Dent's Disease

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1. Introduction

Dent's disease (MIM #300009) is a rare X-linked disorder characterized by various degrees of proximal tubular (PT) dysfunction, nephrocalcinosis and nephrolithiasis. The exact prevalence is unknown. The disease was first reported by Dent and Friedman, who described two males with vitamin D resistant rickets, hypercalciuria and low molecular weight proteinuria (LMWP) (Dent & Friedman, 1964). Based on these data and another 13 patients with a similar phenotype, Wrong et al. coined the term "Dent's disease" for the combination of X-linked low molecular weight proteinuria, hypercalciuria, nephrocalcinosis, metabolic bone disease and progressive renal failure (Wrong et al., 1994). With the advent of molecular genetics it has become clear that the phenotypically similar disorders *X-linked recessive nephrolithiasis with renal failure* (MIM #310468) and *X-linked recessive hypophosphatemic rickets* (MIM #300554) are also due to mutations in the *CLCN5* gene (Lloyd et al., 1996). Familial idiopathic LMW proteinuria with hypercalciuria in Japanese patients (MIM #308990) – also referred to as Dent's Japan disease (Igarashi et al., 1995) - is a fourth clinical entity resulting from *CLCN5* mutations (Nakazato et al., 1997). Therefore, Scheinman proposed to summarize *CLCN5*-associated renal disease under the term "X-linked hypercalciuric nephrolithiasis" (Scheinman, 1998). The same clinical phenotype has been observed with some mutations in the oculo-cerebrorenal syndrome of Lowe (*OCRL*) gene and is referred to as Dent-2 disease (MIM #300555) (Hoopes et al., 2005; Utsch et al., 2006).

2. Clinical manifestations

The clinical presentation of Dent's disease is frequently subtle with the majority of patients being asymptomatic during childhood. Therefore, many patients are identified through urine screening for hematuria and proteinuria as it is done systematically in Japanese school children (Lloyd et al., 1997).

A summary and the frequency of the major clinical and biochemical characteristics of Dent's disease are presented in table 1. Hereby it should be noted that the manifestations of Dent's

disease are highly variable even within the same family and there is no genotype-phenotype correlation (Ludwig et al., 2006).

	Dent 1 (*CLCN5*)	Dent 2 (*OCRL*)
LMWP	100% (212/212)	100% (28/28)
Hypercalciuria	90% (180/200)	86% (24/28)
Nephrocalcinosis	75% (137/182)	39% (11/28)
Aminoaciduria	41% (31/75)	52% (11/21)
Renal tubular acidosis	3% (2/68)	4% (1/27)
Phosphate wasting	22% (35/156)	24% (6/25)
Potassium wasting	15% (10/67)	6% (1/18)
Glycosuria	17% (18/108)	11% (3/28)
Renal failure	30% (60/203)	32% (8/25)

Table 1. Spectrum of renal dysfunction in Dent's disease due to *CLCN5* (Dent 1) and *OCRL* (Dent 2) mutations (adapted from Bökenkamp et al., 2009).

Although nephrocalcinosis and hypercalciuria are characteristic findings in Dent's disease, it is the presence of LMWP, which distinguishes patients with *CLCN5* mutations from other hypercalciuric stone-formers (Scheinman et al., 2000). Protein excretion in Dent's disease is around 0.5 to 1 g per day, with LMWP accounting for 50 to 70% of the total protein (Scheinman et al., 1998). LMWP can be detected by means of SDS-PAGE urine electrophoresis, or by measurement of marker proteins such as alpha-1 microglobulin, beta-2-microglobulin, cystatin C, lysozyme or retinol-binding protein in the urine. As albumin absorption by endocytosis in the proximal tubule is also impaired, albuminuria is present as well and can be detected by urine dipstick analysis. Recently, two papers reported asymptomatic nephrotic-range proteinuria of up to 50 mg/m^2/h in 6 patients with *CLCN5* mutations (Frishberg et al., 2009; Copelovitch et al., 2007). Of note, serum albumin was normal in all these patients and urine protein consisted largely of low molecular proteins, which underscores the need to measure low molecular proteins in patients with unexplained proteinuria.

