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The Systems Biology of Uric Acid Transporters: The Role of Remote Sensing and Signaling

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Abstract

Purpose of review—Uric acid homeostasis in the body is mediated by a number of SLC and ABC transporters in the kidney and intestine, including several multispecific ‘drug’ transporters (e.g., OAT1, OAT3, and ABCG2). Optimization of uric acid levels can be viewed as a ‘systems biology’ problem. Here, we consider uric acid transporters from a systems physiology perspective using the framework of the ‘Remote Sensing and Signaling Hypothesis.’ This hypothesis explains how SLC and ABC ‘drug’ and other transporters mediate interorgan and interorganismal communication (e.g., gut microbiome and host) via small molecules (e.g., metabolites, antioxidants signaling molecules) through transporters expressed in tissues lining body fluid compartments (e.g., blood, urine, cerebrospinal fluid).

Recent findings—The list of uric acid transporters includes: SLC2A9, ABCG2, URAT1 (SLC22A12), OAT1 (SLC22A6), OAT3 (SLC22A8), OAT4 (SLC22A11), OAT10 (SLC22A13), NPT1 (SLC17A1), NPT4 (SLC17A3), MRP2 (ABCC2), MRP4 (ABCC4). Normally, SLC2A9, – along with URAT1, OAT1 and OAT3, – appear to be the main transporters regulating renal urate handling, while ABCG2 appears to regulate intestinal transport. In chronic kidney disease (CKD), intestinal ABCG2 becomes much more important, suggesting remote organ communication between the injured kidney and the intestine.

Summary—The remote sensing and signaling hypothesis provides a useful systems-level framework for understanding the complex interplay of uric acid transporters expressed in different tissues involved in optimizing uric acid levels under normal and diseased (e.g., CKD, gut microflora dysbiosis) conditions.

Keywords

kidney; organic anion transporter; remote sensing and signaling; transporters; uric acid

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Conflicts of interest

There are no conflicts of interest.

INTRODUCTION

Although serum uric acid seems to function as a major antioxidant in the body and is thought to exert protective effects at normal levels; at higher levels, uric acid is detrimental, acting as a prooxidant and activator of inflammatory pathways [1–3,4*]. Elevated serum uric acid is associated with the risk of gout and uric acid stones across patient populations [5,6]. Moreover, it is also associated with major related comorbidities including, chronic kidney disease (CKD), cardiovascular disease, hypertension, diabetes, and metabolic syndrome [2,4*,7,8]. Thus, a J-shaped association between serum uric acid and all-cause mortality among patients with CKD [9], and a J-shaped association with the risk of CKD, has been shown [10].

How serum uric acid exerts detrimental effects on organs such as the kidney or heart has yet to be fully elucidated. In the broader context, uric acid is considered a ‘uremic toxin’; uric acid and other uremic toxins such as indoxyl sulfate increase with declining renal function [11–14]. These substances also accumulate within cells and may be directly cytotoxic to cells, including those of the proximal tubule of the kidney which are the main cells involved in urate elimination from the plasma to the urine [6]. Until recently, the bulk of attention regarding uric acid homeostasis has been on the role of renal uric acid transporters, but there is growing attention with regards to intestinal transporters, particularly in the setting of renal dysfunction [6,15,16]. Many of these are multispecific SLC and ABC ‘drug’ transporters as well as their close relatives that have more limited substrate selectivities [11,17,18].

Thus, uric acid homeostasis can be aptly viewed through the lens of systems biology in order to understand the larger picture. Purine metabolism by enzymes in the liver and elsewhere results in the formation of uric acid, whereas SLC and ABC transporters in the kidney and intestine (as well as other barrier epithelia of the body) maintain normal levels of this antioxidant/prooxidant organic anion through the regulation of cellular influx and efflux. In the setting of hyperuricemia, damage to the kidney, urinary tract, joints, vessels, and other tissues occurs, presumed in part to be the result of uric acid being taken up into some of these tissues by the transporters that regulate uric acid homeostasis [4*,5,6,11]. Thus, the relatively tight regulation of plasma uric acid can be viewed as an optimization problem – one of hundreds, if not thousands, of such problems the body faces with respect to transported small organic molecules in settings of health and disease. Optimization of uric acid is particularly interesting from this point of view because most of the key genes—which have been identified. The question is this: How do combinations of multispecific ‘drug’ transporters (e.g., OAT1, OAT3, ABCG2, MRP2, and MRP4) work together with much more selective uric acid transporters (e.g., URAT1, SLC2A9) – differentially expressed in multiple organs – to maintain plasma, tissue, and nonplasma body fluid levels of uric acid at an optimal level? Here, we attempt to integrate recent findings into a systems physiology view under the framework of the remote sensing and signaling hypothesis regarding inter-organ and inter-organismal (e.g., gut microbiome–host) crosstalk involving organic anions transported by SLC and ABC transporters [11,17,18,19*,20]. Applying the remote sensing and signaling framework to the problem of uric acid homeostasis should help with understanding the systems pathophysiology of hyperuricemia and even suggest new therapeutic approaches.

