



Pathophysiology, current treatments and future targets in renal Fanconi syndrome

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**Pathophysiology, current treatments and future targets
in renal Fanconi syndrome**

For Peer Review Only

Abstract

1 Abstract

Introduction

Renal Fanconi syndrome describes a general dysfunction of the proximal tubules characterised by urinary losses of water, electrolytes, low-molecular weight proteins, amino acids and glucose. The heterogeneity of its underlying causes has complicated the understanding of renal Fanconi syndrome for many years. Recent studies of its isolated form, only affecting the proximal tubule and no other nephron segments, allow new insights into the understanding of pathophysiology and development of disease models.

Areas Covered

In this review, we discuss the most recent insights into pathophysiology of renal Fanconi syndrome as well as novel disease and potential developments of new therapeutic strategies.

Expert Opinion

The importance of fatty acid oxidation in proximal tubules has just recently been established. So far this has not yet led to pharmaceutical development of medicines, due to lack of understanding of the exclusive use of fatty acids by mitochondria in the proximal tubule for energy generation. Nevertheless, novel insights have resulted in potential targets for development of new therapeutic strategies, including mir21 and mTORC1.

Key words

Renal Fanconi syndrome, pathophysiology, proximal tubule, EHHADH

2 Introduction

Renal Fanconi Syndrome (RFS) is a generalised dysfunction of the first post-glomerular segment, the proximal renal tubule, leading to excessive urinary loss of fluid and solutes. It is named after Guido Fanconi, a Swiss paediatrician who was among the first describing this syndrome in the early 1930s [1] in parallel with De Toni and Debre [2, 3]. RFS might cause massive and life-threatening losses of free water, bicarbonate, sodium chloride and potassium, as well as losses of other freely filtered substances such as phosphate, amino-acids, uric acid, low-molecular-weight (LMW) nutrients and glucose. Many of these valuable solutes can be reabsorbed along the kidney only through the highly specialized proximal tubule epithelial cells [4]. Children might present with failure to thrive, polyuria, polydipsia, dehydration, and rickets, whereas adults might develop osteoporosis and osteomalacia. Clinical features also include renal salt wasting, hypokalaemia, metabolic acidosis and LMW proteinuria [5]. In adults, the renal glomeruli produce more than 150 litres of ultrafiltrate every day, containing approximately 20 mol of sodium (the equivalent of more than 1 kg of salt) and >150 g of sugar [6, 7]. Normally, approximately 70% of filtered salt and water and virtually all of filtered sugars, amino acids and proteins are reabsorbed along the proximal tubule [4]. Thus, with complete loss of PT function, up to 120 L of water and solutes, would be lost per day, indicating the importance of PT function. Complete loss of function is probably not compatible with life and to a degree other nephron segments can compensate, but it is the overspill of water and solutes into the urine that defines the RFS phenotype.

3 Maintaining proximal tubule homeostasis

The enormous reabsorptive capacity is provided by a whole orchestra of specialized apical, basolateral and paracellular transporters driven by the electrochemical gradient generated by the basolateral Na⁺-K⁺-ATPase (see figure 1). To optimise the reabsorption, cell and transport properties change along the PT. We distinguish three sub-segments, S1-S2-S3, each one lined with different cell types. Moreover, PT cells (mainly S1-S2), express large multiligand endocytic receptors, namely, megalin, cubilin and, perhaps, amnionless that mediate the uptake of the freely filtered LMW proteins [8]. In order to increase the available apical surface area, those PT cells are decorated with differentiated brush borders. The paracellular spaces have a highly dynamic membrane structure: tight junctions, adherens junctions and gap junctions, which play a vital role in epithelial barrier function. Claudin-2 is the main protein responsible for the selective paracellular transport pathway for various ions (mainly sodium) and water [9, 10].

3.1 Proximal tubule controlling the Acid –base balance

Tight regulation of the extracellular H⁺ concentration is essential for almost all enzyme activity, as alteration in charge might disrupt their function [11]. About 80% of the filtered HCO₃⁻ (which is the major buffer in the extracellular fluid) is indirectly reabsorbed by the PT cells. Bicarbonate reabsorption relies on a complicated sequence of events which start at the apical side by active secretion of hydrogen ion through Na⁺/H⁺ (isoform 3, NHE3) antiporter, using the electrochemical gradient for sodium uptake into the cell as driving force, which is maintained by the basolateral Na⁺/K⁺ ATPase [7, 12]. In this way, sodium and thus volume homeostasis is molecularly coupled to acid-base homeostasis. The secreted hydrogen ion combines

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3 with filtered bicarbonate and is the resultant carbonic acid is converted by carbonic
4
5 anhydrase IV into water and carbon dioxide. The latter diffuses into the proximal
6
7 tubular cells via aquaporin 1 [13], where hydroxylation occurs to form bicarbonate in
8
9 the presence of intra-cellular carbonic anhydrase II. Intracellular HCO_3^- is co-
10
11 transported with Na^+ at the basolateral membrane via kNBCe1-A in a 1:3 ratio.
12
13 Interestingly, plasma CO_2 and HCO_3^- at the basolateral membrane appear to be
14
15 critical for regulation of bicarbonate reabsorption rather than plasma pH [13].
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19 **3.2 Proximal tubule controlling water and salt balance**