The majority of patients have nephrocalcinosis, while nephrolithiasis is observed in some 40% of patients (Claverie-Martin et al., 2011). The kidney stones are composed of calcium phosphate, calcium oxalate or a combination of both (Wrong et al., 1994; Scheinman, 1998). Nephrolithiasis and nephrocalcinosis are also observed in the absence of hypercalciuria (Ludwig et al., 2006), which may be explained by a defect in the clearance of microcrystals in the collecting duct as demonstrated in *CLCN5*-disrupted collecting duct cells (Sayer et al.,

2003, 2004). Urinary excretion of citrate and oxalate is normal in the majority of cases (Wrong et al., 1994; Scheinman et al., 1998), while urinary acidification may become impaired with progressive nephrocalcinosis (Ludwig et al., 2006).

Mild to moderate hypercalciuria of 4 to 6 mg/kg per day is characteristic for Dent's disease, with higher calcium excretion being found in childhood (Scheinman, 1998). In about 10% of patients with *CLCN5* mutations, hypercalciuria is missing, in particular in patients with renal failure because calcium excretion diminishes with decreasing GFR (Ludwig et al., 2006). Half of the patients are reported to have fasting hypercalciuria and almost all have an exaggerated calciuric response after an oral calcium load (Reinhart et al., 1995). Serum parathyroid hormone levels are usually low, while levels of 1,25-dihydroxyvitamin D are frequently high (Scheinman, 1998). This reflects the complex balance between the loss of 25-hydroxyvitamin D along with vitamin D binding protein and the stimulation of 1,25-dihydroxyvitamin D synthesis by increased luminal parathyroid hormone delivery (Günther et al., 2003).

Kidney function is normal during childhood in most patients with a slowly progressive decline during adulthood leading to end-stage renal failure in 30 to 80% of affected patients in the 3rd to 5th decade (Wrong et al., 1994; Bökenkamp et al., 2009). Histological studies may be normal or show tubular atrophy and interstitial fibrosis, foci of calcinosis and non-specific glomerular changes as hyalinosis, sclerosis and periglomerular fibrosis (Wrong et al., 1994). Recently, two papers reported focal segmental glomerulosclerosis with asymptomatic nephrotic range proteinuria associated with *CLCN5* mutations (Frishberg et al., 2009; Copelovitch et al., 2007). As pointed out by Wrong et al., the progressive decline in renal function is more severe than would be expected as a result of nephrocalcinosis alone (Wrong et al., 1994), but is characteristic for various forms of the renal Fanconi syndrome (Norden et al., 2001). Norden et al. demonstrated increased concentrations of potentially bioactive hormones and chemokines such as parathyroid hormone, insulin, insulin-like growth factor 3, growth hormone and monocyte chemoattractant protein 1 in the urine of patients with Dent's disease, autosomal dominant Fanconi syndrome and Lowe syndrome which may be involved in the pathogenesis of the progressive tubulointerstitial damage (Norden et al., 2001).

The proximal-tubular defect in Dent's disease may lead to hypophosphatemia. However, there is no clear correlation between the degree of hypophosphatemia and the presence of rickets, which can be observed in about 1/3 of Dent's patients (Scheinman, 1998). Renal potassium wasting – although relatively infrequent - may be exacerbated by the use of thiazide diuretics as reported by Blanchard et al. (Blanchard et al., 2008). Another finding in patients with Dent's disease as well as in other conditions with proximal tubular dysfunction is the decreased uptake of [99mc]Tc-DMSA (dimercaptosuccinic acid) in renal parenchyma with rapid excretion of the tracer into the urine (Lee et al., 2009).

Depending on the degree of lionization, female carriers display a milder phenotype. LMWP is seen in 60 to 90%, while hypercalciuria was observed in around 30% (Reinhart et al., 1995). Although abnormal, the amount of LMWP is 10 to 100 times lower than in males (Scheinman, 1998). Nephrolithiasis and nephrocalcinosis are infrequently seen, and there is only 1 case of end stage renal disease in a female carrier reported so far (Devuyst & Thakker, 2010).

