017.

43. Takata T, Hamada S, Mae Y, et al. Uromodulin regulates murine aquaporin-2 activity via thick ascending limb-collecting duct cross-talk during water deprivation. Int J Mol Sci **23**: 9410, 2022.

44. Trudu M, Janas S, Lanzani C, et al. Common noncoding *UMOD* gene variants induce salt-sensitive hypertension and kidney damage by increasing uromodulin expression. Nat Med **19**: 1655-1660, 2013.

45. Ponte B, Pruijm M, Ackermann D, et al. Uromodulin, salt, and 24-hour blood pressure in the general population. Clin J Am Soc Nephrol **16**: 787-789, 2021.

46. Boder P, Mary S, Mark PB, et al. Mechanistic interactions of uromodulin with the thick ascending limb: perspectives in physiology and hypertension. J Hypertens **39**: 1490-1504, 2021.

47. Furusho T, Uchida S, Sohara E. The WNK signaling pathway and salt-sensitive hypertension. Hypertens Res **43**: 733-743, 2020.

48. Hirohama D, Fujita T. Evaluation of the pathophysiological mechanisms of salt-sensitive hypertension. Hypertens Res **42**: 1848-1857, 2019.

49. Nomura N, Shoda W, Uchida S. Clinical importance of potassium intake and molecular mechanism of potassium regulation. Clin Exp Nephrol **23**: 1175-1180, 2019.

50. Mo L, Liaw L, Evan AP, Sommer AJ, Lieske JC, Wu XR. Renal calcinosis and stone formation in mice lacking osteopontin, Tamm-Horsfall protein, or both. Am J Physiol Renal Physiol **293**: F1935-F1943, 2007.

51. Wolf MTF, Zhang J, Nie M. Uromodulin in mineral metabolism. Curr Opin Nephrol Hypertens **28**: 481-489, 2019.

52. Wolf MTF, Wu XR, Huang CL. Uromodulin upregulates TRPV5 by impairing caveolin-mediated endocytosis. Kidney Int **84**: 130-137, 2013.

53. Peach RJ, Day WA, Ellingsen PJ, McGiven AR. Ultrastructural localization of Tamm-Horsfall protein in human kidney using immunogold electron microscopy. Histochem J **20**: 156-164, 1988.

54. Steubl D, Buzkova P, Ix JH, et al. Association of serum and urinary uromodulin and their correlates in older adults - the Cardiovascular Health Study. Nephrology (Carlton) **25**: 522-526, 2020.

55. El-Achkar TM, Dagher PC. Tubular cross talk in acute kidney injury: a story of sense and sensibility. Am J Physiol Renal Physiol **308**: F1317-F1323, 2015.

56. Liu Y, El-Achkar TM, Wu XR. Tamm-Horsfall protein regulates circulating and renal cytokines by affecting glomerular filtration rate and acting as a urinary cytokine TRAP. J Biol Chem **287**: 16365-16378, 2012.

57. El-Achkar TM, Wu XR, Rauchman M, McCracken R, Kiefer S, Dagher PC. Tamm-Horsfall protein protects the kidney from ischemic injury by decreasing inflammation and altering TLR4 expression. Am J Physiol Renal Physiol **295**: F534-F544, 2008.

58. El-Achkar TM, McCracken R, Rauchman M, et al. Tamm-Horsfall protein-deficient thick ascending limbs promote injury to neighboring S3 segments in an MIP-2-dependent mechanism. Am J Physiol Renal Physiol **300**: F999-F1007, 2011.

59. LaFavers KA, Hage CA, Gaur V, et al. The kidney protects against sepsis by producing systemic uromodulin. Am J Physiol Renal Physiol **323**: F212-F226, 2022.

60. LaFavers K. Disruption of kidney-immune system crosstalk in sepsis with acute kidney injury: lessons learned from animal models and their application to human health. Int J Mol Sci **23**: 1702, 2022.

61. Alesutan I, Luong TTD, Schelski N, et al. Circulating uromodulin

inhibits vascular calcification by interfering with pro-inflammatory cytokine signalling. Cardiovasc Res **117**: 930-941, 2021.

62. Yanagihara S, Kanaya T, Fukuda S, et al. Uromodulin-SlpA binding dictates *Lactobacillus acidophilus* uptake by intestinal epithelial M cells. Int Immunol **29**: 357-363, 2017.

63. Rysz J, Gluba-Brzózka A, Franczyk B, Jabłonowski Z, Ciałkowska-Rysz A. Novel biomarkers in the diagnosis of chronic kidney disease and the prediction of its outcome. Int J Mol Sci **18**: 1702, 2017.

64. Takata T, Koda M, Sugihara T, et al. Left renal cortical thickness measured by ultrasound can predict early progression of chronic kidney disease. Nephron **132**: 25-32, 2016.

65. Hoi S, Takata T, Sugihara T, et al. Predictive value of cortical thickness measured by ultrasonography for renal impairment: a longitudinal study in chronic kidney disease. J Clin Med **7**: 527, 2018.

66. Pivin E, Ponte B, de Seigneux S, et al. Uromodulin and nephron mass. Clin J Am Soc Nephrol **13**: 1556-1557, 2018.

67. Pruijm M, Ponte B, Ackermann D, et al. Associations of urinary uromodulin with clinical characteristics and markers of tubular function in the general population. Clin J Am Soc Nephrol **11**: 70-80, 2016.

68. Risch L, Lhotta K, Meier D, Medina-Escobar P, Nydegger UE, Risch M. The serum uromodulin level is associated with kidney function. Clin Chem Lab Med **52**: 1755-1761, 2014.

69. Steubl D, Block M, Herbst V, et al. Plasma uromodulin correlates with kidney function and identifies early stages in chronic kidney disease patients. Medicine (Baltimore) **95**: e3011, 2016.

70. Borštnar Š, Večerić-Haler Ž, Boštjančič E, et al. Uromodulin and microRNAs in kidney transplantation-association with kidney graft function. Int J Mol Sci **21**: 5592, 2020.

71. Kemmner S, Holzmann-Littig C, Sandberger H, et al. Pretransplant serum uromodulin and its association with delayed graft function following kidney transplantation - a prospective cohort study. J Clin Med **10**: 2586, 2021.

72. Zimmerhackl LB, Pfleiderer S, Kinne R, Manz F, Schuler G, Brandis M. Tamm-Horsfall-protein excretion as a marker of ascending limb transport indicates early renal tubular damage in diabetes mellitus type I. J Diabet Complications **5**: 112-114, 1991.

73. Thulesen J, Jørgensen PE, Torffvit O, Nexø E, Poulsen SS. Urinary excretion of epidermal growth factor and Tamm-Horsfall protein in three rat models with increased renal excretion of urine. Regul Pept **72**: 179-186, 1997.

74. Leiherer A, Muendlein A, Saely CH, et al. Serum uromodulin is associated with impaired glucose metabolism. Medicine (Baltimore) **96**: e5798, 2017.

75. Then C, Then H, Meisinger C, et al. Serum uromodulin is associated with but does not predict type 2 diabetes in elderly KORA F4/FF4 study participants. J Clin Endocrinol Metab **104**: 3795-3802, 2019.

76. Leiherer A, Muendlein A, Saely CH, et al. The value of uromodulin as a new serum marker to predict decline in renal function. J Hypertens **36**: 110-118, 2018.

77. Köttgen A, Hwang SJ, Larson MG, et al. Uromodulin levels associate with a common UMOD variant and risk for incident CKD. J Am Soc Nephrol **21**: 337-344, 2010.