20
21 Alterations in sodium balance maintain intravascular volume rather than sodium
22
23 concentration. Regulation of plasma volume occurs as a response to renal perfusion,
24
25 as the kidney cannot sense serum sodium. Approximately 60-70% of the filtered
26
27 NaCl is reabsorbed by the PT, which therefore plays a critical role in the regulation of
28
29 plasma volume and blood pressure. The basolateral $2\text{K}^+/3\text{Na}^+$ ATPase pump is
30
31 crucial in generating the electrochemical driving force with low intracellular sodium
32
33 concentration, high intracellular potassium concentration, which via potassium
34
35 channels establish a negative intracellular potential difference across the apical and
36
37 basolateral membranes. The sodium gradient and the intra-cellular electronegativity
38
39 are the driving force for sodium reabsorption along the apical membrane of the PT.
40
41 This electrochemical driving force for sodium uptake is utilised for multiple transport
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43 processes, such as coupled transport (sodium co-transport with glucose, phosphate,
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45 or amino-acids), exchange (Na^+/H^+ exchanger type 3 NHE3), and passive diffusion
46
47 via channels [14]. Water is reabsorbed along with these solutes, as the proximal
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49 tubule is fully water permeable due to the constitutive expression of aquaporin 1
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51 water channels. Consequently, the urinary fluid leaving the proximal tubule has the
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3 same tonicity as the initial glomerular filtrate as solute reabsorption occurs
4 isotonically [5]. In patients with RFS there is impaired reabsorption of sodium and
5 other solutes, as well as water in the proximal tubules leading to hypotension and
6 dehydration. Increased delivery of sodium to the distal tubules, as well as the
7 hypovolaemia, activates renin-angiotensin system, which leads to potassium wasting
8 in the distal tubules and to clinical hypokalaemia as a consequence.
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17 **3.3 Proximal tubule controlling phosphate reabsorption**

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20 Under physiological conditions, around 80% of the freely filtered phosphate (Pi) is
21 reabsorbed along the proximal tubules mainly along the convoluted segment. The
22 involved Pi transporters (mainly NaPi IIa, NaPi IIc) are secondary-active sodium
23 phosphate co-transporters, confined to the apical brush border membrane. Tubular
24 Pi reabsorption is controlled by a number of hormones (parathyroid hormone, 1,25-
25 dihydroxyvitamin D3, FGF-23, glucocorticoids) and metabolic factors (phosphate
26 loading, metabolic acidosis), by changing the apical expression of Na⁺/Pi co-
27 transporters at the brush border membrane [15, 16].
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38 Most of the patients with RFS present with low tubular reabsorption of phosphate
39 (<80–85%) and decreased serum phosphate. Of note, with very low plasma
40 phosphate levels, the reabsorptive capacity of the PT may keep up reabsorption with
41 this decreased filtered phosphate load, so that TRP can be normal in RFS. For this,
42 reason, the TmP/GFR (= SP-UP x SCr:UCr) is a better tool to assess renal
43 phosphate handling [17]. Rickets in children and osteomalacia in adult are
44 secondary to the increased urinary wasting of phosphate and impaired 1-alfa
45 hydroxylation of vitamin D (see below).
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3.4 Proximal tubule controlling LMW protein reabsorption

The glomeruli filter significant amounts of protein into the primary human urine, yet the finally excreted urine is almost entirely protein-free. The glomerular filtration membrane retains proteins larger than about 60 kDa, with some exceptions, such as albumin (66 kDa) and transferrin (81 kDa), which pass through to some extent [18]. In the kidney, the proximal tubule is the only nephron segment involved in the reabsorption of LMW proteins. The renal proximal tubule reabsorbs almost the entire physiologically filtered protein load, including albumin and LMW proteins. LMW proteins and albumin are reabsorbed via a luminal receptor mechanism. The active processes by which the renal proximal tubule reabsorbs filtered plasma proteins, vitamins, vitamin-binding proteins, and hormones are vital for body homeostasis and take place mainly in the first two segments of the proximal tubule [8]. The apical cubilin-megalin complex plays an essential role in this process [19]. The three promiscuous receptors, megalin, cubilin and amnionless, cooperate in the proximal tubule in order to reabsorb nearly all filtered plasma protein. They work in concert notwithstanding their considerable structural differences. In RFS, proteinuria, which can be within the nephrotic range, is predominantly caused by the dysfunction of protein reabsorption in the proximal tubules [20].

Proximal tubule and vitamin D metabolism

Vitamin D, a lipid, is mostly bound to a specific carrier protein in plasma, vitamin D binding protein (VDBG). VDBG is a LMW protein, that is filtered by the glomerulus and then reabsorbed in the proximal tubules via megalin. In this way it becomes available for the critical activation step of 1- α hydroxylation, which occurs in the PT mitochondria.

4 Disease model

4.1 Part of multisystem metabolic diseases causing accumulation of toxic metabolites

4.1.1 Cystinosis

Cystinosis is an autosomal recessive lysosomal storage disorder caused by mutations in the CTNS gene coding for the lysosomal cystine/proton transporter cystinosin. It is characterized by the accumulation of cystine in all organs, mainly kidney, cornea, bone marrow, thyroid, lymph nodes, liver and spleen [21]. It is the most common cause of inherited RFS in children with an estimated incidence of 0.5-1.0 per 100 000 live births [22]. There are three main clinical forms described depending on the age of onset and severity of disease: Infantile, juvenile or adult form [23]. The infantile (nephropathic) form is the most severe and most common (95%) form leading to symptoms of renal RFS during the first year of life. Patients may also develop severe rickets and growth retardation due to phosphaturia. At onset patients usually have normal kidney function, but progress to end stage kidney disease (ESKD) around the age of 10 years if no adequate treatment is provided. The juvenile (nephropathic) form and the adult (non-nephropathic) form are less severe and less common. Patients with the juvenile form present with milder forms of RFS with later progression to renal failure, whereas the adult form is characterized by isolated corneal cystine crystal deposition [24].