The diagnosis of Dent's disease is based on the presence of low molecular weight proteinuria, hypercalciuria, nephrocalcinosis/nephrolithiasis and various degrees of generalized proximal dysfunction and decreased GFR in otherwise phenotypically healthy males.

Differential diagnosis should include other inherited and acquired causes of proximal tubular dysfunction such as cystinosis, Lowe syndrome, mitochondrial nephropathy or ifosfamide nephropathy.

3. Underlying genetic causes

3.1 *CLCN5* gene (Dent 1, MIM #300008)

The *CLCN5* gene, affected in patients with Dent 1 disease, was initially identified in a family with a microdeletion on the X-chromosome (Fisher et al., 1995). The inheritance is X-linked with ~10% of the mutations being *de novo* (Devuyst & Thakker, 2010). *CLCN5* encodes an electrogenic Cl^-/H^+ antiporter (ClC-5) (Picollo & Pusch, 2005; Scheel et al., 2005) with a transport stoichiometry of 2 Cl^- / 1 H^+ (Zifarelli & Pusch 2009). ClC-5 contains two phosphorylation and one N-glycosylation sites and comprises 18 helices (A - R), which show an internally repeated pattern (helices B - I and J - Q, respectively) forming two roughly repeated halves that span the membrane in opposite (antiparallel) orientations (Dutzler et al., 2002) (Fig.1). The selective flow of chloride ions across cell membranes is catalyzed by a ClC-5 homodimer, with each channel subunit forming its own chloride pore (Dutzler et al., 2002; Jentsch, 2002).
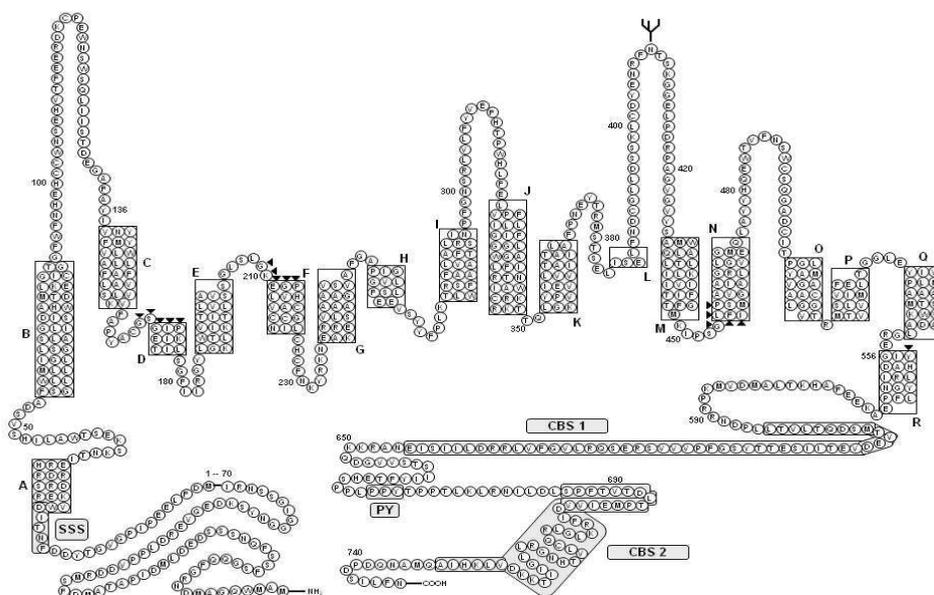

Fig. 1. Topology diagram of the ClC-5 protein adopted from Dutzler et al. (2002, 2003) and Wu et al. (2003)**.** Boxed areas depict helices A-R with the extracellular region shown above, and the cytoplasmic region shown below. Amino acids (helices D, F, N, and R) involved in chloride selectivity filter formation are indicated by black triangles; helices H, I, P, and Q are involved in formation of the dimer interface. Further regions of functional significance are boxed in light gray: SSS, sorting signal sequence (Schwappach et al., 1998); CBS1 and CBS2, cystathionine-β-synthase sequences forming the so-called Bateman domain (Bateman, 1997) that binds ATP (Scott et al., 2004); PY, proline/tyrosine-like internalization signal motif (Schwake et al., 2001). The additional 70 aminoterminal residues in the enlarged ClC-5 isoform (Ludwig et al., 2003) are shown with overall numbering starting with the methionine of the short variant (from Ludwig et al., 2005 printed with kind permission of Springer Science and Business Media).

