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Lysosome dysfunction in the pathogenesis of kidney diseases

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Abstract

The lysosome, an organelle central to macromolecule degradation and recycling, plays a pivotal role in normal cell processes, ranging from autophagy to redox regulation. Not surprisingly, lysosomes are an integral part of the renal epithelial molecular machinery that facilitates normal renal physiology. Two inherited diseases that manifest as kidney dysfunction are Fabry's disease and cystinosis, each of which is caused by a primary biochemical defect at the lysosome resulting from loss of function mutations in genes that encode lysosomal proteins. The functions of the lysosomes in the kidney and how lysosomal dysfunction might contribute to Fabry's disease and cystinosis are discussed. Unlike most other pediatric renal diseases, therapies are available for Fabry's disease and cystinosis, but require early diagnosis. Recent analysis of ceroid neuronal lipofuscinosis type 3 (*Cln3*) null mice, a mouse model of lysosomal disease that is primarily associated with neurological deficits, revealed renal functional abnormalities. As current and future therapeutics increase the life-span of those suffering from diseases like neuronal ceroid lipofuscinosis, it remains a distinct possibility that many more lysosomal disorders that primarily manifest as infant and juvenile neurodegenerative diseases may also include renal disease phenotypes.

Keywords

Fabry's; Batten disease; cystinosis; nephrogenic diabetes insipidus

Introduction

In all mammalian cells, including renal cells, the primary organelle responsible for catabolism and recycling of macromolecules and even entire damaged organelles is the lysosome. This specialized function of lysosomes requires that this versatile degradation powerhouse maintains an acidified environment stocked with hydrolytic enzymes that are secluded from other cellular contents by the lysosomal membrane. This isolation allows for regulated degradation of cellular components, whereby macromolecules targeted for degradation are transported to the lysosomes. Once broken down, the lysosomal catabolites

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need to exit from the lumen of the lysosome into cytosol in order to be reused and make room within lysosomes for new components targeted for degradation. Thus, apart from the multitude of enzymes required for degrading macromolecules, proper lysosome function requires the cellular machinery that transports macromolecules to the lysosomes and the transporters that allow for the timely exit of catabolites out of the lysosomes. Fabry's and cystinosis are examples of diseases that are caused by mutations in a lysosomal enzyme and a transporter that can result in renal failure, respectively.

Fabry's disease and cystinosis are two lysosomal disorders that involve the accumulation of catabolites within lysosomes of renal cells and have been accompanied by inflammation and/or tubulointerstitial fibrosis [1–6], which are common mediators of end-stage renal disease. Here, we examine how lysosomal disorders result in abnormal renal functions and chronic kidney disease. First, we illustrate some of the normal functions of lysosomes in renal physiology, which in theory could be directly perturbed due to inappropriate degradation of a protein or may be indirectly disrupted as a consequence of accumulation of material within lysosomes that occurs in lysosomal storage disorders. We then go into the details of Fabry's disease and cystinosis, before summarizing the current and future approaches to restore renal function in patients with renal diseases originating from lysosomal defects.

The functions of lysosomes in renal physiology

A. Recycling of low molecular weight proteins that cross the glomerular filter

Lysosomes are an integral part of the molecular machinery that facilitates normal renal physiology. One critical function of the lysosome is in the catabolism of low molecular weight proteins that make it through the glomerular filter and into the lumen of the nephrons. The normal filtration of blood by the glomeruli effectively prevents the entry of high molecular weight proteins into the filtrate that enters the lumen of the nephrons, but not low molecular weight proteins. A majority of the filtered low molecular weight proteins that enter the renal tubular lumen are immediately endocytosed by the cells of the proximal convoluted tubules in a megalin and cubilin dependent manner [7–9] and targeted to the lysosomes for degradation. Both megalin and cubilin are multi-ligand receptors expressed in microvilli and in clathrin-coated pits of proximal tubular epithelial cells. Mice with conditional inactivation of megalin and cubilin in their nephrons excrete a lot of low molecular weight proteins in their urine [8]. The large extracellular domain of megalin acts as a receptor for multiple ligands, whereas its intracellular domain interacts with adaptors that mediate endocytosis [7]. These endosomes filled with low molecular weight proteins are then targeted to the lysosomes for degradation. The devastating consequence of disrupting this lysosomal mediated degradation of low molecular weight proteins is revealed in different forms of renal Fanconi syndrome in humans. Examples of renal diseases resulting in low molecular weight proteinuria and even progressive renal failure that are associated with defective lysosome function in proximal tubules include deficiencies in the lysosomal protein Scavenger Receptor Class B member 2 (SCARB2), deficiencies in the voltage-gated chloride/proton antiporter, CLC-5, and deficiencies in OCRL1, a lipid phosphatase [10–12].