Pathophysiology

Current evidence shows that cystinosis is a monogenic-recessive disease with complete penetrance. The underlying bi-allelic mutations are located in the CTNS gene encoding the lysosomal cystine transporter cystinosin. The gene consists of 12

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3 exons and the most common mutation (>70% in Caucasians) is a 57kb deletion,
4
5 which includes the first nine exons and a part of exon 10 of the CTNS gene [1, 25].
6
7 The mutation also involves the adjacent CARKL gene and the first two non-coding
8
9 exons of the TRPV1 gene. However, no clinical correlation has been reported so far
10
11 with the CARKL and TRPV1 genes in affected patients [26], except for perhaps an
12
13 increased tolerance to spicy food. More than 100 mutations in the CTNS gene are
14
15 described with novel mutations still being reported [27, 28]. The differences of the
16
17 clinical phenotype in the different forms are explained by more severe mutations in
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19 both alleles in the infantile cystinosis versus milder mutations in the juvenile and
20
21 adult form.
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25 The CTNS gene codes for cystinosin, which is a 367 amino acid protein with seven
26
27 transmembrane domains . It functions as a proton/cystine co-transporter and is
28
29 driven by the high proton content within the lysosomal lumen. A defect in the
30
31 transport mechanisms causes accumulation of cystine in the lysosomal lumen with
32
33 formation of cystine crystals and cell atrophy [29]. The mechanistic links between
34
35 lysosomal cystine accumulation and the development of RFS have been studied in
36
37 several in vitro studies but still remain not fully understood [30]. A recent Ctns^{-/-} mice
38
39 study provided some insight into the pathophysiology by showing that lysosomal
40
41 cystine inclusion leads to apical proximal tubular cell (PTC) dedifferentiation with
42
43 reduced expression of multi-ligand megalin and cubilin receptor and NaPi-IIa,
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45 followed by PTC atrophy [31]. It has been shown that lesions start developing in
46
47 segments adjacent to the glomerulotubular junction and then extend longitudinally
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49 along the proximal tubulus. This explains proximal tubular cell flattening, also
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51 referred as “swan neck lesions”, the typical finding seen in biopsies from cystinotic
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53 children [32, 33].
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Clinical presentation and diagnosis

Clinical symptoms of RFS in the infantile form are heterogeneous. Affected children generally present early and manifest symptoms at the age of 6-12 months. Presenting symptoms are polyuria, polydipsia, dehydration, fluid and electrolyte loss, aminoaciduria, glucosuria, proteinuria, failure to thrive and/or rickets. Development of ESKD depends on the age of treatment initiation [34]. Diagnosis is usually confirmed by elevated cystine levels in peripheral leukocytes along with corneal cystine crystals demonstrated by the split lamp exam and consecutive genetic analysis of the CTNS gene.

Treatment

Fluid and electrolyte management is the main supportive therapy in patients with Fanconi syndrome secondary to cystinosis. Additionally, the supplement of oral cysteamine, a cystine-depleting agent, is crucial in the treatment for cystinosis [35-39]. Early initiation of cysteamine treatment has been proven to delay the progress of ESKD and should be provided to every patient with the diagnosis of cystinosis. A new treatment target, transcription factor EB (TFEB) has been suggested recently. TFEB activates the transcription of different proteins involved in the cell clearance and has been shown to promote clearance of cystine storage in cells within 24 hrs and might also lead to a rescue of the lysosomal compartment of cells affected by cystinosis [40].

4.1.2 Fanconi–Bickel syndrome

Pathophysiology

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3 Fanconi-Bickel syndrome (FBS) is an autosomal recessive disease of carbohydrate
4 metabolism caused by mutations of the GLUT2 gene (also referred as SLC2A2)
5 coding for a glucose transporter in hepatocytes, pancreatic beta-cells, enteral cells
6 and renal tubular cells [41]. Over 34 different mutations have been reported. These
7 mutations included missense, nonsense, frameshift and splice-site mutations,
8 scattered over the whole coding sequence of SLC2A2 gene and with none of those
9 mutations being particularly frequent [41, 42].

18 *Clinical presentation*

20 FBS is characterized by hepatomegaly and nephromegaly caused by glycogen
21 accumulation. Further, impaired utilization of glucose and galactose leads to fasting
22 hypoglycemia and postprandial hyperglycemia, combined with galactose intolerance
23 and development of Fanconi syndrome, rickets and severe short stature [43].

29 *Treatment*

31 Therapy is mainly supportive and focuses on maintaining glucose homeostasis,
32 with frequent feeding including night-time. Moreover, treatment should aim to
33 compensation of renal solute losses including sodium bicarbonate, potassium and
34 phosphate supplements.