The *CLCN5* gene spans ~170 kb on chromosome Xp11.23/p11.22 and comprises 17 exons with transcription initiating from at least four different start sites. Transcripts including the untranslated exon 1a (Hayama et al., 2000) or 1b (Fisher et al., 1995) are spliced to exon 2 containing the start-ATG, whereas a third mRNA comprises a larger exon 1b and retains intron 1 (Forino et al., 2004). Two further transcripts (harbouring additional exons I-IV), arise due to alternative splicing of exon II, and are also spliced to exon 2 (Ludwig et al., 2003). Both transcripts carry the start-ATG in exon III, thereby coding for a longer isoform of the ClC-5 protein with additional 70 amino acids at the intracellular amino terminus. Since these two mRNAs maintain the reading frame, the start-codon of the shorter form (746 amino acids) here resides at position 71. So far, the longer variant has only been detected at mRNA but not at protein level (Ludwig et al., 2003).

More than 140 distinct *CLCN5* mutations, distributed along the entire gene, have been reported in patients with Dent 1 disease and no major mutational hot spots have been observed (Wu et al., 2009). There is also no evidence for a genotype-phenotype correlation. Various mutations were found to be associated with quite different clinical phenotypes ranging from 'classic' Dent 1 disease to very slight urinary abnormalities, not only in unrelated patients, but even within the same family (Ludwig et al., 2006).

Dysfunction of mutant ClC-5 channels may be caused by various mechanisms and a lot of the mutations observed are predicted to result in a truncated or absent protein. Complete loss of antiporter function might be caused by impaired homodimerization, altered current kinetics, altered ion selectivity, or defective intracellular trafficking. Heterologous expression of various *CLCN5* mutants, in either *Xenopus laevis* oocytes or HEK293 cells, determined a loss of Cl- conductance in the majority of mutations tested (Lloyd et al., 1996; Ludwig et al., 2005). Further consequences of *CLCN5* mutations were (i) improper N-glycosylation with endoplasmic reticulum retention and degradation of ClC-5 (ii) defective endosomal acidification, (iii) altered endosomal distribution of ClC-5 but not defective endosomal acidification (IV) delayed processing with reduced stability and lower cell surface expression, or impaired internalization (Ludwig et al., 2005; Smith et al., 2009; Grand et al., 2011). The majority of missense mutations cluster at the dimer interface and have been shown to disrupt the assembly of the homodimers (Wu et al., 2003; Smith et al., 2009).

ClC-5-deficient mice recapitulate the human phenotype of Dent's disease with LMWP, generalized aminoaciduria, glycosuria, hypercalciuria and renal calcium deposits. Proximal tubular endocytosis is severely impaired in ClC-5-deficient mice, proving a role for ClC-5 in endosomal uptake of low molecular weight proteins (Wang et al., 2000).

3.2 *OCRL* gene (Dent 2, MIM #300555)

Recent investigations have revealed defects in the *OCRL* gene in about 15% of patients with a Dent's phenotype (Hoopes et al., 2005; Böckenhauer et al., 2011). This gene, located at Xq26.1 comprises 24 exons occupying 52 kb, and alternative splicing of exon 18a enlarges the resultant 893 amino acids-long protein by eight (in frame) additional amino acids (Nussbaum et al., 1997). *OCRL* encodes a phospatidylinositol 4,5-bisphosphate 5-phosphatase and mutations herein were initially found to cause Lowe syndrome (MIM #309000), a pleiotropic disease, characterized by the triad of congenital cataracts, mental retardation and incomplete renal Fanconi syndrome (Böckenhauer et al., 2008). In the OMIM database, Dent's disease associated with *OCRL* mutations is now termed Dent 2 disease (MIM #300555) to distinguish these patients from the more severe Lowe phenotype. Except a lower prevalence of nephrocalcinosis, the renal phenotype is comparable to Dent 1 cases

harbouring a *CLCN5* mutation (Table 1). Dent 2 may present with (mild) extra-renal Lowe symptoms (peripheral cataracts, stunted growth, mild retardation, elevation of serum CK/LDH), implying that Dent 2 disease actually represents a mild form of Lowe syndrome (Bökenkamp et al., 2009; Böckenhauer et al., 2011).

