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REVIEW

Proteinuria and events beyond the slit

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Abstract The origin of proteinuria is found in either the glomerular filtration device or the proximal tubular reabsorption machinery. During equilibrium, small amounts of predominantly low molecular weight proteins are filtered and reabsorbed by the receptor complex megalin/cubilin/amnionless. This results in a protein-free filtrate passing further down the tubule. During glomerular damage, the reabsorption machinery in the proximal tubule is challenged due to elevated amounts of proteins passing the glomerular filtration slits. Even though it is considered to be a high-capacity system, several conditions result in proteinuria, thus exposing the cells in the rest of the nephron to a protein-rich environment. The impact on cells in the more distal part of the nephron is uncertain, but studies support an involvement in fibrosis development. Protein accumulation in lysosomes of the proximal tubule, due to increased protein internalization, is thought to mediate inflammation and fibrosis, eventually leading to renal failure. In contrast, low molecular weight proteinuria develops when the endocytic machinery is malfunctioning either by direct or indirect causes such as in Imerslund-Gräsbeck syndrome (IGS) or Dent's disease, respectively. This review discusses the origin of proteinuria and describes the structural fundament for protein reabsorption in the proximal tubule as well as conditions resulting in low molecular weight proteinuria.

Keywords Renal proximal tubule · Megalin · Cubilin · Amnionless · Endocytosis · Tubular proteinuria

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Abbreviations

IGS	Imerslund-Gräsbeck syndrome
DB/FOAR	Donnai-Barrow/facio-oculo-acoustico-renal
AMN	Amnionless
LDL	Low-density lipoprotein
RAP	Receptor-associated protein
RBP	Retinol-binding protein
DBP	Vitamin-D-binding protein

Introduction

Proteinuria is the presence of nonphysiological levels of a mixture of proteins in the urine (>200 mg/l). It is a characteristic of many renal diseases, and proteinuria correlates with disease progression ending in nephrotic syndrome with an excretion of >2.3 g/l. The etiology of this type of proteinuria is a condition that directly or indirectly affects the glomerular filtration barrier. This view has recently been questioned by an alternative hypothesis (the albumin retrieval hypothesis), which, together with the facts pointing against it, are discussed later in this review.

In contrast, several renal syndromes are characterized by a tubular or low molecular weight proteinuria. These syndromes include Imerslund-Gräsbeck syndrome (IGS), Dent's disease, Lowe syndrome, Donnai-Barrow syndrome (DB/FOAR syndrome), and cystinosis. At the outset, the glomerular filtration process works normally and the defect is due to modified reabsorption in the proximal tubule. The urinary protein composition mirrors more or less the composition in the primary ultrafiltrate. These proteins are normally reabsorbed very efficiently by the two receptors megalin and cubilin and the cooperating protein amnionless (AMN) [1, 2], resulting in an almost protein-devoid urine

(<20 mg/l). The receptors are thus involved in clearing the ultrafiltrate, which not only rescues essential molecules such as vitamins [2], but probably also provides a nontoxic protein-free milieu for cells further down the tubule. Together, the receptors act as a high-capacity, dynamic uptake system, reabsorbing a large amount of a variety of compounds. The reabsorbed constituents are directed to the lysosomes, where proteins are degraded and constituents such as vitamins are exported to the circulation for reuse.

In IGS and DB/FOAR syndrome, proteinuria is caused by mutations in the receptor complex: cubilin-AMN and megalin, respectively. In cystinosis and Dent's disease, the defective proteins have been identified as a lysosomal cystine transporter (cystinosin) and an endosomal CL^-/H^+ exchanger (CLC-5), respectively, but the mechanism underlying decreased protein reabsorption by the receptor complex has not been fully resolved. In Lowe syndrome, mutations have been found in the *OCRL1* gene encoding an inositol polyphosphate 5-phosphatase, but the molecular mechanisms underlying the phenotype of Lowe syndrome have not been resolved. This paper reviews the structure and function of the receptors as well as our present understanding of the mechanisms responsible for proteinuria in the above-mentioned syndromes.