MECHANISMS OF URIC ACID HANDLING AND THE 'REMOTE SENSING AND SIGNALING HYPOTHESIS'

Over the past 2 decades, in the area of uric acid homeostasis, there has been a remarkable convergence of data from human Mendelian genetic disease, genome-wide association studies (GWAS), analyses of knockout mice, and in-vitro assays of cells engineered to overexpress cloned urate transporters. Together, these studies provide a detailed in-vivo and in-vitro portrait of how SLC and ABC uric acid transporters, many of which are better known as multispecific 'drug' transporters, involved in absorption, distribution, and elimination of common organic anion drugs, work along with liver enzymes involved in purine metabolism, to regulate uric acid levels [11,18,19*,21]. Although many of these uric acid transporters are most highly expressed in the kidney, where they function in urate handling by the proximal tubule resulting in net renal excretion (Fig. 1), they are also expressed in extrarenal tissues, such as the intestine [22–24]. In the setting of renal disease, intestinal excretion of urate appears to become important for maintaining uric acid levels, suggesting some sort of mechanism for remote communication between the failing kidney and intestine with respect to uric acid homeostasis (Fig. 2) [15,25].

Indeed, much of the current data on the role of renal and extrarenal urate transporters in maintaining uric acid homeostasis seems compatible with the remote sensing and signaling hypothesis regarding the systems biology of SLC and ABC multispecific 'drug' and other transporters. This hypothesis proposes that these SLC and ABC transporters, which are expressed in different tissues lining distinct body fluid compartments (including blood, urine, bile, CSF, and amniotic fluid), play an essential role in regulating interorgan and interorganismal (e.g., gut microbiome–host) communication by transporting key small molecule metabolites and signaling molecules throughout the body (Fig. 3) [11,17,18, 19*, 21]. The remote sensing and signaling system is thus envisioned to be a communication network of small molecules with high informational content (from the perspective of the organism's need to maintain local and systemic homeostasis), regulated by multispecific SLC and ABC transporters in different body tissues and thereby function similarly to the neuroendocrine system, with which it is functionally intertwined. The potential contribution of the gut–microbiome and gut flora dysbiosis can be considered through the lens of transporter-mediated interorganismal communication in health and disease.

Before we further discuss uric acid disorders in the context of perturbed remote sensing and signaling via SLC and ABC transporters, it is worthwhile to examine the main transporters involved in uric acid homeostasis (Table 1).

SLC2A9

In recent years, there has, as a result of GWAS studies, been a tendency to think of SLC2A9 (encodes GLUT9) as a urate transporter, but it is also important to remember that it was initially identified as a fructose transporter and has high sequence homology to other sugar transporters of the SLC2 family [26–30]. Polymorphisms in SLC2A9 may account for up to 5% of uric acid variation in healthy populations [30].

ABCG2

The ABC transporters are transmembrane proteins found in nearly all tissues and are dependent upon adenosine triphosphate hydrolysis for the efflux of a variety of molecules or substrates, including organic and inorganic anions, amino acids, and metals [18,23,31]. ABCG2, also known as the breast cancer-resistant protein, was identified as a transporter of drugs [32]. The role of intestinal secretion of uric acid has been recently reviewed [24].

Unlike most of the transporters discussed here, which largely mediate renal tubular influx and efflux of uric acid, ABCG2 is highly expressed in intestinal tissue [22] where it excretes up to one third of all uric acid and is thus thought to be the main extrarenal site of uric acid elimination [24,33]. In addition, ABCG2 knockout mice have lower intestinal excretion and higher levels of serum uric acid [34], whereas a common ABCG2 variant, Q141K (rs2231142), is associated with an increase of uric acid levels among European and East Asian populations [23,35,36]. Additionally, ABCG2 dysfunction may also account for much of early onset gout [37].

Thus, ABCG2 in conjunction with SLC renal transporters, maintain uric acid homeostasis. In mice with a 5/6th nephrectomy, the expression of intestinal ABCG2 increased and serum uric acid levels remained stable [25]. In keeping with the idea of remote communication (remote sensing and signaling) between organs in the setting of injury (possibly via substrates transported by transporters in distinct organs), the role of intestinal excretion of uric acid may be essential in the setting of renal failure. Consistent with this view, human single nucleotide polymorphisms (SNPs) in ABCG2 become more important in the setting of renal disease [15].

URAT1 (RST)

Many SLC uric acid transporters are organic anion transporters from the SLC22 family, first described in 1997 when it was noticed that the prototypical organic anion transporter OAT1 (SLC22A6, originally identified as NKT in mouse) was related to two other transporters, NLT (SLC22A7) and OCT1 (SLC22A1) [38]. The family now has about 30 members, including organic anion transporters (the largest group), organic cation transporters, and organic zwitterion/carnitine transporters. Many of the OAT group of the family have some ability to transport urate.