By now, 44 Dent 2 patients having *OCRL* mutations have been reported (Böckenhauer et al., 2011; Hichri et al., 2011). Whereas frame shift mutations or splice defects leading to a premature stop codon in Dent 2 patients all cluster in exons 1-7, they exclusively affect exons 8-23 in Lowe syndrome. Dent 2 was also observed with several missense mutations in exons 9-19, exons typically implicated in Lowe syndrome. Initially, none of the mutations observed in Dent 2 cases had been found in association with classic Lowe syndrome and there was no explanation why the phenotypic consequences of premature termination mutations, expected to cause classic Lowe syndrome, led to the milder form of Dent 2. Most recently, however, Hichri et al. (2011) reported two different *OCRL* mutations (p.Ile274Thr, p.Arg318Cys) each causing both phenotypes even in the same family. Moreover, a patient showing the complete phenotypic Lowe spectrum but absence of any ocular involvement harboured an exon 8 termination mutation (p.Gln199X) (Ludwig et al., 2011), thereby presenting the most severe clinical intermediate between Dent disease and Lowe syndrome.

Given these observations, there exists a phenotypic continuum between patients with Dent 2 disease and Lowe syndrome, not only between patients harbouring different *OCRL* mutations but also between family members affected by the same *OCRL* defect. Nonetheless, the reason(s) why different *OCRL* mutations manifest with the respective phenotype remain(s) to be elucidated. This may be related to the expression profile of inositol polyphosphate 5-phosphatase (INPP5B), which has been shown to compensate for Ocrl deficiency in a mouse model (Jänne et al., 1998). Mice deficient in Ocrl or Inpp5b show little or no phenotype, whereas deficiency of both genes leads to death before implantation. Interestingly, mouse *Inpp5b* and human *INPP5B* differ in expression and splice-site choice (Bothwell et al., 2010). Most recently a mouse model for Lowe syndrome and Dent 2 disease tubulopathy was established by expressing human *INPP5B* in the *Ocrl*-/- mice (Bothwell et al., 2011). These mice showed reduced postnatal growth, LMWP, and aminoaciduria and suggest that human *INPP5B* genotype may influence the clinical manifestation of Dent 2/Lowe syndrome.

It has also been speculated that the use of alternative initiation codons (methionine at position 158, 187, and 206) in exons 7 and 8 will allow the synthesis of truncated OCRL proteins. Indeed, Hichri et al. (2011) have detected two smaller proteins (around 80 kDa) instead of the 104 kDa full-length protein in a Dent 2 case lacking the normal initiator ATG in exon 1. Hence, some residual activity of these smaller products might contribute to the phenotypic differences observed.

3.3 Dent's disease and other candidate genes

Molecular analyses provided evidence for genetic heterogeneity in Dent's disease as in around 25% of patients with typical features of Dent's disease no *CLCN5* or *OCRL* mutations could be detected (Böckenhauer et al., 2011). These patients may carry a *CLCN5/OCRL* mutation undetectable by the common PCR analysis (e.g. in the promoter or an intron, thereby leading to a decrease in expression or a cryptic splice product). On the other hand, a defect in another gene phenocopying Dent's disease might be responsible. Four candidate genes (*CLCN4, CFL1, SLC9A6, TMEM27*) have been investigated so far.