The endocytic complex in the proximal tubule

Megalin

In the light of the close association of proteinuria and renal disease, it is not surprising that the molecular mechanism underlying protein reabsorption in the proximal tubule has been studied intensively. Megalin was the first receptor to be identified, in 1982, by Kerjaschki and Farquhar [3, 4]. It is a giant protein (600 kDa after glycosylation) belonging to the low-density lipoprotein (LDL) receptor family [5–7]. It turned out to be a multispecific receptor, with four binding clusters in its extracellular domain, which is build by three components: (1) 36 cysteine-rich complement-type motifs organized in four binding domains [8, 9]; (2) 16 growth factor repeats separated by eight YWTD spacer regions, which are involved in pH-dependent release of ligands [10]; and (3) one epidermal growth-factor-like repeat (Fig. 1). The receptor has one membrane-spanning region and a short intracellular tail (209 amino acids). It contains two endocytic motifs (NPXY) necessary for clustering into coated pits and an NPXY-like motif (NQNY) involved in apical sorting of the receptor [11]. The tail of megalin differs from the other members of the LDL receptor family by further harboring several phosphorylation, signaling, and protein interaction motifs [7], giving rise to the assumption that megalin has signaling roles [2, 12]. It is intriguing to speculate that the state of these interaction/phosphorylation sites might be changed in syndromes associated with low molecular proteinuria, as for example, the phosphorylation of a PPSP motif involved in recycling and surface expression of megalin [13], or Dab2 interaction with the second NPXY motif [14–16].

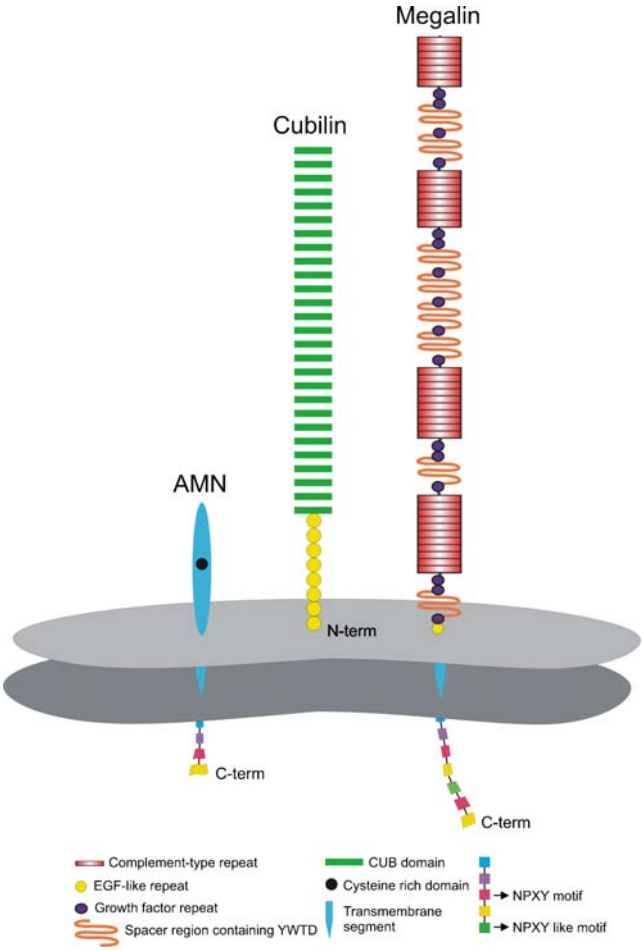

Fig. 1 Megalin, cubilin, and amnionless (AMN) presenting known domains and motifs. The three receptors colocalize in the renal proximal tubule (PT), where they cooperate in ultrafiltrate clearance. Megalin binds a variety of filtered molecules (>50 ligands have been identified) through its complement type repeats and is able to mediate endocytosis via NPXY motifs in the cytoplasmic tail. Cubilin, on the other hand, includes multiple binding domains (CUB domains), but only around 15 ligands have been identified. Cubilin is a peripheral membrane protein and is thereby dependent on megalin and/or AMN to assure internalization of its ligands. AMN contains an NPXY and probably assists cubilin in endocytosis as well as in transport during synthesis