43 **4.1.3 Tyrosinemia type I**

46 *Pathophysiology*

48 Tyrosinemia type 1 is an autosomal recessive disease of the amino acid metabolism
49 caused by a mutation in the fumarylacetoacetate hydrolase (FAH) gene coding for
50 the last enzyme in the tyrosine catabolic pathway, which catabolizes the conversion
51 of fumarylacetoacetate (FAA) into fumarate and acetoacete. FAH is mainly
52 expressed in the liver and kidney, where lack of FAH causes accumulation of toxic
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3 metabolites such as maleylacetoacetate (MAA) and fumarylacetoacetate (FAA) and
4
5 their derivatives succinylacetone, leading to progressive liver disease and RFS [44].
6
7 The accumulation of those metabolites disrupt the sulfhydryl metabolism by forming
8
9 glutathione adducts which makes cells more vulnerable to free radical damage.
10
11 Further FAA and MAA are known mutagens and can promote cell apoptosis [44]. As
12
13 a response to those intracellular effects hepatic and renal cells developing cell
14
15 apoptosis or mutation if they are exposed to high levels of FAA or MAA. In the kidney
16
17 that leads to glomerulosclerosis and interstitial fibrosis [45]. Symptoms include
18
19 progressive hepatic dysfunction beginning in early childhood with progression to
20
21 cirrhosis and hepatocellular carcinoma. Kidney involvement is represented by the
22
23 development of RFS and hypophosphatemic rickets.
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26

27 *Clinical presentation and diagnosis*

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29 Clinical symptoms can be related to progressive liver damage with reduced
30
31 coagulation factors, hypoglycemia and acute hepatic crisis such as ascites,
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33 jaundices and gastrointestinal bleeding. One third of the patients will develop liver
34
35 cancer [46]. In regards to the renal involvement, patient show abnormal renal
36
37 architecture (increased size and echogenicity on renal ultrasound) and development
38
39 of tubular dysfunction including hypophosphatemic rickets with hypercalciuria,
40
41 generalized aminoaciduria, renal tubular acidosis and mild proteinuria. Glycosuria is
42
43 less common due to in general low blood glucose levels.
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48 Diagnosis includes confirming elevated levels of succinylacetone in plasma and
49
50 urine. Plasma tyrosine and methionine levels are usually elevated in untreated
51
52 patients.
53

54 *Treatment*

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3 First line treatment includes a low phenylalanine and low tyrosine diet and early
4 treatment with NTBC [2-(2-nitro-4-trifluoro-methylbenzyl)-1,3-cyclohexanedione] an
5 inhibitor of 4-hydroxyphenylpyruvate-dioxygenase. NTBC has been shown to prevent
6 the accumulation of fumarylacetoacetate and its conversion to succinylacetone, and
7 can rapidly improve tubular function in patients with Tyrosinemia type 1, leading to
8 significant improvement of proteinuria and mean plasma phosphate levels [44, 47].
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19 **4.1.4 MODY 1**

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21 Recently, RFS has been described in association with MODY 1 (maturity onset
22 diabetes of the young type 1) caused by a heterozygous mutation R63W (previously
23 annotated as R76W) in the HNF4A gene [48]. Different mutations in the HNF4A
24 gene have been described to cause neonatal hyperinsulinism followed by decreased
25 insulin secretion later on in life. Why only this particular dominant mutation also
26 causes RFS remains to be investigated [6].
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38 **4.1.5 Others**

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40 Other genetic forms of RFS include **Galactosemia**, an autosomal recessive disease
41 of the galactose metabolism caused by deficiency of galactose-1-phosphate
42 uridyltransferase (GALT). Patients normally present in the neonatal period after first
43 intake of galactose with severe symptoms including lethargy, jaundice, liver disease,
44 sepsis, cataract and RFS [49].
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51 **Wilson's disease**, an autosomal recessive inborn error of copper metabolism
52 caused by defects in the copper-transporting P-type ATPase beta-polypeptide
53 (ATP7B) with reduced ceruloplasmin synthesis and biliary excretion of copper.
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3 Patients develop progressive liver disease, progressive neurological disorders and
4
5 RFS [50, 51].
6

7 **Hereditary fructose intolerance**, an autosomal recessive disorder with deficiency
8
9 of aldolase B which catalyses the metabolism of fructose and leads to an inability to
10
11 metabolize fructose. Patients presents with vomiting, hypoglycemia,
12
13 hypophosphatemia, hyperuricosuria, hyperuricemia and growth retardation [51, 52].
14
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16 17 **4.2 Disruption of endocytosis and intracellular transport** 18

19 20 **4.2.1 Lowe syndrome** 21

22
23 Oculo Cerebro Renal Syndrome of Lowe (OCRL) is an X-linked recessive
24
25 multisystem disorder characterised by congenital cataracts, intellectual disability, and
26
27 renal tubulopathy (OMIM 309000). Lowe syndrome results from loss-of-function
28
29 mutations in *OCRL* which encodes phosphatidylinositol 4,5-bisphosphate 5-
30
31 phosphatase (PtdIns(4,5)P₂ 5-phosphatase) [53]. In humans, this enzyme is
32
33 expressed primarily in the kidney, brain, and eyes, which are consequently the main
34
35 organs affected by *OCRL* syndrome [54, 55]. Localisation of the *OCRL* enzyme to
36
37 the endosomal apparatus suggests that it may play a role in intracellular trafficking,
38
39 sorting, and recycling of apical membrane multi-ligand receptors megalin-cubilin [56-
40
41 58]. The precise molecular link between the *OCRL* enzyme and receptors on the cell
42
43 surface remains elusive [59, 60]. Treatment is symptomatic due to absence of
44
45 efficient therapy [61].
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50 **4.2.2 Dent disease** 51