CLCN4, the gene encoding ClC-4 has been analyzed (Ludwig and Utsch, 2004; Hoopes et al. 2005; Wu et al., 2009), since it is located on Xp22.3 and mutations herein would consequently show an X-linked mode of inheritance. ClC-4 (i) is also a member of the ClC-family of chloride channels, giving rise to strongly outwardly rectifying anion currents closely resembling those of ClC-5 (Friedrich et al., 1999), (ii) alike ClC-5, contributes to endosomal acidification and trafficking by epithelial cells of the renal proximal tubule (Mohammad-Panah et al., 2003), and (iii) could be co-immunoprecipitated with ClC-5, indicating that both channels may interact *in vivo* (Mohammad-Panah et al., 2003). In a total of 30 unrelated cases no defect was observed.

Hoopes et al. (2005) investigated the *SLC9A6* gene in a panel of 13 patients that met the strict criteria for Dent's disease. *SLC9A6*, located at Xq26.3, encodes the Na+/H+ exchanger 6 (NHE6; Numata et al., 1998). This sodium-proton exchanger localizes to early recycling endosomes and may contribute to the maintenance of the unique acidic pH values of Golgi and post-Golgi compartments (Nakamura et al., 2005). The X-linked *TMEM27* gene has also been suggested a good candidate since it codes for collectrin, a transmembrane glycoprotein expressed on the apical membrane of proximal tubuli that was shown to be essential for renal amino acid transport (Danilczyk et al., 2006). However, mutation analysis was negative in 26 Dent-like patients as well (Tosetto et al., 2009) as was the case in 10 patients analyzed for defects in *CFL1* (Wu et al., 2009). This autosomal gene locates on chromosome 11q13.1 and encodes cofilin, a protein shown to interact with ClC-5 in regulating albumin uptake in the proximal tubule (Hryciw et al., 2003).

Given these negative results, a further causative gene still awaits identification. Moreover, effects of (a) modifier locus(i) may influence the phenotype in Dent's patients. This would explain the heterogeneity in the clinical features observed among non-related patients sharing the same mutation or even between family members affected by the same defect (Ludwig et al., 2006).

4. Pathophysiology of Dent's disease

4.1 Localisation of ClC-5 in the kidney

In the kidney ClC-5 is found predominantly expressed in the proximal tubule and in α-intercalated cells of the distal nephron. A small fraction may be present at the cell surface of the medullary thick ascending limb of Henle's loop. In the proximal tubule ClC-5 is mainly located in the intracellular subapical endosomes, where it is co-expressed with the proton pump (V-type H^+ ATPase).

4.2 Role of ClC-5 in endosomal acidification

Along the endocytic pathway a successively decreasing pH from 6.3 to 4.7 is detected in early endosomes, late endosomes and lysosomes with a change in the ionic composition along the endocytic pathway (Casey et al., 2010; Scott et al., 2010). The acidification is mainly due to vacuolar H^+ ATPase, mediating ATP-dependent transport of protons. The movement of H^+ across the endosomal membrane results in a net charge translocation, which has to be neutralized by a passive influx of counter ions such as chloride or by efflux of another cation. Na^+ entry increases the membrane potential and limits acidification.

TRPML3 belongs to the mucolipin family of the TRP ion channels and is present in the early endosomes (Puertollano et al., 2009). Shortly after internalisation of the endosomes there is rapid release of Ca^{2+} from early endosomes through TRPML3 that is necessary for allowing

acidification of this compartment. Once late endosomes or lysosomes become highly acidic, the low pH inhibits TRPML3 channel activity, stopping Ca^{2+} exit and preventing further acidification (Martina et al., 2009; Lelouvier et al., 2010) (Fig.2).

In a study in isolated endosomes performed by Saito et al. (2007) the presence of two poor channels (TPC), releasing Ca^{2+} from the endosome, was demonstrated. Ca^{2+} release was inhibited by the endosome luminal Cl^- with a K50 of 82 mM. Reduction of Cl^- activated Ca^{2+} release, which in turn stimulates H^+ transport to the lumen (Fig.2).