Cubilin

The cooperating extracellular receptor cubilin is also a huge protein (glycosylated 460 kDa), which shares no homology with other known receptors. It binds intrinsic-factor B12 and was originally identified and named (intrinsic factor

receptor) based on this ability [17, 18]. Its membrane association is mediated by a putative amphipathic helix and a palmitoylation site [19]. Cubilin consists of three domains: (1) a 110 amino acid N-terminal stretch, (2) eight epidermal growth-factor-like repeats, and (3) 27 CUB domains [complement c1r/C1s, Uegf (epidermal growth-factor-related sea urchin protein) and bone morphogenic protein 1 (BMP1)] [20, 21] (Fig. 1). The 27 CUB domains of cubilin are ligand-binding determinants, and numerous ligands are expected to exist. However, only a few have been identified. CUB domains 12−17 and 22−27, as well as the N-terminus of cubilin (including CUB domains 1 and 2), are further involved in indirect membrane anchorage, as they associate cubilin to megalin [22, 23].

Amnionless

Besides megalin, cubilin also interacts on the apical membrane as well as during the biosynthetic pathway with AMN [24, 25]. AMN exists in at least five different sizes ranging from 38−50 kDa [26]. It is build up by a 70 amino-acid N-terminal domain containing a cysteine-rich region, a transmembrane domain, and a cytoplasmic tail, which contains an NPXY motif [27] (Fig. 1). The association to cubilin occurs through the epidermal growth-factor-like repeats in cubilin [24].

Ligands

The ligand repertoire of megalin includes a variety of compounds; many have been identified by studies of the urinary profile in megalin knock-out mice. The milieu to which megalin is exposed differs from tissue to tissue, thereby making the relevance of each ligand dependent on its location. Ligands include vitamin-binding proteins, enzymes and enzyme inhibitors, hormones, drugs and toxins, lipoproteins, calcium, albumin, hemoglobin, myoglobin, and receptor-associated protein (RAP) [1, 2]. Some ligands are shared with cubilin, as for example, vitamin-D-binding protein (DBP), albumin, immunoglobulin light chains, myoglobin, and hemoglobin. Transferrin, intrinsic-factor B12, and apolipoprotein AI are examples of pure cubilin ligands. In total, 14 ligands, including megalin, AMN, and RAP, have been identified for cubilin, whereas more than 50 have been identified for megalin [2].

Expression

Megalin is expressed in many absorptive epithelia, of which the renal proximal tubule exhibits a very high level [3, 28, 29]. For more information on megalin expression in other epithelia, see Christensen et al. [2]. On the cellular level, the receptor is present on microvilli, coated pits, and subsequent compartments of the endocytic route [29, 30]. Megalin is also present in lysosomes in very small amounts, but the majority of megalin is recycled to the apical membrane from endosomes through dense apical tubules [31]. Cubilin colocalizes closely with megalin in the renal proximal tubule [17, 32, 33]. Both receptors are escorted to the membrane by chaperone proteins. In the case of megalin, RAP is essential for protecting megalin from potential ligands during synthesis and probably also important for receptor folding [34–36]. Cubilin is dependent on AMN for its normal translocation from the endoplasmic reticulum (ER) to the membrane as well as for consequent endocytosis [24, 25]. As mentioned, megalin and cubilin are also able to interact in vitro, and this interaction was initially thought to be the motor for cubilin internalization [21]. Other observations supported this concept, as for example their colocalization and decreased uptake of cubilin ligands, such as transferrin and apolipoprotein A-I/high-density lipoprotein by antimegalin antibodies [37, 38] as well as by megalin antisense oligonucleotides [39]. Even if the cubilin/AMN complex is able to work independently of megalin in uptake of intrinsic-factor B12 in vitro [25], it does not seem to pertain to the renal proximal tubule, as pure cubilin ligands are found in urines of megalin knock-out mice, and pure cubilin, and shared ligands are undetectable in proximal tubule cells of these mice (unpublished observations). It should be noted, however, that the endocytic apparatus is less well-developed in megalin knock-out mice [40]. Whether this is due to megalin being a major endocytic player in the proximal tubule or an indirect effect of megalin deficiency on other endocytic systems is unknown.