Loss of CLC-5 impairs trafficking of megalin to the apical membrane resulting in defective endocytosis of low molecular weight proteins by the proximal tubules [13, 14]. Additionally, CLC-5 along with megalin is required for the endocytosis of circulating lysosomal enzymes that are filtered through the glomeruli. These lysosomal enzymes, such as procathepsin B, an important cysteine protease, are then incorporated into lysosomes of proximal tubules and play a critical role in proximal tubule lysosome function [15]. Mutations in *CLCN5* which codes for CLC-5 are associated with Dent's disease in humans, a common feature of which is low molecular weight proteinuria, along with hypercalciuria, nephrolithiasis, nephrocalcinosis and progressive renal failure. Mutations in *CLCN5* account for 50 to 60% of Dent's disease patients, with approximately 15% having mutations in *OCRL1* and the genetic basis of 25 to 35% of Dent's disease patients remaining unknown. Interestingly, mutations in *OCRL1* have also been associated with Lowe syndrome, an oculo-crebro-renal syndrome. Missense mutations that occur in *OCRL1* exons 4 to 15, involving the phosphatidylinositol phosphate 5-phosphatase domain, are associated with Dent's disease, whereas *OCRL1* mutations occurring in exons 9 to 22 have been associated with Lowe syndrome [11]. Studies have reported that much like CLC-5, OCRL1 is necessary for the proper membrane trafficking, including that of megalin to the cell surface, which would explain the low molecular weight proteinuria observed in Lowe syndrome patients [16, 17]. SCARB2 deficiency in humans is associated with action myoclonus renal failure syndrome that results in progressive neurological diseases, focal and segmental glomerular sclerosis (FSGS), severe proteinuria and renal failure [10]. A less severe pathology observed in humans with SCARB2 deficiency is tubular proteinuria, which is also observed in Scarb2 deficient mice. The absence of SCARB2 results in the failure of endosomes containing reabsorbed proteins to fuse with lysosomes in the proximal tubular epithelial cells [18]. These are examples of how improper membrane trafficking of molecules destined for the lysosomes result in renal disease. Hence, failure of lysosome mediated proteolysis in the proximal tubule can result in low molecular proteinuria and is associated with focal segmental glomerulosclerosis and progressive renal failure.

B. Regulation of water reabsorption by the principal cells and electrolyte homeostasis

A second critical role for lysosomes and lysosomal proteins is in mediating the central kidney function of maintaining water and electrolyte homeostasis. Inactivation of *lysosomal integral membrane protein 1* (*Limp1*; also known as *CD63*) in mice results in abnormal intracellular lamellar inclusions in the principal cells (suggestive of lysosomal dysfunction), along with polyuria, and reduced urine osmolality [19]. The precise reason for the impaired water reabsorption by *Limp1* deficient principal cells remains unknown. Normal water homeostasis is dependent on the regulated transport of the aquaporin2 (Aqp2) water channel containing intracellular vesicles to the apical surface of principal cells to make the apical plasma membrane permeable to water. In addition the apical Aqp2 is constitutively internalized by the endosomal system and is either recycled or targeted for lysosomal degradation [20]. In the *Limp1* deficient principal cells, it is possible that there is a partial reduction in transport of Aqp2 to the apical surface due to defective membrane trafficking/Aqp2 recycling in the presence of a lot of abnormal intracellular inclusion bodies.