52 *Dent 1* 53

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55 Dent disease is an X-linked recessive disease, often associated with progressive
56
57 kidney function impairment. The first identified causative gene was *CLCN5*
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3 (Xp11.22) (Dent 1 disease), which accounts for approximately 60% of reported
4
5 pedigrees. *CLCN5* is a chloride/proton anti-porter that works together with the
6
7 electrogenic H⁺-ATPase to achieve endosomal acidification, which is a crucial step
8
9 in normal endosomal function [62]. Loss-of-function mutations of *CLCN5* result in
10
11 hypercalciuria, nephrolithiasis, metabolic acidosis, aminoaciduria, glycosuria,
12
13 hypophosphatemic rickets due to hyperphosphaturia, and LMW proteinuria [63].
14
15 Norden et al. [64] found a striking deficiency of urinary megalin protein in Dent's
16
17 disease patients compared with normal controls. They concluded that reduced
18
19 shedding of megalin receptor from the apical membrane to the urine flow reflects the
20
21 abnormal recycling of the receptor back to the apical membrane. This defect would
22
23 interfere with the normal endocytic function of megalin, resulting in losses of potential
24
25 ligands into the urine and leading to tubular proteinuria.
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32 *Dent 2*

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34 Investigations in families with Dent disease in whom *CLCN5* mutations had been
35
36 excluded led to the surprising discovery of mutations in *OCRL*, the gene previously
37
38 identified as the cause of Lowe syndrome. Mutations in this gene account for about
39
40 15–20% of cases of Dent's syndrome and these are now referred to as Dent 2
41
42 disease [54, 65]. The cause for the pleiotropy of *OCRL* is not fully elucidated,
43
44 although there is some genotype-phenotype correlation in that the vast majority of
45
46 Dent 2 mutations are located on exon 9, whereas mutations causing Lowe syndrome
47
48 are typically located in exon 8-23 [66]. Nevertheless, there is no clear separation with
49
50 nonsense mutations with assumed complete loss of function found in both Dent 2
51
52 and Lowe patients. These phenotypes are now believed to be two ends of a
53
54 phenotypic spectrum [67]. Bockenbauer et al. [56] investigated eight boys with Dent
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3 2. All had LMW proteinuria and hypercalciuria, but none developed renal tubular
4
5 acidosis. Hoopes et al. reported on five families with a similar phenotype [65].
6

7 The care of patients with Dent's disease is supportive, focusing on the prevention of
8
9 nephrolithiasis [63].
10

11 12 13 14 15 16 17 **4.3 Genetic renal Fanconi syndrome** 18

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20 Three genetic forms of renal Fanconi syndrome have been described: Fanconi
21
22 renotubular syndrome FRTS types 1 -3.
23

24 25 **4.3.1 FRTS1** 26

27
28 The first form has been mapped on chromosome 15, although the gene has not
29
30 been identified yet [68]. FRTS 1 is also associated with progressive chronic kidney
31
32 disease, but the underlying mechanism remains unknown and as such no
33
34 therapeutics are available yet.
35

36 37 **4.3.2 FRTS2 - SLC34A1** 38

39
40 FRTS2 is caused by homozygous in-frame 21 bp duplications in SLC34A1, which
41
42 codes for the phosphate transporter NAPI-IIa [15]. It has only been reported in few
43
44 patients so far [15, 69]. The phenotype is dominated by phosphate wasting and
45
46 rickets despite high 1,25 OH vitamin D levels. Interestingly not all proximal tubular
47
48 functions are affected and renal tubular acidosis was not present in the reported
49
50 cases. However, the underlying mutation in SLC34A3 has been described before to
51
52 cause hereditary hypophosphatemic rickets with hypercalciuria [70]. Mutations in
53
54 SLC34A1 are now recurrently identified in patients with infantile hypercalcaemia [71].
55
56 The reason for this pleiotropy is again poorly understood but for the RFS, the
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3 underlying mechanism has been proposed to be intracellular phosphate depletion
4
5 leading to insufficient ATP generation [6].
6
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8 **4.3.3 FRTS3 - EHHADH**

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10 The third form is an isolated full blown RFS caused by heterozygous missense
11 mutation in a gene called EHHADH first described by Klootwijk et al. [72]. The
12 phenotype presents as isolated Fanconi syndrome with no progression to chronic
13 kidney disease. An interesting aspect of this disease is the realisation that despite
14 lifelong loss of water and solutes glomerular kidney function is preserved. The
15 disease mechanism has been identified as a dominant negative effect from
16 intracellular mistargeting of the mutated enzyme [72, 73]. Whilst the enzyme (and
17 thus the mutation in patients) is expressed ubiquitously, symptoms only manifest in
18 the proximal tubule. The reason for this is the dependency on fatty acid metabolism
19 for energy generation in the proximal tubule [74]. EHHADH interferes with a
20 mitochondrial enzyme that is involved in mitochondrial fatty acid oxidation and has a
21 high degree of homology to EHHADH. So the erroneous assembly of mutant
22 mislocalised EHHADH into this enzyme leads to a defect in ATP production causing
23 RFS. In other tissues, glucose can be metabolised and ATP generation is thus not
24 affected [6].
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48 **4.4 Acquired forms of renal Fanconi syndrome**

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50 Multiple drugs have been described to cause tubular damage and consequently
51 RFS. Those include HIV therapy, heavy metals (cadmium/lead administration),
52 antibiotics, valproic acid as well as exogenous factors as glue sniffing and exposure
53 to suramin, fumaric acid, or ifosfamide [75, 76]. Most of those drugs are freely
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3 filtrated in the glomerulus and reabsorbed in the tubules, where they interfere with
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5 different parts of the proximal tubules [77].
6