URAT1 (SLC22A12) was initially described in mouse as Rst [39]. The name URAT1, as well as considerable human genetic data from Mendelian diseases as well as GWAS and other association studies, has sometimes created the impression that URAT1 is a monospecific urate transporter. The gene has been found to be mutated in certain Japanese patients with hypouricemia and exercise-induced uric acid stones [40]. It is important to remember, however, that URAT1 is a member of the OAT major clade of the SLC22 family and closely related to OAT1, OAT3, and OAT6 [41]. Although much more limited in specificity than OAT1 and OAT3, and with a strong preference for urate, URAT1 nonetheless binds a few molecules other than urate. Recent metabolic reconstructions of the pathways affected by URAT1, based on metabolomics and transcriptomics data from the URAT1 (Rst) knockout mouse, suggest a broader role for URAT1 in metabolism than

usually appreciated [42]. When URAT1 (Rst) is knocked out in mice, urate handling is affected [42,43]. Even so, this effect was not as great as might have been expected for the major renal urate transporter; thus, at the time the knockout was published, it was predicted that other transporters might be equally or more important in urate handling [43]. Subsequently, SLC2A9 and ABCG2 were discovered to be major urate transporters. In whites and African-Americans with renal disease and hyperuricemia, URAT1 is one of the few genes discussed in this review that do not appear to significantly contribute to the hyperuricemia. Although there is no doubt about the role of URAT1 in renal urate handling, SNPs in URAT1 may be more important in certain Asian populations than in whites and African-Americans [15]. This highlights the need, in future studies, to understand the key genes regulating uric acid levels in different ethnicities.

OAT1 AND OAT3

OAT1 (SLC22A6) and OAT3 (SLC22A8) are, like URAT1 (SLC22A12), members of the OAT major clade of the SLC22 transporter family [19*,41]. Indeed, they are among the best known members of this family because, like ABCG2, they are widely regarded as among the major multispecific 'drug' transporters of the body [18]. Highly expressed in the kidney proximal tubule, OAT1 and OAT3 not only transport many common organic anion drugs and classic physiological probes [e.g., beta-lactam antibiotics, NSAIDs, antivirals, methotrexate, paraamino-hippuric acid (PAH)], they also transport many metabolites and signaling molecules, including tricarboxylic acid (TCA) cycle intermediates, gut microbiome products, bile acids, dietary phytochemicals, short chain fatty acids, uremic toxins, and odorants [19*,20,44–46]. There is a growing appreciation of the roles of OAT1 and OAT3 in regulating systemic metabolism, particularly anionic organic molecules flowing through the gut–liver–kidney axis [19*,44].

On the basis of high expression and localization in the basolateral surface of the proximal tubule cell, in-vitro transport assays, and knockout mice, OAT1 and OAT3 are considered to be the main transporters involved in the uptake of uric acid from the blood into the proximal tubule cell [43,47–49]. In GWAS studies, however, these OATs (and others such as OAT4 and OAT10), although implicated, do not nearly achieve the levels of significance seen for genes like SLC2A9 and ABCG2 [15].

NPT1 AND NPT4

So-called sodium-phosphate transporters (NPT, SLC17 family) actually transport urate and a number of organic anions [50], a fact underappreciated in the organic anion transporter field. SNPs in NPT1 and NPT4 weakly to moderately correlate with altered uric acid levels [15,49–51].

MRP2 AND MRP4

Multidrug-resistant proteins MRP2 (ABCC2) and MRP4 (ABCC4) are known transporters of PAH and other organic anions. In general, their substrate specificity in the kidney overlaps with OAT1 and OAT3. They are expressed in apical membrane proximal tubules—where they efflux organic anions—and to a lesser extent in the intestine. They are ATP-

dependent mediators of uric acid efflux from tubular cells into the lumen [24], and SNPs in these genes generally have a weak association with high uric acid levels.

PDZK1

PDZK1 is a cytoskeleton-associated protein that helps localize SLC transporters to the apical membrane. Mutations and SNPs in this protein which appear to be important for URAT1 localization to the apical membrane have been associated with hyperuricemia and gout [52,53]. The urate transporter OAT4 (SLC22A11) is also localized to the apical membrane via PDZK1 [54].

URATE HANDLING IN THE SETTING OF CHRONIC KIDNEY DISEASE: AN EXAMPLE OF REMOTE SENSING AND SIGNALING TO REOPTIMIZE URIC ACID LEVELS?

From the forgoing discussion, it is clear that many SLC and ABC transporters regulate uric acid levels in humans. In the kidney proximal tubule, multispecific SLC and ABC ‘drug’ transporters work in parallel (on either the basolateral or apical membrane) or in series (on both the basolateral or apical membranes) to cause net uric acid movement across the cell and to optimize secretion and reabsorption of uric acid. With the recognition of the importance of the intestinal contribution to urate handling via transporters such as ABCG2, a systems physiology picture is emerging that multiple organs ‘cooperate’ to optimize uric acid levels via transporters in these organs. Moreover, the expression and/or function of these transporters may be regulated by the substrate – the plasma and tissue levels of uric acid [55*]. These data, and that described below in the context of CKD, can be framed in terms of the remote sensing and signaling hypothesis.

Although mentioned above, it is worth elaborating here on this hypothesis, which was proposed a decade ago to explain interorgan and interorganismal communication of metabolites and signaling molecules via transporters in tissues lining body fluid compartments and spaces (e.g., gut, liver, kidney, choroid plexus, placenta, and blood–brain barrier) [11,17,18,19*,21].