Yet another endosomal/lysosomal protein implicated in water reabsorption in mice is ceroid neuronal lipofuscinosis type 3. The recessive inheritance of mutations in *CLN3* is correlated with the juvenile form of neuronal ceroid lipofuscinosis, also known as Batten disease [21]. The symptoms that begin to manifest in children include visual problems, seizures and a deterioration of cognitive and motor skills. The loss of neurons in *Cln3* deficient mice is well documented and could explain the decline in cognitive and motor skills [22]. More recently *Cln3^{LacZ/LacZ}* mice on a C57BL/6J background have been reported to have a mild urine concentrating defect along with polyuria and hyperkalemia [23]. In these mice the LacZ open reading frame fused with a nuclear localization signal has been knocked into the *Cln3* locus to replace exon 1 to intron 8 of *Cln3*. Consistent with a function for *Cln3* in water reabsorption, the expression of beta-galactosidase (β -gal) coded for by the LacZ in the *Cln3^{LacZ/+}* reporter mouse has been detected in the cortical, medullary and papillary collecting ducts. Even more specifically, β -gal is expressed in the principal cells and not in the intercalated cells of the collecting ducts [23]. Insufficient reabsorption of water from the filtrate by principal cells is usually a consequence of lower than normal levels of Aqp2 water channels in apical surface. Mutations in *AQP2* and *AVPR2* genes in humans result in severe water concentrating defects resulting in nephrogenic diabetes insipidus (NDI) [20]. Interestingly, NDI patients are highly susceptible to dehydration and if left undiagnosed frequently incur mental and growth retardation, and in approximately 5 to 9% of inherited NDI the genetic basis is unknown [20, 24]. Seizures rarely occur in NDI patients, and usually as a result of rehydrating too rapidly. The fact that *Cln3* is specifically transcribed in principal cells and not in most other renal epithelial cells is suggestive of a specialized function for *Cln3* in principal cells [23]. A direct involvement of *Cln3* in water reabsorption may involve *Cln3* directly mediating the trafficking of Aqp2 containing vesicles, or *Cln3* targeting a vesicle containing a negative regulator of Aqp2 transport to the apical surface to the lysosome for degradation, or targeting a positive regulator of Aqp2 endocytosis from the apical surface of principal cells for degradation. However, first it will be important to determine by electron microscopy whether there is an accumulation of intercellular vesicles, lamellar inclusions or lysosomes in the *Cln3* deficient principal cells to rule out an indirect effect of lysosomal accumulation on membrane trafficking in the principal cells. Apart from the urine concentrating defect, the *Cln3^{LacZ/LacZ}* mice also have increased serum K^+ levels with a concomitant reduction in fractional excretion of K^+ in the urine. Interestingly, K^+ secretion is primarily dependent on the potassium ion channels ROMK and BK expressed in the distal nephrons, and the apical membrane of principal cells of the cortical and medullary collecting ducts. Once again the trafficking of these ion channels is tightly regulated to maintain physiologic levels of K^+ in the serum which may be disrupted either directly or indirectly by the absence of *Cln3* in principal cells.

Another manifestation of the critical involvement of lysosomes in mediating renal functions comes from studies on With No Lysine (WNK) family of serine/threonine kinases. WNK4 is a serine/threonine kinase that regulates the amount of cell surface sodium chloride co-transporter (NCC) by inhibiting forward trafficking of NCC to the plasma membrane and targeting NCC for lysosomal degradation [25, 26]. Mutations in WNK4 cause the human disease *Familial Hyperkalemic Hypertension*, in which the serum K^+ levels are increased.

Hence, lysosome mediated degradation of transporter proteins is critical in maintaining electrolyte balance.

Lysosomal dysfunction in Fabry's disease disrupts podocyte foot processes, and induces inflammation and fibrosis

Fabry's disease is caused by germ-line mutations in an X-linked gene coding for the enzyme α -galactosidase (α -GalA) and leads to the lysosomal accumulation of glycosphingolipids, including globotriaosylceramide, in the kidney and other tissues. This accumulation of glycosphingolipids in lysosomes primarily impairs renal function often resulting in end-stage renal disease in the third to fifth decades of life. In which kidney cells do glycosphingolipids accumulate in Fabry's disease and how does this result in renal failure?