Proteinuria

Traditionally, proteinuria has been subdivided in glomerular and tubular proteinuria. In addition, in specific overload, proteinurias such as, for example, hemoglobinuria, myoglobinuria, or multiple myeloma with excess glomerular filtration of immunoglobulin light chains, the disease cause is located outside the kidney. Glomerular proteinuria is usually caused by a defect in the glomerular filtration barrier, i.e. the endothelium, the glomerular basement membrane, or the podocyte filtration slit membrane. The pathogenesis of glomerular proteinuria is highly variable, but the most common disease is diabetes mellitus, which results in a thickened basement membrane and proteinuria progression. Notably, large plasma proteins that normally are not filtered or only to a limited extent now appear in the ultrafiltrate in large amounts and start to interfere with the normal tubular reabsorption of low molecular weight proteins, competing for the binding sites on megalin and cubilin (Fig. 2). Examples of such proteins are plasma

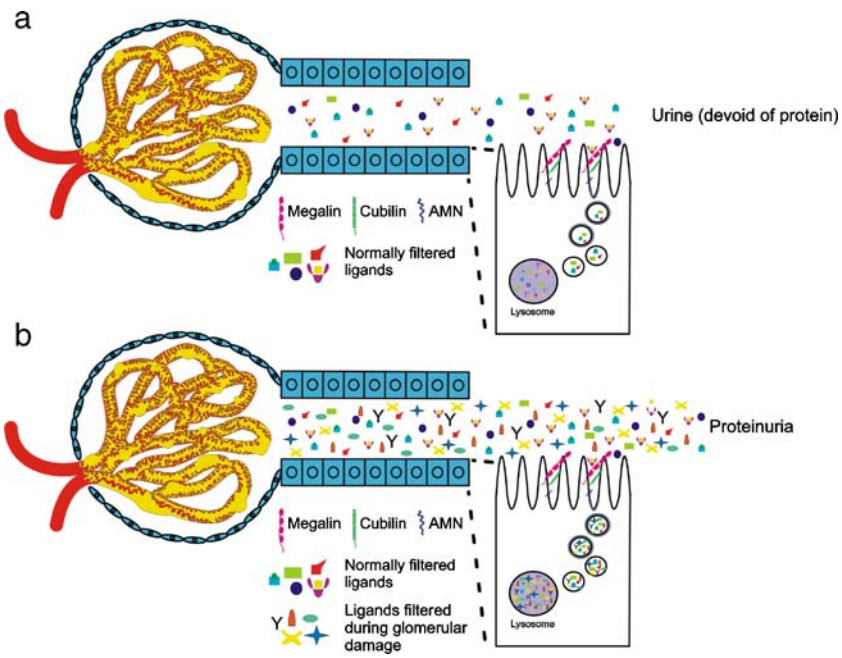

Fig. 2 Events in the proximal tubule after glomerular filtration under normal physiological conditions and after glomerular damage. **a** During normal physiological conditions, all filtered proteins are efficiently internalized by the receptor complex megalin/cubilin/amnionless (AMN), resulting in a virtually protein-devoid urine. Proteins are degraded in lysosomes, and substances such as vitamins are transported basally for reuse. **b** During glomerular damage, filtration of low molecular weight proteins increases and larger proteins start to penetrate the glomerular barrier. Cells in the proximal tubule are thereby exposed to more, and new, proteins that compete for receptor-binding sites, eventually resulting in proteinuria. Further, in the cell, lysosomal degradation is unable to handle the increased amount of internalized protein, resulting in protein-clotted lysosomes

immunoglobulins, transferrin, and albumin. Albumin in this respect is important for several reasons. It is the protein with the highest plasma concentration: 5.5 g/100 ml. It is an important carrier of a variety of substances such as fatty acids, bilirubin, hormones, and vitamins [41]. It has a molecular weight of ~65 kDa, and its size, form, and surface charge make it generally accepted that it is filtered only in very small amounts. This makes it very suitable as a marker for a beginning glomerular proteinuria, which is typically seen as, for example, microalbuminuria in the early stages of the kidney disease in diabetes mellitus [42, 43].