There is ample evidence that ClC-5 has an essential role in the acidification of the endosomes (Plans et al., 2009; Wellhouser et al., 2010; Smith & Lippiat, 2010). Two research groups demonstrated that ClC-5 functions as a voltage–dependent electrogenic chloride/proton exchanger (Picollo et al., 2005; Scheel et al., 2005). In their studies the currents required 20-40 mV voltages, which are not observed *in vivo*. When transposed to endosomal membranes, it means a movement of a positive charge (H^+) into and of negative charge (Cl^-) out of the endosome. Sonawane et al. (2009) showed that within 60 s Cl^- concentration in the lumen is decreased from 120 to 20-30 mmol. Zifarelli and Pusch (2009) determined the absolute proton fluxes using *Xenopus* oocytes from the extracellular proton gradient using a pH sensitive dye. A transport stochiometry of $2Cl^-/1H^+$ was demonstrated. Smith and Lippiat (2010) demonstrated using a targeted pH sensitive fluorescent protein in opossum proximal tubular cells that endosomal acidification was only partially sensitive to the inhibitor of V-ATPase bafilomycin–A1. In the presence of bafilomycin-A1, the acidification was almost fully ablated by the knockdown of endogenous ClC-5 by siRNA. Contrasting previous assumption, these authors suggested that ClC-5 exchanges two Cl^- ions from the endosomal lumen for a proton from the cytoplasm. This leads to endosomal acidification directly by ClC-5 in parallel with V-ATPase (Fig.2).
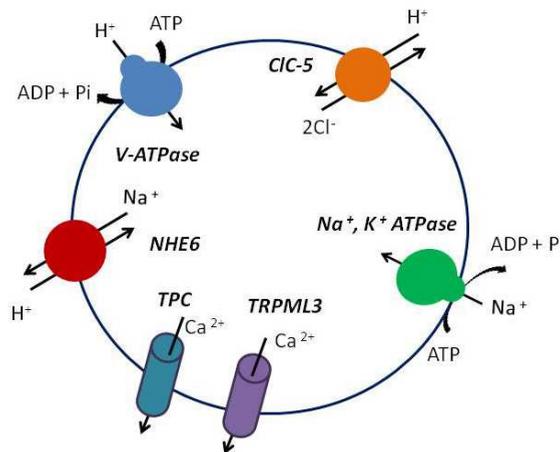
V-ATPase; vacuolar ATPase. ClC-5; chloride channel 5 mutated in Dent 1 disease. NHE6; Na^+/H^+ exchanger 6. TRPML3; mucolipin 3. TPC; two poor channel.

Fig. 2. Major classes of transporters in the early endosome; protons can enter endosome via V-ATPase, ClC-5 and NHE6. Ca^{2+} exit via TRPM3 and via TPC counteracting net charge translocation facilitating endosomal acidification. Na^+ entry increases endosomal membrane potential and limits acidification.

4.3 Role of decreased endosomal acidification in the disturbed proximal tubule transport

A remarkable study was performed by Novarino et al. (2010). They generated mice with a mutation that converted ClC-5 exchanger into a pure Cl^- conductor. In these conditions ATP-dependent acidification of renal endosomes was normal however, proximal tubular endocytosis was impaired. Because the mutation was introduced into the intramembraneous part of the protein, this study made it unlikely that a disturbed interaction between ClC-5 and other partners is involved in the pathogenesis of Dent's disease (Reed et al., 2010). The impaired reabsorption in the proximal tubule is still presumably due to the failure to recycle specific transporters, released by the low endosomal pH, to the apical membrane. A definite pathogenetic concept, however, is still lacking.

4.4 Consequences of ClC-5 dysfunction for the α-intercalated cells

As the acidifying capacity after ammonium chloride loading is normal in the initial phase of Dent's disease, normal H^+ ATPase has to be present at the apical surface of the α-intercalated cells. Carr et al. (2006) demonstrated in a collecting duct cell line, in which ClC-5 was disrupted, a marked increase in annexin A2, a crystal-binding molecule at the plasma membrane. This leads to an accumulation of crystal binding molecules at this site and might underlie nephrocalcinosis in patients with Dent's disease. Interestingly, aquaporin 6 co-localizes with H^+ ATPase in α-intercalated cells and functions as an anion channel, facilitating Cl^- transport (Yasui et al., 1999). The physiological role of aquaporin 6 and its relation to ClC-5 in α-intercalated cells remains to be established.