The normal expression pattern of α -galactosidase in human kidneys includes renal interstitial cells, and epithelial cells of the proximal convoluted tubules, loop of Henle, distal tubules, and collecting ducts. The expression of α -galactosidase was not detected in podocytes of glomeruli or the parietal cells of the Bowman's capsule or the endothelial cell of the renal vasculature [27]. However glycosphingolipid (GSL) accumulation in the Fabry human kidneys has been observed predominantly in cells of the renal corpuscles including podocytes, mesangial cells and parietal epithelial cells, suggestive that α -galactosidase is also required in these cell types. GSL accumulates in the proximal and distal tubular epithelial cells, interstitial cells and endothelial cells, but at a lower frequency than in the glomerular cell types. In contrast, the α -galactosidase deficient mice (GLA knock-out mice) do not develop a progressive kidney disease and the GSL accumulation occurs predominantly in proximal and distal tubular epithelial cells and only in a smaller percentage of mesangial cells and podocytes as compared with GLA-deficient human kidneys [28]. This differential GSL accumulation between mice and humans deficient in GLA is likely of significance in understanding how GSL accumulation leads to renal failure in humans, but not in mice. Other histologic features unique to the human and not mouse GLA deficiency that correlate with the decline in renal function are glomerulosclerosis and tubulointerstitial fibrosis [1, 3, 28], which are common pathologic cellular processes to many different primary causes of kidney diseases that result in renal failure [29]. It is likely that accumulation of lysosomes containing GSL in podocytes and mesangial cells triggers glomerulosclerosis and tubulointerstitial fibrosis, which in turn impair renal function.

The question remains as to how lysosomes accumulating GSL in podocytes and mesangial cells trigger renal failure. Ultrastructural analysis of glomeruli from Fabry patients revealed mesangial hypercellularity, vacuolated podocytes and podocyte foot process effacement in most cases, along with the occurrence of proteinuria [30]. One hypothesis is that the abnormal catabolism of glycosphingolipids results in the loss of net negative charge on the surface of the podocytes. It is known that removal of the negatively charged sialic acid from the podocyte plasma membrane triggers podocyte foot process effacement and subsequently proteinuria. An alternate hypothesis as to how lysosomal dysfunction in Fabry's disease leads to kidney failure is that abnormal GSL metabolism triggers inflammation, which then results in a self-sustaining process of fibrosis and eventually results in renal failure [31, 32]. Hence, Fabry's disease may be considered to be a specific type of glomerulonephritis in

which GSL accumulation, and/or the increased production of autoantibodies in Fabry's disease [33], triggers glomerular inflammation and fibrosis, resulting in proteinuria and chronic kidney disease. In further support of this hypothesis, there have been numerous reports of the co-occurrence of glomerulonephritis and Fabry's disease [32, 34–36].

Cystinosis primarily prevents proximal tubular functions and eventually destroys the proximal tubules resulting in non-functional nephrons

Cystinosis is an autosomal recessive pediatric lysosomal disorder in which cystine accumulates within lysosomes due to the absence of functional cystinosin resulting from mutations in the gene *CTNS* [37–40]. Cystinosin mediates transport of cystine from the lysosomal compartment into the cytosol, where it is reduced to two cysteine molecules that are used in protein synthesis and other processes, such as glutathione synthesis [41, 42].

There are varying degrees of disease severity, which are dependent upon the nature of the mutation in cystinosin and can range from a mild form that manifests as ocular defects to the most severe nephropathic form ([43]; most recently reviewed in [44]). Nephropathic cystinosis, which comprises about 95% of the cases of cystinosis, manifests as Fanconi syndrome in the first year of life and, if left untreated, progresses to renal failure by 10 years of age. Patients with this severe infantile form of cystinosis are born with nephrons that appear normal, but the proximal tubules become narrower with age, eventually resulting in atubular glomeruli. Nephrons dissected from cystinotic patients during the proximal tubule degeneration have the swan neck deformity that has long been recognized as the hallmark of cystinosis [45, 46]. The progressive loss of the proximal tubular compartment and presence of predominantly atubular glomeruli accounts for the eventual loss of renal function if left untreated. Histopathology of the kidney in cystinosis reveals progressive tubular atrophy and interstitial nephritis accompanying the decline in renal function [5].