The concept of a very low glomerular filtration of albumin (filtration fraction 0.0005−0.0007) is based on many years of research using a variety of techniques, as well as physiological and pathological conditions. Recently, however, a study using two-photon microscopy challenged this concept, apparently demonstrating a much higher glomerular filtration of albumin by a factor of 40 [44]. This observation was immediately seriously questioned by several investigators [45–48], and very recently, a couple of reports using similar or identical techniques concluded that the findings by Russo et al. [44] were probably an artifact [49, 50]. In order to account for all the filtered albumin not appearing in the urine, Russo et al. [44] also suggested that the bulk of filtered albumin was reabsorbed by non-receptor-mediated endocytosis and transported across the tubular wall by transcytosis. However, when we looked at mosaic-pattern kidney-specific megalin-knock-out mice, there was no uptake of albumin in cells not expressing megalin and no signs of transcytosis in either megalin-expressing or non-megalin-expressing cells [2]. By electron microscope immunocytochemistry on rat renal tissue, there were also no indications of transcellular transport of endogenous albumin. Instead, albumin accumulated in the lysosomes of the proximal tubule cells (Fig. 3).

The competition for binding sites in overload proteinuria, whether the course is glomerular or outside the kidney, also results in addition to proteinuria in increased proximal tubular uptake of proteins such as albumin and transferrin. These proteins are potentially harmful to cells due to the amounts reabsorbed but probably more reasonably due to potentially toxic substances carried by the proteins. A discussion of the subsequent tubular damage and interstitial fibrosis is outside the scope of this review (for recent reviews, see Abbate et al. and Kriz and LeHir [51, 52]). We emphasize normal physiological tubular reabsorption of circulating lysosomal enzymes used to renew the proximal tubular lysosomal enzyme pool—a recent finding by us—may contribute to this damage [53]. Thus, this process may also be impaired by increased competition for uptake, resulting in increased