4.5 Role of OCRL in endosomal trafficking

Detailed description of the cellular phenotype caused by *OCRL* mutations is beyond the scope of this chapter. OCRL protein belongs to a type II polyphosphate 5-phosphatases and is ubiquitously expressed in the Trans-Golgi Network (TGN), endosomes and plasma membrane. OCRL interacts with a broad range of small Rab GTPases, a family of proteins, which together with phosphatidylinositols regulate cellular vesicle trafficking (Vicinanza et al., 2008). Other OCRL interactors include clathrin and adaptor proteins AP1 and AP2. Some mutations detected in patients with Lowe syndrome disturb interaction between OCRL-protein and several Rab GTPases (Hou et al., 2011), however, functional consequences of the other mutations found in Lowe syndrome or in Dent 2 disease are unknown and a mechanistic explanation of differences between the two phenotypes remains to be clarified.

5. Treatment of Dent's disease

At this moment there is no curative treatment of Dent's disease. Supportive therapy is focused on preventing renal stone formation and slowing down the deterioration of renal function. Increased fluid intake and administration of hydrochlorothiazide (HCT) decrease urinary calcium concentrations (Raja et al., 2002), however, hypovolemia and hypokalemia can complicate thiazide treatment (Blanchard et al., 2008). High citrate diet has a positive effect on renal stone formation in the ClC-5 knockout mice (Chebotaru et al., 2005), but its efficiency has not been proven in humans. Inhibition of the renin-angiotensin-aldosterone system (RAAS) might be of potential benefit by reducing proteinuria, but its effect in Dent's disease patients has not been studied. Treatment of rickets with vitamin D and phosphate

supplementation should be performed with caution as it can enhance hypercalciuria and nephrocalcinosis.

Smith et al. (2009) reported that some ClC-5 missense mutants are retained in the endoplasmatic reticulum. The authors suggested that the export of mutant channels might be improved by exposure to chaperones improving forward trafficking by allosteric means. Therefore, the identification of allosteric modulators, specific for ClC-5, may provide a therapy for Dent 1 disease at least caused by this type of mutation.

6. Conclusions

Dent's disease is a rare X-linked disorder characterized by various degrees of proximal tubular dysfunction, nephrocalcinosis and nephrolithiasis. The disease leads to progressive loss of kidney function and causes end stage renal failure (ESRD) mostly in the 3rd to 4th decades of life. Dent's disease mostly affects males, however, female carries can develop mild proximal tubular dysfunction and more rarely nephrolithiasis. Approximately 60% of all Dent's patients (i.e. Dent 1 patients) have inactivating mutations in the *CLCN5* gene encoding the electrogenic Cl-/H+ exchanger ClC-5, which is extensively expressed on the early endosomes in renal PT and is involved in the receptor-mediated endocytosis.

About 15% of Dent's patients have mutations in the *OCRL* gene and are classified as having Dent 2 disease. *OCRL* gene, encoding phosphatidyl-inositol phosphate 5-phosphatase, is known to cause Lowe syndrome, a severe form of X-linked mental retardation associated with proximal tubular dysfunction and congenital cataract.

Studying the pathogenesis of Dent's has elucidated the crucial role of the ClC-5 protein in endosomal acidification required for the progression along the endocytotic machinery. Recent studies demonstrated that ClC-5 functions as a 2Cl-/H+ exchanger, which is directly involved in the acidification of early endosomes.

Treatment of patients with Dent's disease is supportive and focused on preventing renal stone formation and slowing down the deterioration of their renal function. Increased fluid intake and cautious administration of HCT can decrease urinary calcium concentrations. Inhibition of RAAS might be of potential benefit by reducing proteinuria.

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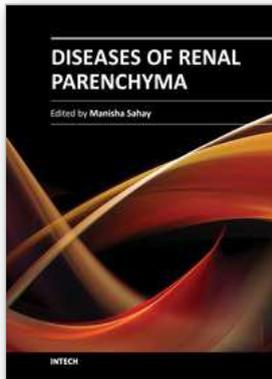
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