The question of how cystine accumulation within lysosomes compromises the function and survival of the proximal tubular compartment of the nephron remains elusive. In the first 6 months of life, cystinotic patients present with symptoms such as loss of amino acids, phosphate, glucose and low molecular weight proteins in the urine, which are consequences of the insufficient reabsorption by the proximal tubules [5, 47]. Low molecular weight proteins that pass through the glomerular filtration apparatus are normally captured by megalin and cubulin receptors present in the apical brush borders of the proximal tubules [9]. Receptor-mediated endocytosis via the formation of clathrin-coated pits allows for the reabsorption of low molecular weight proteins into endosomes within proximal tubules. These endosomes are then targeted to lysosomes within which the low molecular weight proteins are catabolized. The occupation of lysosomes by cystine in patients with mutations in cystinosin likely results in a backlog of substrates, such as the low molecular weight proteins, destined for lysosome mediated catabolism [48–50]. This in turn may result in defective endocytosis within proximal tubules which would explain the impairment of proximal tubular reabsorption in general. Indeed, up-regulation of Rab27-dependent transport appears to ameliorate some of the cellular defects in cystinosis [51]. In addition, autophagy may be compromised in cystinotic cells [48, 49] lending to kidney injury, since

autophagy-dependent lysosome recycling and biogenesis is important for normal kidney function [52].

The molecular hypotheses as to how accumulation of cystine in lysosomes results in the loss of proximal tubular cells emerge from a number of studies [53]. Protein hydrolysis in the lysosomes yields the dimer cystine. Cystine is transported into the cytosol where it is reduced to two cysteine monomers and used in downstream cellular processes. However, because cystinotic lysosomes lack a functional cystine transporter, this recycling of cystine is defective, probably resulting in the apoptosis that is observed [54, 55]. It has been proposed by several groups that glutathione levels are limited and ATP is depleted, and disruption of glutathione-mediated protection from oxidative stress and/or ATP metabolism results in apoptosis of the cystinotic proximal tubular cells [49, 53, 56–63]. Swollen and morphologically abnormal mitochondria, increased mitophagy, and increased expression of caspase-4, a cysteine protease that plays a role in programmed cell death, have been observed in cystinotic tubular cells [49, 64].

Another mechanism may also contribute to apoptosis in cystinosis. It has been postulated that as the lysosomes accumulate cystine, they fragment, releasing cystine into the rest of the cell. The resulting cystine modifies proteins, changing their function. Indeed, a pro-apoptotic kinase protein kinase C δ is cysteinylated in cystinotic cells, presumably causing the increased activity of the kinase that is also observed [65].

Of course, yet another possibility is that cystinosin is promiscuous, having other uncharacterized function(s) in addition to cystine transport or that cystine accumulation is affecting a yet unidentified pathway. Using a single-celled eukaryotic model organism with a well-annotated genome such as the yeast *Saccharomyces cerevisiae* may give clues to other functions for human cystinosin and the role of cystine recycling in downstream cellular processes such as respiration and redox regulation. Although it has been suggested that, unlike patients, yeast do not store cystine and characterization of the cystine transport activity of the yeast ortholog Ers1p is yet to be reported, expression of human *CTNS* complements the deletion of the *ERS1* gene in *ers1*- cells [66]. Furthermore, preliminary studies on genetic interactions of the *ERS1* and *in silico* promoter analysis all indicate a conserved function. Investigation of compensatory pathways for correcting cystine accumulation in yeast may prove useful in understanding the molecular details of how cells respond to defects in cystine recycling.

Are there links between lysosomal disorders and tubulointerstitial fibrosis?

A common element involved in progressive loss of renal function regardless of the primary defect is tubulointerstitial fibrosis [29]. Tubulointerstitial fibrosis involves the sustained activation of interstitial cells, termed myofibroblasts, which synthesize excessive amounts of extracellular matrix proteins that accumulate in the interstitium. Fabry's disease appears to involve tubulointerstitial fibrosis as a mediator of the progressive loss of renal function [2] and glomerulosclerosis and interstitial fibrosis have been reported even in early stages of human Fabry's disease [1, 4]. In one analysis combining several human Fabry studies, the renal histopathologic feature in Fabry patient biopsies that best correlates with chronic

kidney disease stage turned out to be tubulointerstitial fibrosis [3]. Recent studies of mice with conditional inactivation of the mammalian homologue of yeast vacuolar protein sorting defective 34 (mVps34) reveal a critical role for endocytosis in maintaining podocyte function [67] and preventing proteinuria and severe renal lesions including renal interstitial inflammation and fibrosis [68]. The Vps34-deficient podocytes accumulate large LAMP1 and LAMP2 positive vacuoles, indicative of deficient lysosomal degradation [67, 68]. Although, tubulointerstitial fibrosis is a logical link between persistent focal renal injuries and progressive decline in renal function resulting in chronic renal disease, the evidence for the occurrence of tubulointerstitial fibrosis in cystinosis is lacking. It will be critical to understand how intracellular accumulation of lysosomes in renal cells triggers fibrosis in some of the lysosomal storage disorders such as Fabry's, especially for assisting patients where the disease is not diagnosed early[6].