The hypothesis arose when it became clear that OATs and other ‘drug’ transporters were transporting key metabolites for many biochemical pathways (e.g., TCA cycle intermediates, carnitine), signaling molecules [e.g., prostaglandins, short chain fatty acids, cyclic adenosine monophosphate (cAMP), bile acids], vitamins, and molecules with antioxidant activity [11,18,19*,20]. Close relatives of these drug transporters were also found to have high specificity for signaling molecules. For example, OAT6, the closest relative of OAT1 and OAT3, among 30 or so SLC22 transporters, is most highly expressed in the olfactory mucosa and appears to be an odorant transporter [56–58]. Later, the hypothesis was supported by Oat1 and Oat3 knockout metabolomics, genome-scale metabolic reconstructions from the knockouts, as well as GWAS studies and human mutations in (non-OAT) drug transporters, all of which indicated that a major, if not the major, endogenous role of these multispecific SLC and ABC transporters (e.g., various OATs, MRPs, and ABCG2) was the regulation of systemic as well as local (e.g., proximal tubule cell) metabolism. There was also increasing

evidence to support the notion of interorgan crosstalk, as in the case of uric acid, indicating that SLC and ABC ‘drug’ and other transporters in multiple tissues (e.g., kidney and intestine) were primary determinants of the levels of key molecules and that the dysregulation of transport resulted in pathology.

The role of many of these same transporters in normal and pathologic interorganismal communication (e.g., gut microbiome–host) became evident. For instance, one of the major uremic toxins, indoxyl sulfate, arises as a tryptophan derivative in the gut microbiome that is transported across the intestine, sulfated by phase 2 enzymes in the liver, and in the absence of severe CKD, eliminated via OAT1 and OAT3 in the proximal tubule [59]. As with uric acid, indoxyl sulfate can affect cellular function, in this case by binding the aryl hydrocarbon receptor [60]. Interestingly, recent studies indicate that the gut microbiome ‘senses’ host uric acid levels, apparently altering the gut flora in response, which in turn has the potential through bacterial enzymes, to alter purine metabolism and thus affect the host [61–63]. Thus, the framework of the remote sensing and signaling hypothesis seems very appropriate for understanding both the interorgan and interorganismal systems pathobiology of hyperuricemia and the uremic syndrome.

In CKD, renal urate excretory mechanisms are compromised due to loss of renal function. Thus, the transporters discussed above, all expressed in the proximal tubule, are unable to achieve sufficient net urate excretion. This results in hyperuricemia. In this scenario, extrarenal urate excretion becomes more important for maintaining reasonable serum uric acid levels. Of the transporters described above, ABCG2 is also expressed in the intestine. Indeed, there are a number of studies that now suggest this is the major route of intestinal urate excretion in humans [15,24,25,33,34,37,64–66].

Moreover, in rats that have undergone 5/6th nephrectomy, not only does renal urate excretion decrease but intestinal expression of ABCG2 increases, suggesting some sort of remote regulation of intestinal urate transport when renal transport is compromised [25]. That this applies to humans is supported by a recent study. In a population of CKD patients with low renal function, polymorphisms in ABCG2 had the strongest association with serum uric acid in patients of European ancestry. Although SLC2A9 polymorphisms were the next most significant associations, the strength of association was over orders of magnitude less. However, in keeping with other GWAS studies [26–30], SLC2A9 polymorphisms were most strongly associated with serum uric acid in a healthy comparison patient population.

Taken together with experimental murine data, this is interpreted as indicating that intestinal ABCG2 function becomes particularly important for maintaining uric acid levels in humans with poor renal function; loss of ABCG2 functionality results in a higher uric acid in CKD patients, but not in patients with normal kidney function.

Thus, this appears to be a human example of remote sensing and signaling via SLC and ABC transporters. With normal kidney function, urate is primarily handled by SLC2A9, URAT1, OATs, NPTs, MRPs and, perhaps to some extent, ABCG2 in the proximal tubule. But in the damaged kidney, when these transporters are unable to work in concert to achieve sufficient net urate excretion, some mechanism exists to increase ABCG2-mediated urate

extrusion in the intestine. Perturbation of this mechanism, in this case as a result of a SNP in the ABCG2 gene, results in a higher serum uric acid level.

Substrate induction of drug transporters is a well-described phenomenon [67–69], and this notion is supported by increased expression of ABCG2 (and PDZK1) in cultured intestinal epithelial cells in the presence of uric acid via a mechanism involving the inflammasome and PI3 kinase [55*]. Thus, it is possible that urate directly induces ABCG2 expression. Another possibility is the presence of uremic solutes which accumulate in the setting of declining renal function. These include indoxyl sulfate, p-cresol sulfate, kynurenine, hippurate, 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF), polyamines, and many other putative uremic toxins. Although most of these are known OAT substrates, some are likely to enter the intestinal epithelium, where they may affect the expression and/or function of ABCG2, thereby serving as a potential means of remote signaling between the diseased kidney and the relatively normal intestine, serving to help restore perturbed urate levels.