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8 Further RFS has been described in association with monoclonal gammopathies
9
10 (adult) nephrotic syndrome, Sjörger syndrome and others [78-81].
11

12 13 14 15 **5 Expert opinion**

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18 The clinical experience leading the research of the last decades has partially
19
20 unravelled the pathogenic mechanisms leading to different forms of RFS. Thus, the
21
22 common element involved in the heterogeneous nature of RFS, including from
23
24 acquired to different genetic causes, with seemingly different molecular pathologies,
25
26 is the dysfunction of a cellular organelle, mitochondria.
27

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30 The renal toxicity of some of the therapeutic agents including anti-retroviral
31
32 therapeutics, and the anti-epileptic valproic acid [82] has been intensively discussed
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34 even though the pathologies for these acquired RFS forms are not completely
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36 deciphered [6, 82-84]. The key findings in the field of RFSs focused on identification
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38 of mono-genetic causes [72, 84]. A recent study about a large mono-genetic RFS
39
40 family validated mitochondria's role by showing defective fatty acid oxidation due to a
41
42 particular mutation (E3K) in EHHADH. Surprisingly this mutation resulted in
43
44 mistargeted EHHADH resulting in disruptive formation of the mitochondrial
45
46 trifunctional protein complex now encompassing the mutated EHHADH. These
47
48 findings provide new clues for treatment of this type of renal Fanconi syndrome
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50 (FRTS3), and other RFS as well.
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55 Future therapeutic strategies could be directed in strengthening or protecting the
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57 mitochondria against toxic substances either through controlling the import of
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3 proteins to mitochondria or through therapeutically targeting mitochondrial fatty acid
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5 oxidation in RFS (Figure 2). In contrast with the findings related to fatty acid
6
7 oxidation, apoptosis has been for a long time associated with certain types of RFS
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9 [85].
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12 All these future therapeutic strategies for treatment of RFS that came to existence
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14 due to novel research findings in identification of the patho-mechanistic nature of
15
16 RFSs will be discussed in the next few paragraphs.
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22 **5.1. Potential Treatment options**

23 24 25 26 27 **5.1.1. Targeting protein import problems in ATP deficiency related RFS**

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31 FRTS3 patients have been shown to have a fatty acid accumulation problem leading
32
33 to a decreased ATP production [72, 73]. In order to address the fatty acyl
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35 accumulation problem in FRTS3, the import of the causative mutated protein could
36
37 be prevented by using the FDA approved drug Dequalinium chloride (DECA),
38
39 recently shown to be effective in restoring mitochondrial function in a cell model for
40
41 primary hyperoxaluria I [86]. The agent DECA holds great promise as a therapeutic
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43 targeting strategy in FRTS3, although there is only one FRTS3 family known to date.
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49 In other forms of RFS, where there is general mitochondrial dysfunction, achieving
50
51 the opposite by increasing protein import may be a therapeutic option. Thus, the
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53 FDA-approved mitochondrial protein import stimulator sodium pyrithione has recently
54
55 been shown to improve mitochondrial bioenergetics in Leigh patients [87]. This might
56
57 also be relevant for acquired forms of RFS that are associated with ATP deficiency
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3 and/or oxidative phosphorylation defects, e.g. aminoglycosides and valproic acid
4 associated RFS.
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8 9 10 **5.1.2. Anti-oxidant therapy for RFSs**

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14 The use of anti-oxidants like sirtuins and SS-peptides, MitoQ, and plastoquinone
15 analogues and stanniocalcin-1 have also been suggested as potential therapeutical
16 agents for RFS [88].
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19
20 In addition, due to their nature of boosting the fatty acid oxidation, anti-oxidants like
21 carnitine, fibrates and poly unsaturated fatty acids in form of a specific ketogenic diet
22 could be investigated in the future as a potential treatment option for specific forms
23 of RFS, like valproic acid induced RFS. These type of RFS have been shown to
24 have inhibited fatty acid oxidation master-regulators like peroxisome proliferator-
25 activated receptor-alpha activity or PGC-1alpha, leading to deficient fatty acid
26 oxidation [89, 90].
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38 **5.1.3 Anti-apoptotic therapy for fumaric acid ester induced RFS, Tyrosinemia** 39 **type I and Cystinosis** 40 41

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45 Mitochondrial drug targeting to prevent apoptosis from happening has the potential
46 to be used in RFS forms triggered by apoptosis, such as tyrosinemia type I,
47 cystinosis, light-chain proximal tubulopathy or fumaric acid ester associated RFS. To
48 this end caspase inhibitors can be used A good candidate that was proven
49 successfully in a mouse model for fumaric acid ester associated proximal
50 tubulopathy is the anti-apoptotic caspase inhibitor YVAD [91]. Other caspase
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3 inhibitors with clinically approved status that could potentially be used are:
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5 EmricasaN for which a clinical trial is ongoing for non-alcoholic steatohepatitis
6
7 fibrosis and IDN-6556 in phase 2 clinical trial for Hepatitis C.
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10 11 12 **5.1.4 mTORC stimulation**