Current and future approaches to restore renal function in patients with renal diseases originating from lysosomal defects

For diseases of organs other than the brain caused by the absence or reduction in a soluble lysosomal enzyme, the standard approach to improve the quality of life and slow disease progression has been enzyme replacement therapy (ERT). This takes advantage of the presence of plasma membrane Mannose 6-phosphate receptor mediated endocytosis and targeting of exogenous enzyme to the lysosomes. Currently, two different forms of ERT are available for treatment of Fabry disease: A galsidase alfa (Repalagal, Shire Human Genetic Therapies, Inc., Cambridge, MA) and agalsidase beta (Fabrazyme, Genzyme Corporation, a Sanofi company, Cambridge, MA). It is hypothesized that ERT from the early stages of the Fabry disease will be beneficial, however this remains to be proven [69]. Not surprisingly, ERT is unlikely to be as beneficial if treatment is initiated late in the course of a lysosomal disease, as many secondary and self-sustaining processes such as inflammation and fibrosis are likely to have taken hold to further disrupt renal structure and function.

Current treatment for cystinosis includes administration of aminothiols cysteamine bitartrate (Cystagon®, Mylan Pharmaceuticals Inc., Morgantown, WV) pills and eye-drops and renal transplantation (most recently reviewed in [44]). Cysteamine aids in the clearance of cystine from the lysosome and is very effective in reducing both renal and non-renal complications [5, 70]. Interestingly, cysteamine may also restore glutathione in proximal tubule cells [63]. However, cysteamine needs to be administered early in life, requiring prompt diagnosis and full compliance for the patient's entire life, and does not fully ameliorate the Fanconi syndrome [71–73]. Cysteamine compliance is difficult due to nausea and other gastrointestinal issues, but the delayed-release form of cysteamine called PROCYSBI™ (Raptor Pharmaceuticals, Novato, CA) is just as effective at reducing intracellular cystine with reduced side effects [74]. Gene therapy is another attractive preventative option for renal dysfunction and early studies of *CTNS* transgene delivery via hematopoietic stem and progenitor cells in a mouse model are promising [75].

Conclusions

As can be seen through a comparison of Fabry's disease and cystinosis, there is not one simple all-encompassing explanation as to why lysosomal dysfunction, specifically an enzyme and transporter, respectively, results in kidney abnormalities. Considering that lysosomes contribute to a myriad of renal functions it is intriguing that many lysosomal disorders adversely impact the nervous system and very few lysosomal defects are known to cause renal diseases. The scarcity of renal defects associated with lysosomal disorders is likely an illusion. For one the renal system has a lot more redundancy built into it with on average a million nephrons per human kidney carrying out the same function, whereas at best a small number of neurons are likely capable for compensating for the loss of each other's functions. In addition the nephrons are capable of undergoing repair following acute injuries, and this is likely to allow for the turnover of renal epithelia that are severely compromised by the accumulation of storage material in lysosomes. All this is likely to delay the overt manifestation of renal functional deficits, with early structural abnormalities going unnoticed without careful investigation in many of the lysosomal diseases. In support of this view is the recent identification of renal functional defects in *CLN3^{lacZ/LacZ}* mice whereas children with *CLN3* mutations are known to have neurological and not renal problems. As disorders such as Batten disease that do not have renal defects as the primary manifestation are treated more effectively, there may be an unmasking of renal defects in these disorders that were once thought to exclude the kidney. While our understanding of the involvement of the lysosome in renal processes has improved dramatically, future studies to characterize the cellular and molecular implications of lysosomal enzymes and transporters on overall kidney function are invaluable for synthesis of new treatments.

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Table 1

Summary of discussed lysosomal deficiencies mediating kidney diseases.