CONCLUSION

The antioxidant versus prooxidant nature of uric acid, and the local and systemic consequences of high uric acid levels, requires uric acid transporters in the kidney and intestine – along with liver enzymes regulating purine metabolism – to function so as to help optimize plasma and tissue levels of uric acid. The remote sensing and signaling hypothesis is a fertile framework for understanding normal uric acid homeostasis and hyperuricemia (in the absence and presence of renal disease). The theory emphasizes the role of SLC and ABC multispecific ‘drug’ transporters and their close relatives (which are often more selective) in regulating small molecule interorgan (e.g., gut–liver–kidney) and interorganismal (e.g., gut microbiome–host) remote communication in health and disease. In CKD, intestinal transporters that efflux uric acid become much more important for maintaining uric acid levels. The mechanism of remote regulation of intestinal ABCG2 in the setting of decreased renal function may be mediated by a high urate level in intestinal cells, leading to increased ABCG2 expression and/or functionality, although it is possible that uremic toxins or dysbiosis of the gut microbiome also play a role.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest

1. Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. *Proc Natl Acad Sci U S A* 1981; 78:6858–6862. [PubMed: 6947260]
2. Sautin YY, Johnson RJ. Uric acid: the oxidant-antioxidant paradox. *Nucleosides Nucleotides Nucleic Acids* 2008; 27:608–619. [PubMed: 18600514]
3. Mikami T, Sorimachi M. Uric acid contributes greatly to hepatic antioxidant capacity besides protein. *Physiol Res* 2017; 66:1001–1007. [PubMed: 28937257]
- *4. El Ridi R, Tallima H. Physiological functions and pathogenic potential of uric acid: a review. *J Adv Res* 2017; 8:487–493. [PubMed: 28748115] This short review covers a number of aspects of uric acid metabolism not discussed here.
5. Desai J, Steiger S, Anders HJ. Molecular pathophysiology of gout. *Trends Mol Med* 2017; 23:756–768. [PubMed: 28732688]
6. Mandal AK, Mount DB. The molecular physiology of uric acid homeostasis. *Annu Rev Physiol* 2015; 77:323–345. [PubMed: 25422986]
7. Chen C, Lu JM, Yao Q. Hyperuricemia-related diseases and xanthine oxidoreductase (XOR) inhibitors: an overview. *Med Sci Monit* 2016; 22: 2501–2512. [PubMed: 27423335]
8. Pascart T, Liote F. Gout: state of the art after a decade of developments. *Rheumatology (Oxford)* 2018; in press, 3 13. doi: 10.1093/rheumatology/key002. [Epub ahead of print]
9. Suliman ME, Johnson RJ, Garcia-Lopez E, et al. J-shaped mortality relationship for uric acid in CKD. *Am J Kidney Dis* 2006; 48:761–771. [PubMed: 17059995]
10. Srivastava A, Kaze AD, McMullan CJ, et al. Uric acid and the risks of kidney failure and death in individuals with CKD. *Am J Kidney Dis* 2018; 71:362–370. [PubMed: 29132945]
11. Nigam SK, Wu W, Bush KT, et al. Handling of drugs, metabolites, and uremic toxins by kidney proximal tubule drug transporters. *Clin J Am Soc Nephrol* 2015; 10:2039–2049. [PubMed: 26490509]
12. Masereeuw R, Mutsaers HA, Toyohara T, et al. The kidney and uremic toxin removal: glomerulus or tubule? *Semin Nephrol* 2014; 34:191–208. [PubMed: 24780473]
13. Niwa T Targeting protein-bound uremic toxins in chronic kidney disease. *Expert Opin Ther Targets* 2013; 17:1287–1301. [PubMed: 23941498]
14. Duranton F, Cohen G, De Smet R, et al. Normal and pathologic concentrations of uremic toxins. *J Am Soc Nephrol* 2012; 23:1258–1270. [PubMed: 22626821]
15. Bhatnagar V, Richard EL, Wu W, et al. Analysis of ABCG2 and other urate transporters in uric acid homeostasis in chronic kidney disease: potential role of remote sensing and signaling. *Clin Kidney J* 2016; 9:444–453. [PubMed: 27274832]
16. Bobulescu IA, Moe OW. Renal transport of uric acid: evolving concepts and uncertainties. *Adv Chronic Kidney Dis* 2012; 19:358–371. [PubMed: 23089270]
17. Ahn SY, Nigam SK. Toward a systems level understanding of organic anion and other multispecific drug transporters: a remote sensing and signaling hypothesis. *Mol Pharmacol* 2009; 76:481–490. [PubMed: 19515966]
18. Nigam SK. What do drug transporters really do? *Nat Rev Drug Discov* 2015; 14:29–44. [PubMed: 25475361]
- *19. Nigam SK. The SLC22 transporter family: a paradigm for the impact of drug transporters on metabolic pathways, signaling, and disease. *Ann Rev Pharmacol Toxicol* 2018; 58:663–687. [PubMed: 29309257] A detailed exploration of the role of SLC22 transporters in remote inter-organ and inter-organismal small molecule remote communication, including that involving uric acid, framed in the context of the Remote Sensing and Signaling Hypothesis.
20. Nigam SK, Bush KT, Martovetsky G, et al. The organic anion transporter (OAT) family: a systems biology perspective. *Physiol Rev* 2015; 95:83–123. [PubMed: 25540139]
21. Wu W, Dnyanmote AV, Nigam SK. Remote communication through solute carriers and ATP binding cassette drug transporter pathways: an update on the remote sensing and signaling hypothesis. *Mol Pharmacol* 2011; 79:795–805. [PubMed: 21325265]
22. Cleophas MC, Joosten LA, Stamp LK, et al. ABCG2 polymorphisms in gout: insights into disease susceptibility and treatment approaches. *Pharmacogenomics Pers Med* 2017; 10:129–142. [PubMed: 28461764]