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16 Very recently a novel drug target for RFS has surfaced in a study published by
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18 Grahammer and co-workers [92]. The deficiency of mTORC1, an important regulator
19
20 of lipid metabolism, was shown in a mouse model, to lead to a renal FS with reduced
21
22 expression of PGC1-alpha, a key regulator of mitochondrial fatty acid oxidation [90].
23
24 The development of specific drugs targeting mTORC1 continues to grow, mainly for
25
26 specific forms of cancer, including renal cell carcinoma, based on its function as a
27
28 nutrient, redox, oxygen sensor and as an important stimulant for protein synthesis.
29
30 Its activity is up-regulated by the amino acid leucine and its derivative beta hydroxyl
31
32 beta methylbutyrate. The current knowledge supports the hypothesis that the
33
34 stimulation of mTORC1 by amino acids like amino-acid-directed therapies may
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36 provide a mitochondrial-directed therapeutic approach for RFS [93].
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43 **5.1.5. RNA silencing in MODY1 with RFS, FRTS1, FRTS3, and acquired forms** 44 **of RFS**

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49 Recently RNA silencing has been successfully used to develop novel management
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51 strategies, like for instance the use of the FDA-approved mipomersen, an
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53 apolipoprotein B synthesis inhibitor to lower LDL cholesterol in patients with
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55 homozygous familial hypercholesterolaemia. RNA silencing shows potential
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3 applicability in future clinical trials for the down-regulation of the disease specific
4 alleles in dominant genetic diseases, in this way allowing the on-going functionality
5 of the wild type allele. So far this has only been demonstrated using disease models
6 [94]. This approach could then be used for FRTS1, FRTS3, and MODY1 with renal
7 Fanconi syndrome giving the dominant nature of the inheritance.
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16 Recently a novel target for a RNA silencing therapeutic approach in RFS emerged
17 as the MicroRNA Mir21. This microRNA appeared to be a novel biomarker for
18 proximal tubulopathies underlying AKI [95]. These novel findings, interestingly, point
19 towards an important role of Mir21 in regulating metabolic activity in epithelial cells,
20 in particular of lipid metabolism [96], as well as apoptosis related genes [95, 97],
21 which are important pathways that are affected in several forms of RFS [98]. Mir21
22 could therefore be considered as an outstanding candidate to develop novel anti-
23 sense therapeutics (antagomirs and mimics) for acquired forms of RFS in which
24 these pathways are affected: tyrosinemia type I [85], cystinosis [99] and fumaric acid
25 ester associated RFS [100]. This could also be the therapeutical target for RFS with
26 defective fatty acid oxidation pathways.
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43 **5.2. Conclusion**

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45 Unequivocally clinicians and researchers are increasingly aware of the impact of
46 RFS. Although the area of the treatment is at the moment the most disappointing,
47 new experimental approaches and more testing of novel and existing therapeutic
48 agents to will decipher potential model systems for RFS.
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3 Moreover, understanding of the impact of mitochondria and its relevance in the area
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5 of RFS hold much promise for future development of novel therapeutics for this
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7 complex class of diseases.
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11 Our understanding of the pathogenesis of RFS will continue to improve also by
12
13 unravelling the pathomechanism for the mono-genetic RFS FRTS2, and other
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15 families, where the causative genetic component has not yet been identified.
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18 In this manuscript we discussed several potential future options for therapy in
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20 specific types of RFS.
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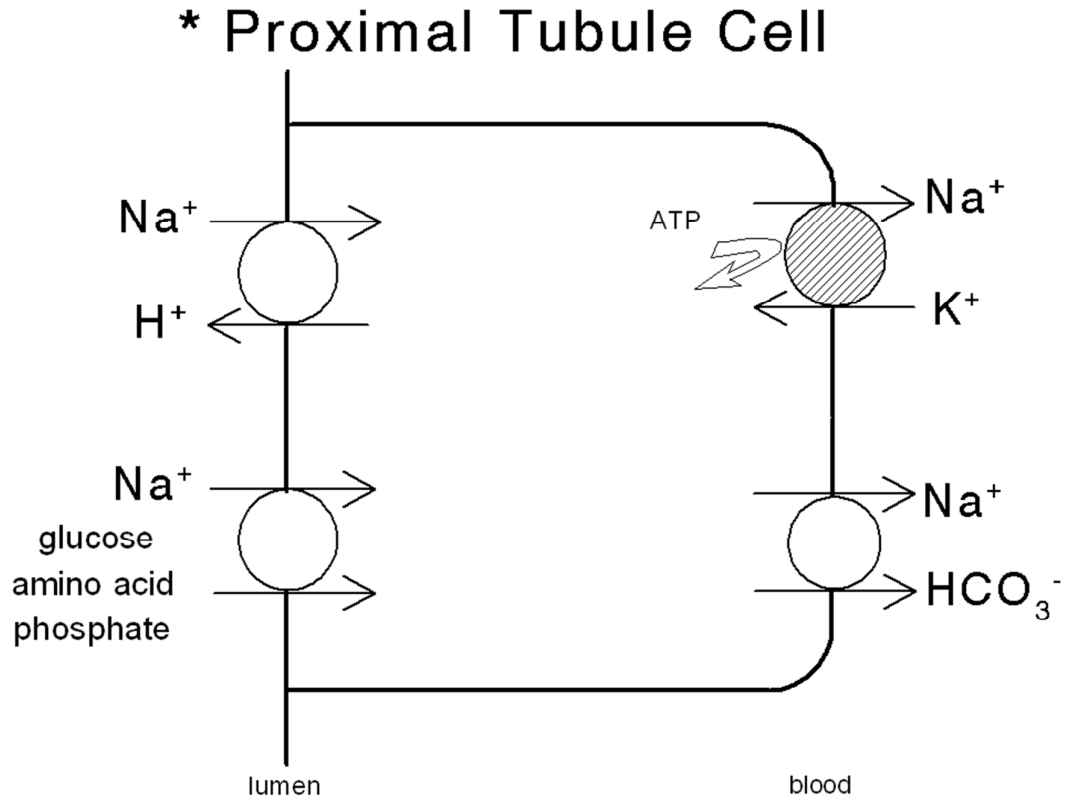
- 23 • Targeting protein import problems in ATP deficiency related RFS
- 24
25 • Anti-apoptotic therapy for fumaric acid ester induced RFS, tyrosinemia type I
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27 and cystinosis
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29 • RNA silencing in MODY1 with RFS, FRTS1, FRTS3, and acquired forms of
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Table 1: Overview of different types of renal Fanconi syndrome