Disease	Gene Symbol; Protein	Intracellular localization	Function	Storage material in kidney	Effect of genetic mutations on human kidney	Effect of genetic mutations on mouse kidney
Cystinosis	<i>CTNS</i> ; Cystinosis [39]	Lysosome [76]	Cystine transporter [42]	Cystine [37]	Acquired severe proximal tubule 'swan neck' deformity [45, 46]	Mild tubular dysfunction in C57BL/6 <i>ctns</i> ^{-/-} [77]
Fabry's	<i>GLA</i> ; α -galactosidase [4, 28]	Lysosome [1, 28]	Enzyme [28]	GSL [31]	GSL accumulates predominantly in podocytes, mesangial cells and parietal epithelial cells leading to glomerulosclerosis, interstitial fibrosis, proteinuria and resulting in renal failure [1, 3, 27]	GSL accumulates predominantly in proximal and distal tubular epithelial cells and does not result in renal failure [28]
Batten (JNCL)	<i>CLN3</i> ; ceroid lipofuscinosis, neuronal 3 [21]	Early and late endosomes, and lysosomes; subcellular localization changes in response to osmotic stress [78]	Transmembrane protein possibly involved in membrane trafficking.	Not known	No human kidney defects have been reported.	<i>Cln3</i> ^{luc2/luc2} mice on a C57BL/6J background have urine concentrating defect, polyuria and hyperkalemia [23]
Pseudo-hypoadosteronism, type IIB	<i>WNK4</i> ; with no lysine 4 [79]	Tight junctions [79]; perinuclear and peripheral granular structures [25]	Serine/threonine Kinase [79]; maintains homeostasis of ion channels and transporters in part by regulating the targeting of NCC to lysosomes [25]	None known	Hypertension, hyperkalemia, metabolic acidosis [79]	<i>Wnk4</i> ^{D561A/+} mice develop hypertension, hyperkalemia, metabolic acidosis [80]
Action myoclonus-renal failure syndrome (AMRF)	<i>SCARB2</i> / <i>LIMP2</i> ; Scavenger receptor class B, Member 2 [18]	Lysosomes and endosomes [18]	Endosome to lysosome trafficking [18]	None known	Renal failure, FSGS, Nephrotic-proteinuria [10]	Proteinuria [18], hydronephrosis [81]
Dent's/Dent 1 [11]	<i>CLCN5</i> ; CLC-5 [12]	Endosomes [14]	Voltage-gated chloride/proton antiporter; vesicle trafficking [14]	None known	LMW proteinuria, hypercalciuria, nephrocalcinosis, nephrolithiasis and renal failure [12]	LMW proteinuria, hypercalciuria and nephrocalcinosis, [14, 82]
Oculo-Cerebro-Renal syndrome of Lowe (OCRL)/Dent 2 [11]	<i>OCRL1</i> ; OCRL [17]	Golgi and early endosomes [17]; primary cilium [83]	Lipid phosphatase; membrane trafficking regulator [17]	None known	LMW proteinuria, hypercalciuria, nephrocalcinosis, nephrolithiasis and renal failure [11]	<i>Ocrl1</i> ^{-/-} mice have no renal phenotype. However, <i>ocrl1</i> ^{-/-} ; <i>inpp5b</i> ^{-/-} mice carrying transgenic human <i>INPP5B</i> locus manifest human Dent 2 renal symptoms [84].

Disease	Gene Symbol; Protein	Intracellular localization	Function	Storage material in kidney	Effect of genetic mutations on human kidney	Effect of genetic mutations on mouse kidney
	<i>CD63</i> also known as <i>LAMP3</i> or <i>Limp1</i>	Plasma membrane, late endosomes, lysosomes[19]	Tetraspanin likely regulates membrane trafficking [85].	Abnormal intracellular lamellar inclusions in principal cells [19]	No kidney defects have been reported.	Reduced urine osmolality, polyuria [19]
	<i>PIK3C3</i> ; vacuolar sorting protein defective 34 (vps34) [67]	early endosomes[67]	Lipid kinase, regulates early endosomal sorting, and possibly endosome to lysosome trafficking in podocytes [67]	LAMP1 and LAMP2 positive vacuoles accumulate [68]	No kidney defects have been reported.	Conditional knock out in podocytes results in renal interstitial inflammation, fibrosis, proteinuria, renal failure [67, 68]

Abbreviations in Table 1: GSL = glycosphingolipids, FSGS= focal segmental glomerulo-sclerosis, NCC= sodium chloride co-transporter, LMW= low molecular weight.