23. Fujita K, Ichida K. ABCG2 as a therapeutic target candidate for gout. *Expert Opin Ther Targets* 2018; 22:123–129. [PubMed: 29264928]
24. Xu X, Li C, Zhou P, Jiang T. Uric acid transporters hiding in the intestine. *Pharm Biol* 2016; 54:3151–3155. [PubMed: 27563755]
25. Yano H, Tamura Y, Kobayashi K, et al. Uric acid transporter ABCG2 is increased in the intestine of the 5/6 nephrectomy rat model of chronic kidney disease. *Clin Exp Nephrol* 2014; 18:50–55. [PubMed: 23584883]
26. Anzai N, Jutabha P, Amonpatumrat-Takahashi S, Sakurai H. Recent advances in renal urate transport: characterization of candidate transporters indicated by genome-wide association studies. *Clin Exp Nephrol* 2012; 16:89–95. [PubMed: 22038265]
27. Caulfield MJ, Munroe PB, O'Neill D, et al. SLC2A9 is a high-capacity urate transporter in humans. *PLoS Med* 2008; 5:e197. [PubMed: 18842065]
28. Dehghan A, Kottgen A, Yang Q, et al. Association of three genetic loci with uric acid concentration and risk of gout: a genome-wide association study. *Lancet* 2008; 372:1953–1961. [PubMed: 18834626]
29. Matsuo H, Chiba T, Nagamori S, et al. Mutations in glucose transporter 9 gene SLC2A9 cause renal hypouricemia. *Am J Hum Genet* 2008; 83:744–751. [PubMed: 19026395]
30. Vitart V, Rudan I, Hayward C, et al. SLC2A9 is a newly identified urate transporter influencing serum urate concentration, urate excretion and gout. *Nat Genet* 2008; 40:437–442. [PubMed: 18327257]
31. Vasilou V, Vasilou K, Nebert DW. Human ATP-binding cassette (ABC) transporter family. *Hum Genomics* 2009; 3:281–290. [PubMed: 19403462]
32. Hyndman D, Liu S, Miner JN. Urate handling in the human body. *Curr Rheumatol Rep* 2016; 18:34. [PubMed: 27105641]
33. Hosomi A, Nakanishi T, Fujita T, Tamai I. Extra-renal elimination of uric acid via intestinal efflux transporter BCRP/ABCG2. *PLoS One* 2012; 7:e30456. [PubMed: 22348008]
34. Ichida K, Matsuo H, Takada T, et al. Decreased extra-renal urate excretion is a common cause of hyperuricemia. *Nat Commun* 2012; 3:764. [PubMed: 22473008]
35. 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* 2012; 44:904–909. [PubMed: 22797727]
36. Sakiyama M, Matsuo H, Takada Y, et al. Ethnic differences in ATP-binding cassette transporter, sub-family G, member 2 (ABCG2/BCRP): genotype combinations and estimated functions. *Drug Metab Pharmacokinet* 2014; 29:490–492. [PubMed: 24869748]
37. Matsuo H, Nakayama A, Sakiyama M, et al. ABCG2 dysfunction causes hyperuricemia due to both renal urate underexcretion and renal urate overload. *Sci Rep* 2014; 4:3755. [PubMed: 24441388]
38. Lopez-Nieto CE, You G, Bush KT, et al. Molecular cloning and characterization of NKT, a gene product related to the organic cation transporter family that is almost exclusively expressed in the kidney. *J Biol Chem* 1997; 272:6471–6478. [PubMed: 9045672]
39. Hosoyamada M, Ichida K, Enomoto A, et al. Function and localization of urate transporter 1 in mouse kidney. *J Am Soc Nephrol* 2004; 15:261–268. [PubMed: 14747372]
40. Ichida K, Hosoyamada M, Hisatome I, et al. Clinical and molecular analysis of patients with renal hypouricemia in Japan-influence of URAT1 gene on urinary urate excretion. *J Am Soc Nephrol* 2004; 15:164–173. [PubMed: 14694169]
41. Zhu C, Nigam KB, Date RC, et al. Evolutionary analysis and classification of OATs, OCTs, OCTNs, and other SLC22 transporters: structure-function implications and analysis of sequence motifs. *PLoS One* 2015; 10: e0140569. [PubMed: 26536134]
42. Eraly SA, Liu HC, Jamshidi N, Nigam SK. Transcriptome-based reconstructions from the murine knockout suggest involvement of the urate transporter, URAT1 (slc22a12), in novel metabolic pathways. *Biochem Biophys Rep* 2015; 3:51–61. [PubMed: 26251846]
43. Eraly SA, Vallon V, Rieg T, et al. Multiple organic anion transporters contribute to net renal excretion of uric acid. *Physiol Genomics* 2008; 33:180–192. [PubMed: 18270321]