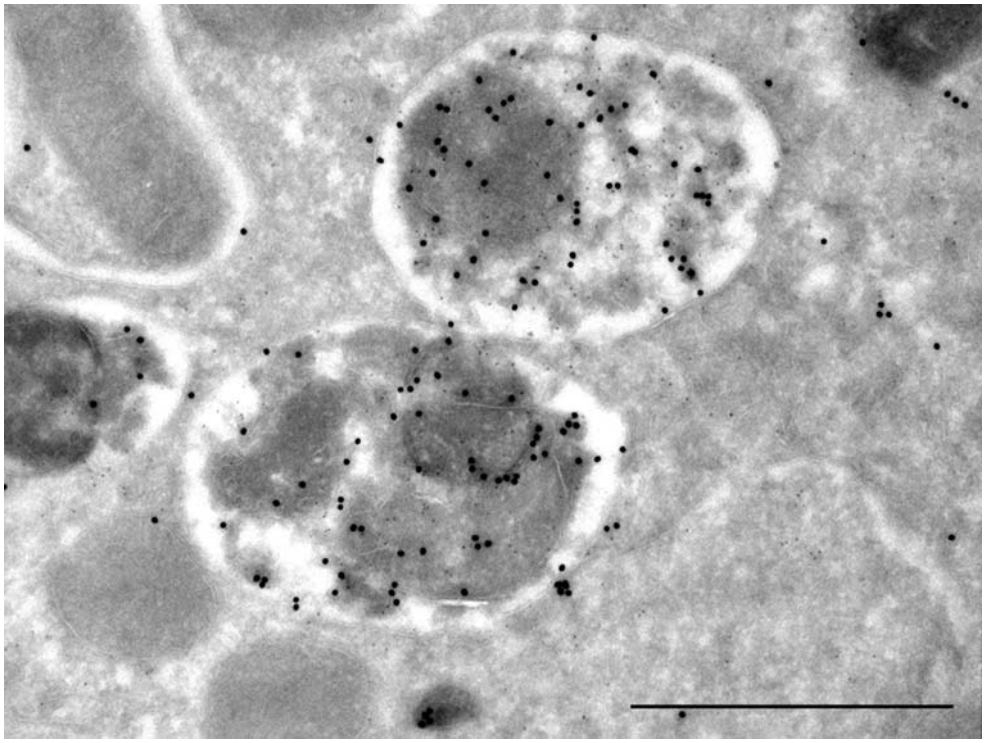

Fig. 3 Electron microscope immunocytochemistry on cryosection from rat renal proximal tubule cell. Endogenous albumin (18-nm gold particles) is intensively accumulated in the lysosomes identified by their content of cathepsin B (6-nm gold particles). There are no signs of any transcellular transport activity. *Bar = 1 μm*

urinary excretion of lysosomal hydrolases and lysosomal enzyme deficiency in the proximal tubule. This deficiency may further accentuate the accumulation of protein in proximal tubules, which was observed many years ago and described as protein droplets [54]. Another consequence of the increased competition is the urinary loss of vital substances such as vitamins and different trace elements such as iron. This can be exemplified by the fact that many patients with proteinuria suffer from vitamin D deficiency due to decreased reabsorption of DBP; we have previously shown that the proximal tubular conversion of 25-OH-Vitamin D3 to 1,25-$(OH)_2$-vitamin D3 is dependent on megalin/cubilin-mediated uptake of DBP [55, 56]. Similarly, retinol and vitamin B12 will be lost due to decreased reabsorption of retinol binding protein (RBP) [57] and transcobalamin-B12 (TC-B12) [58], respectively. When the capacity for protein reabsorption in the proximal tubule is exceeded, it also means that protein is now found in the tubular fluid in more distal parts of the nephron and in collecting ducts. Although neither the distal tubule nor the collecting duct has specific features for endocytosis, both segments have the capability for protein endocytosis [59–61], probably by fluid-phase endocytosis as part of normal membrane internalization in connection with apical receptor/transporter/channel regulation. Therefore, uptake, or maybe only nonspecific binding to the apical plasma membrane, may be potentially harmful to processes normally taking place in these segments (see e.g. Kastner et al. [62]).

Tubular proteinuria involves diseases in which the endocytic machinery suffers either by genetic defects that directly affect the endocytic receptors megalin and cubilin, or diseases in which endocytosis is more indirectly affected, involving changes in endocytic or recycling processes. We briefly describe five of these diseases:

1. Imerslund-Gräsbeck syndrome

IGS is a rare autosomal-recessive disease affecting either the gene for AMN or for cubilin. The disease was first described in the 1960s by Imerslund [63] and Gräsbeck [64] as a megaloblastic anemia type 1 and proteinuria. When the anemia is treated with vitamin B12, treatment does not improve proteinuria. To date, about 300 patients have been identified [65]. The disease is caused by reduced absorption of intrinsic-factor B12 in the small intestine due to mutation of either the gene for AMN or cubilin [26, 66]. Proteinuria varies greatly between patients [67] but is due to reduced function of cubilin/AMN in the proximal tubule. AMN and cubilin are colocalized [25], and AMN appears to be necessary for apical localization of cubilin in the proximal tubule [25]. Thus, in inbred dogs with megaloblastic anemia and "cubilin" proteinuria [38, 68, 69], cubilin is found throughout the cytoplasm but not apically [69] due to mutation of the AMN gene [70]. A mouse

"kidney-specific" AMN knockout [71] also showed increased urinary excretion of transferrin. Typically, the proteins found in the urine of the dogs were, for example, DBP [55, 56] and albumin [69] (both megalin and cubilin ligands), transferrin [37], and apolipoprotein A1 (apoA1) [38] (cubilin ligands) but not, for example, RBP [56] (megalin ligand). A similar pattern was seen in some IGS patients [67]. However, a thorough analysis of patients with different mutations comparing proteinuria is lacking.