Name	OMIM	Gene	Inheritance	Other symptoms
Cystinosis (infantile)	219800	CTNS	AR	Corneal cystine crystals, poor growth, rickets, CKD and ESRF
Fanconi-Bickel Syndrome	227810	GLUT2 (SLC2A2)	AR	Glycogen storage disease, hypoglycemia
Tyrosinemia Type 1	276700	FAH	AR	Progressive liver disease, liver cancer
Galactosemia	230400	GALT	AR	Liver dysfunction, jaundice, encephalopathy, sepsis
Hereditary Fructose Intolerance	229600	ALDOB	AR	Hypoglycemia, vomiting, liver disease
Wilson Disease	277900	ATP7B	AR	Liver disease, neurological abnormalities, Kayser-Fleischer rings
Lowe Syndrome	309000	OCRL	XLR	Cataract, mental impairment, rickets
Dent I	300009	CLCN5	XLR	Male predominance
Dent II	300555	OCRL	XLR	Male predominance
MODY 1	125850	HNF4A	AD	Neonatal hyperinsulinism, maturity-onset of diabetes in the young
FRTS1	134600	?	AD	Chronic kidney disease
FRTS2	613388	SLC34A1	AR	Mainly phosphaturia
FRTS3	615605	EHHADH	AD	No chronic kidney disease

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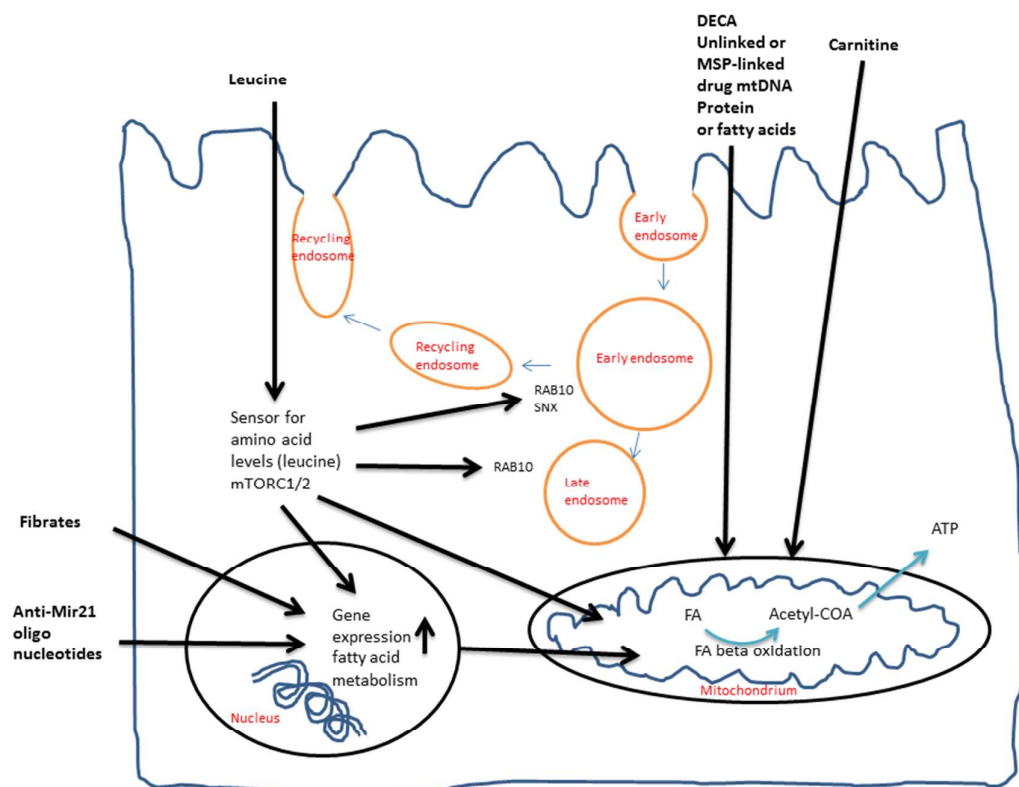
Figure 1: Schematic of renal proximal tubular cell with key transepithelial transport systems.



View Only

Figure 2: Potential therapeutic solutions linked to restoration of mitochondrial energy metabolism in renal Fanconi syndromes.

Drugs could be developed against mTORC1, which has recently been linked to causing a renal Fanconi-like syndrome in a mouse model deficient of mTORC1. Furthermore DECA-associated therapeutics could be developed for renal Fanconi syndromes, in particular for FRTS3, since it is an effective FDA-approved mitochondrial targeting agent. Also antisense-Mir21 could be considered an important target since Mir-21 is considered a biomarker for AKI, and it has been shown to be an effective treatment for restoration of kidney function in Alport nephropathy. Other important therapeutic interventions could be fibrates and carnitine supplementation for acquired forms of renal Fanconi syndrome.



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