44. Bush KT, Wu W, Lun C, Nigam SK. The drug transporter OAT3 (SLC22A8) and endogenous metabolite communication via the gut-liver-kidney axis. *J Biol Chem* 2017; 292:15789–15803. [PubMed: 28765282]
45. Wikoff WR, Nagle MA, Kouznetsova VL, et al. Untargeted metabolomics identifies enterobiome metabolites and putative uremic toxins as substrates of organic anion transporter 1 (Oat1). *J Proteome Res* 2011; 10:2842–2851. [PubMed: 21476605]
46. Wu W, Jamshidi N, Eraly SA, et al. Multispecific drug transporter Slc22a8 (Oat3) regulates multiple metabolic and signaling pathways. *Drug Metab Dispos* 2013; 41:1825–1834. [PubMed: 23920220]
47. Bakhiya A, Bahn A, Burckhardt G, Wolff N. Human organic anion transporter 3 (hOAT3) can operate as an exchanger and mediate secretory urate flux. *Cell Physiol Biochem* 2003; 13:249–256. [PubMed: 14586168]
48. Kusuvara H, Sekine T, Utsunomiya-Tate N, et al. Molecular cloning and characterization of a new multispecific organic anion transporter from rat brain. *J Biol Chem* 1999; 274:13675–13680. [PubMed: 10224140]
49. Xu L, Shi Y, Zhuang S, Liu N. Recent advances on uric acid transporters. *Oncotarget* 2017; 8:100852–100862. [PubMed: 29246027]
50. Reimer RJ. SLC17: a functionally diverse family of organic anion transporters. *Mol Aspects Med* 2013; 34:350–359. [PubMed: 23506876]
51. Dong Z, Zhou J, Jiang S, et al. Effects of multiple genetic loci on the pathogenesis from serum urate to gout. *Sci Rep* 2017; 7:43614. [PubMed: 28252667]
52. Anzai N Molecular mechanism of renal urate transport: urate transporters as novel targets for drug development. *Nippon Yakurigaku Zasshi* 2010; 136:316–320. [PubMed: 21139280]
53. Higashino T, Matsuo H, Sakiyama M, et al. Common variant of PDZ domain containing 1 (PDZK1) gene is associated with gout susceptibility: a replication study and meta-analysis in Japanese population. *Drug Metab Pharmacokinet* 2016; 31:464–466. [PubMed: 27720648]
54. Miyazaki H, Anzai N, Ekaratanawong S, et al. Modulation of renal apical organic anion transporter 4 function by two PDZ domain-containing proteins. *J Am Soc Nephrol* 2005; 16:3498–3506. [PubMed: 16236806]
- *55. Chen M, Lu X, Lu C, et al. Soluble uric acid increases PDZK1 and ABCG2 expression in human intestinal cell lines via the TLR4-NLRP3 inflammasome and PI3K/Akt signaling pathway. *Arthritis Res Ther* 2018; 20:20. [PubMed: 29415757] An in-vitro study of intestinal epithelial cells that explores potential mechanisms by which uric acid increases intestinal ABCG2 expression.
56. Kaler G, Truong DM, Sweeney DE, et al. Olfactory mucosa-expressed organic anion transporter, Oat6, manifests high affinity interactions with odorant organic anions. *Biochem Biophys Res Commun* 2006; 351:872–876. [PubMed: 17094945]
57. Monte JC, Nagle MA, Eraly SA, Nigam SK. Identification of a novel murine organic anion transporter family member, OAT6, expressed in olfactory mucosa. *Biochem Biophys Res Commun* 2004; 323:429–436. [PubMed: 15369770]
58. Wu W, Bush KT, Liu HC, et al. Shared ligands between organic anion transporters (OAT1 and OAT6) and odorant receptors. *Drug Metab Dispos* 2015; 43:1855–1863. [PubMed: 26358290]
59. Leong SC, Sirich TL. Indoxyl sulfate: review of toxicity and therapeutic strategies. *Toxins (Basel)* 2016; 8 pii: E358. [PubMed: 27916890]
60. Kaminski T, Michalowska M, Pawlak D. Aryl hydrocarbon receptor (AhR) and its endogenous agonist - indoxyl sulfate in chronic kidney disease. *Postepy Hig Med Dosw (Online)* 2017; 71:624–632. [PubMed: 28791957]
61. Shao T, Shao L, Li H, et al. Combined signature of the fecal microbiome and metabolome in patients with gout. *Front Microbiol* 2017; 8:268. [PubMed: 28270806]
62. Guo Z, Zhang J, Wang Z, Ang KY, et al. Intestinal microbiota distinguish gout patients from healthy humans. *Sci Rep* 2016; 6:20602. [PubMed: 26852926]
63. Kim HW, Yoon EJ, Jeong SH, Park M- C. The effect of uric acid lowering treatment on the microbiome in gout patients [abstract]. *Arthritis Rheumatol* 2017; 69(suppl 10).