2. Dent's disease

Dent's disease is a rare X-linked genetic disease involving mutations in the gene encoding the CLC-5 CL^-/H^+ exchanger [72, 73] located apically in the proximal tubules and intercalated cells of collecting ducts and less pronounced in the thick ascending limb [74–76]. Symptoms of the disease include nephrolithiasis, hypercalciuria, aminoaciduria, phosphaturia, glycosuria, low molecular weight proteinuria (tubular proteinuria) and—in this respect interesting, but seen less often—rickets [77]. In CLC-5 knock-out mice simulating the human disease, it was shown that renal expression of megalin was reduced [78] and cubilin levels were even more reduced [79], resulting in a significant low molecular weight proteinuria [78, 79]. In addition to generally reduced expression, localization of the two receptors was also changed significantly in the knock-out mice, that is, the brush border expression of the two receptors had virtually disappeared, whereas the apical endosomal expression appeared intact [79]. It was concluded that this effect was due to a changed intracellular trafficking resulting from the lack of CLC-5. How this is instituted, for example, lack of endosomal acidification, remains to be elucidated in detail. A change in megalin expression has also been observed in patients with Dent's disease [80]. It should be noted that the tubular/low molecular weight proteinuria observed in these patients and in mouse models include both megalin and cubilin ligands, which is distinctly different from IGS patients and corresponding dog models in which proteinuria includes only cubilin ligands. It should also be noted that the tubular proteinuria observed in patients and the mouse models is mild compared with, for example, megalin knock-out mouse models [81], as the uptake of proteins is only partially disturbed [79].

3. DB/FOAR syndrome

Lack of functional megalin results in a multifaceted phenotype comprising hypertelorism, large anterior fontanelle, agenesis of corpus callosum, diaphragmatic hernia, omphalocele/umbilical hernia, macrocephaly, ophthalmological abnormalities, sensorineural hearing loss, developmental delay, and proteinuria [82]. Many of these clinical features were described in patients suffering from both Donnai-Barrow and facio-oculo-acoustico-renal (FOAR) syndromes, which were initially thought to be distinct syndromes. Kantarci et al. [83, 84] showed the two syndromes to be allelic, having their origin in the gene LDL-receptor-related protein 2 (*LRP2*) encoding megalin. To date, reports on 27 patients from 15 families presenting with a number of the above-mentioned features have been published [82]. Sixteen patients have been analyzed for mutations in *LRP2*, and in all patients, alterations were identified in the gene [83]. It has not been possible to make positive genotype–phenotype correlations, but hypertelorism, high myopia, hearing loss, and proteinuria seem to be universal, as they have been detected in all patients examined for these features. Large anterior fontanelle, corpus callosum agenesis, developmental delay, diaphragmatic hernia, and omphalocele/umbilical hernia were detected in 95%, 94%, 86%, 56%, and 56%, respectively of examined individuals [82]. Further analysis of urine from eight patients showed a characteristic feature of a "megalopathy", namely, RBP (8/8) and DBP (6/8) excretion [83]. It is not unexpected—with the role played by megalin in endocytosis of an array of compounds in many tissues—that malfunctioning results in diverse malformations, which was also described in megalin-deficient mice in 1996 [85]. The distinct mechanism underlying each phenotype is unknown and not directly explicable. However, failure to absorb ligands at a specific time during development that results in local deficiencies (of vitamins, etc.) might be the basis for the abnormalities present in DB/FOAR-affected patients.

4. Cystinosis

Cystinosis is an autosomal recessive lysosomal storage disorder in which lysosomal efflux of cystine from degraded proteins is defective [86, 87]. The affected protein, cystinosin, is a 367 amino acid H^+-driven cystine transporter located on the lysosomal membrane [88, 89]. It is encoded by CTNS located at 17p13.3 [89]. The disease is characterized by lysosomal accumulation of cystine, which in many tissues forms crystals [86, 87, 90, 91]. Three different variants of the disease exist: (1) infantile cystinosis, which is the most severe form, presents with Fanconi syndrome within the first year of life, inevitably culminating in renal failure. Approximately 5% of end-stage renal disease in children is caused by cystinosis [90]. Renal symptoms are the foremost clinical characteristic of the disease. Other symptoms are growth retardation, diabetes mellitus, hypothyroidism, photophobia, retinal blindness, pulmonary dysfunction, myopathy, and neurological dysfunction (OMIN 219800). (2) Juvenile cystinosis, which demonstrates the same symptoms but is less severe and later in life (OMIN 219900). (3) Nonnephropathic cystinosis manifests in adolescence, with photophobia due to cystine crystals in the cornea (OMIN 219750) [91, 92]. The renal phenotype includes Fanconi syndrome, narrowing of