64. Matsuo H, Ichida K, Takada T, et al. Common dysfunctional variants in ABCG2 are a major cause of early-onset gout. *Sci Rep* 2013; 3:2014. [PubMed: 23774753]
65. Sarkadi B, Ozvegy-Laczka C, Nemet K, Varadi A. ABCG2 : a transporter for all seasons. *FEBS Lett* 2004; 567:116–120. [PubMed: 15165903]
66. Takada T, Ichida K, Matsuo H, et al. ABCG2 dysfunction increases serum uric acid by decreased intestinal urate excretion. *Nucleosides Nucleotides Nucleic Acids* 2014; 33:275–281. [PubMed: 24940679]
67. Hewitt WR, Wagner PA, Bostwick EF, Hook JB. Transport ontogeny and selective substrate stimulation as models for identification of multiple renal organic anion transport systems. *J Pharmacol Exp Ther* 1977; 202: 711–723. [PubMed: 302329]
68. Hirsch GH, Hook JB. Maturation of renal organic acid transport: substrate stimulation by penicillin. *Science* 1969; 165:909–910. [PubMed: 5816327]
69. Hirsch GH, Hook JB. Maturation of renal organic acid transport: substrate stimulation by penicillin and p-aminohippurate (PAH). *J Pharmacol Exp Ther* 1970; 171:103–108. [PubMed: 4243703]

KEY POINTS

- Uric acid levels are regulated by a large number of SLC and ABC transporters in the kidney and intestine. These include multispecific ‘drug’ transporters like OAT1, OAT3, and ABCG2 as well as more selective uric acid transporters like SLC2A9, URAT1 and OAT4.
- The problem of optimization of uric acid levels can be approached through ‘systems biology’. We consider the problem using the framework of the ‘remote sensing and signaling hypothesis’.
- The remote sensing and signaling hypothesis is a general theory of how SLC and ABC ‘drug’ and other transporters optimize levels of metabolites and signaling molecules via transporter-mediated interorgan and interorganismal communication. These regulated processes lead to appropriate levels of metabolites, signaling molecules, and antioxidants in tissues and body fluid compartments (e.g., blood, urine, and CSF). The theory predicts a key role for SLC and ABC ‘drug’ and other transporters in restoring homeostasis after injury to an organ (e.g., CKD).
- In the absence of renal disease, SLC2A9—as well as OAT1 and OAT3—seem to be the main regulators of urate transport in the proximal tubule, whereas ABCG2 seems to be the key intestinal transporter. When CKD sets in, intestinal uric acid handling, largely mediated by ABCG2, gains in importance.
- Although the molecular mechanism for this remote organ communication involving uric acid transporters between the injured kidney and the intestine is not well understood, the evidence so far is consistent with the remote sensing and signaling hypothesis.

FIGURE 1.

Transporters and proteins involved in regulating uric acid transport in the proximal tubule of the kidney. Transporters and other proteins found at both the basolateral membrane and apical membrane of the renal proximal tubule are involved in transporting uric acid across the cell to regulate its level in the plasma. OAT1 and OAT3 are believed to represent the major multispecific influx transporters, moving uric acid from the blood and into the proximal tubule cell. Transporters found on the apical surface are involved in moving uric acid from the cell and into the lumen of the proximal tubule, whereas others are involved in the reabsorption of uric acid from the lumen back into the cell where it can be transported back into the blood across the basolateral membrane, depending on the needs of the body. These include both SLC and ABC transporters.

FIGURE 2.

Uric acid excretion with normal versus diminished renal function: a potential example of remote communication ('remote sensing and signaling') between the injured kidney and the intestine. Analysis of human data as well as physiological data from rodent models with renal dysfunction indicate that extrarenal uric acid transport mediated largely by ABCG2, most likely in the intestine, compensates for altered renal urate handling in the setting of diminished kidney function.

FIGURE 3.

Remote sensing and signaling via SLC and ABC transporters: Relevance to understanding uric acid homeostasis in health and disease. As detailed in the text, multispecific ‘drug’ transporters (and their close relatives) form a small molecule (e.g., metabolites, signaling molecules, and gut microbiome products) communication network involving many transporter-expressing tissues which works in parallel with other regulatory systems to maintain homeostasis. According to the remote sensing and signaling hypothesis, this transporter-mediated remote communication network has a complex organization and emergent properties, particularly after a perturbation such as renal injury. The remote sensing and signaling hypothesis encompasses interorgan communication (e.g., gut–liver–kidney; red arrows) as well as interorganismal communication (e.g., gut microbiome–host; blue arrows). This involves potentially regulated transporter-mediated movement of metabolites, signaling molecules, nutrients, antioxidants, and gut microbiome products between tissues and body compartments. Here, we use this systems biology framework to analyze the role of uric acid transporter-mediated interorgan (e.g., kidney, intestine) and interorganismal (gut microbiome–host) communication in uric acid homeostasis in health and disease. Following [11,17–20].

Table 1**Transporters and Proteins Regulating Uric Acid**

Transporter/Protein	Specificity	Main Expression	Comments
SLC2A9	Mono/oligo	Kidney	Prominent in many studies.
ABCG2	Multi-	Intestine, some kidney	Prominent in many studies.
OAT1 (SLC22A6)	Multi-	Kidney	Key uptake transport function in proximal tubule.
OAT3 (SLC22A8)	Multi-	Kidney	Key uptake transport function in proximal tubule.
OAT4 (SLC22A9)	Mono/oligo	Kidney	Also in placenta.
URAT1 (SLC22A12; Rst)	Mono/oligo	Kidney	May be more important in certain ethnic groups.
NPT1 (SLC17A1)	Mono/oligo	Kidney	Sodium-phosphate cotransporter.
NPT4 (SLC17A3)	Mono/oligo	Kidney	Sodium-phosphate cotransporter.
PDZK1	NA	Kidney	Scaffolding protein helps localize URAT1 to apical membrane.

NA, not available