the proximal tubule due to tubular atrophy (swan neck), followed by interstitial nephritis, glomerular endothelial proliferation, glomerular thickening, and end-stage renal disease. The development of swan neck seems to be correlated temporarily with the presence of Fanconi syndrome and to be proceeded by minute crystal formations [93]. Different mechanisms underlying the pathological manifestations in cystinosis have been presented, of which many have been based on cystine loading by cystine dimethyl ester. However, toxicity of the drug has now been documented, and the results obtained by this method need reevaluation [94, 95]. The proteinuric component of Fanconi syndrome could be caused by decreased levels of megalin and cubilin in the renal proximal tubule. This does not seem to be the case, as neither immunohistological staining of receptors nor endocytosed ligands are decreased in a patient with cystinosis [96]. These findings indicate that increased glomerular permeability contributes to the development of proteinuria in cystinosis patients. Another issue is the cytoplasmic depletion of cystine, which has been shown to result in decreased levels of gluthathione, giving rise to increased susceptibility to oxidative stress [97]. Further, it has been reported that cystinotic cells are more sensitive to apoptotic inducers through activation of PKC δ, which could explain the swan neck phenotype of the proximal tubule found in cystinosis patients [98]. However, the link between these findings and proteinuria has not been resolved. Lysosomal cystine clearance by treatment with cysteamine has been shown to relieve systemic symptoms, including glomerular deterioration, whereas the tubular component seems more unresponsive to treatment [91, 99]. This unresponsiveness combined with the very sparse crystal formation observed in the kidney relates the renal tubular component of cystinosis to the lack of functional cystinosin rather than crystal formation per se.

5. Lowe syndrome

The oculocerebrorenal syndrome of Lowe (OCRL1) is an X-linked disease characterized by growth and mental retardation, cataracts, and renal Fanconi syndrome, ending with renal failure [100, 101]. The affected gene is *OCRL 1*, which encodes a phosphatidylinositol 4,5-biphosphate 5-phosphatase [102, 103]. OCRL 1 preferentially hydrolyzes lipid-anchored substrates with highest activity toward PI(4,5)P2 but also hydrolyzes soluble substrates such as Ins (1,4,5) P3 [103, 104]. OCRL 1 is localized in transgolgi network vesicles and early endosomes [101, 105–107]. Defective OCRL 1 seems to affect targeting of lysosomal enzymes, as Lowe patients exhibit high plasma levels of lysosomal enzymes [108]. It further interacts with AP-2 and heavy-chain clathrin and seems to be incorporated into clathrin cages during assembly [105, 107]. A link to the renal phenotype of Lowe patients has been provided by Erdmann et al. [106]. They show interaction of OCRL 1 with the adaptor/signaling protein APPL1, which is able to regulate TrkA-receptor trafficking [109], and indirectly with the adaptor protein GIPC. Mutations detected in ORCL 1 of Lowe patients were shown to abolish binding to APPL1 in GST pull-down assays. Furthermore, pull-down experiments with megalin recovered both GIPC and APPL1. Thus, focusing on the proteinuric state of Lowe patients, disturbance of the ORCL1/APPL1/GIPC/megalin axis probably underlies the decreased reabsorption ability by affecting receptor recycling in the renal proximal tubule.

It should be noted that patients suffering from Dent 2 disease (having no mutations in ClC5) have been determined to harbor mutations in OCRL 1 [108]. Their phenotype resembles the one found in Lowe patients, except for the lack of cataracts and tubular acidosis.

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