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"A Review Article On: Cystinosis"

Mogili Komali*,Siddhartha Lolla, Kallam Veena Maheshwar Reddy, Outkur Bhagyasri, Maddati Prasanna, Borgau Sai Vaishali, Nagula Ranjith.

Department Of Pharmacology, Pulla Reddy Institute Of Pharmacy, Dundigal, Hyderabad, Telagana,India,502313.

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ABSTRACT:
A rare autosomal recessive condition called cystinosis is characterized by a buildup of cystine in the lysosomes. The transfer of cystine from the lysosomes into the cytosol is disrupted by pathogenic mutations of the cystinosis gene (CTNS). Cysteine buildup inside lysosomes causes cellular malfunction later on. An incidence of 0.5–1/100,000 live birth is associated with cystinosis. Nephropathic cystinosis is the most common disease subtype among the three types of cystinosis: neonatal cystinosis, juvenile cystinosis, and ocular cystinosis. The most prevalent way that disease manifests itself is renal impairment. The extrarenal symptoms of cystinosis include hypogonadism, hyperglycemia, and hypothyroidism." Currently, cysteamine, a substance that depletes cystines, is used to treat cystinosis. The main goal of this treatment is to reduce the disease's progression; it is not a cure. Ninety percent of individuals with cystinosis develop renal failure during their first 20 years of life. Patients who have reached this stage of the disease has no other choice except to have a kidney transplant. The pathophysiology and clinical signs of cystinosis are highlighted in this review, along with possible future therapeutic approaches. Keywords: CTNS, kidney failure, cystinosis, cysteine, and cysteamine.

I. INTRODUCTION:

A uncommon monogenic autosomal recessive disorder is cystinosis. With a global incidence of 0.5–1/100,000 live births, it is categorized as an uncommon disease.[31] A lysosomal storage condition is cystinosis. Cysteine is transported from the lysosome to the cytoplasm by the cystinosin protein, which is encoded by pathogenic variations of the CTNS gene.[93] Driven by an H+ electrochemical gradient, the cystinosin protein is a lysosomal seven-transmembrane protein that exports intra-lysosomal cystine.[54] Cysteine builds up in lysosomes as a result of the malfunctioning cystinosin protein.[93]This encourages the formation of harmful cystine crystals, which can cause harm to downstream organs .[53]The kidney, cornea, thyroid, liver, and spleen are the organs most affected. Cystinosis also affects muscles, peripheral nerves, and bones (cystinosis-associated metabolic bone disease). The most prevalent sign of cystinosis is kidney dysfunction [90]. Nephropathic cystinosis, juvenile cystinosis, and ocular cystinosis are the three kinds of cystinosis. The French-Canadian region (Quebec) has the highest incidence of cystinosis (1:62,500), followed by North-West France (Brittany) (1:26,000) [9, 22]. Although there is a dearth of information in these areas, it is also anticipated that nations with high levels of consanguinity will have greater rates of disease [50]. Additionally, developing nations lack diagnostic resources and knowledge on cystinosis, which could result in inaccurate.

Genetics:

The CTNS gene, which codes for the cystinosin transporter, is found on chromosome 17p13 [93]. Since the CTNS gene was discovered in 1998, more than 140 pathogenic variations have been identified [21]. The first two exons in the 12 exons that make up the CTNS gene are noncoding exons. There is a known linkage between genotype and phenotype, with just 15 and 4 variants linked to juvenile and ocular cystinosis, respectively, and the bulk of harmful variants causing nephropathic cystinosis [21]. The pathogenic cystinosis mutations are widely distributed geographically. A significant 57-kb deletion is the most prevalent cystinosis variant in North America and North Europe. The CTNS gene's first nine exons and a portion of its tenth exon are involved in this removal. This variation also involves the deletion of two upstream genes, CARKL and TRPV1 [34]. Severe nephropathic cystinosis is associated with this genetic variation [85]. Between 50 and 70 percent of patients with nephropathic cystinosis in North America and North Europe have this 57-kb deletion [32]. In other regions of the world, this form is less

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prevalent; in Italy and Turkey, it accounts for 17% and 0% of cystinosis patients, respectively [68,92]. A CTNS non- sense mutation is present in 15% of patients with cystinosis [85]. The most prevalent variant of nonsense is p.W138x (753G>A). Fifty percent of cystinosis patients in the French-Canadian community have this variation, which causes the illness. It is said to have started in Ireland before spreading to the French-Canadian the mid-1800s region. While the French-Canadian population has the highest prevalence of this mutation, it is also present throughout Europe and North America at lower percentages [85]. The W138X variation creates a nonfunctional allele by causing a premature termination codon (PTC) in exon 7 of the CTNS gene [69]. The c.681G>A variant is prevalent in Egypt [86], the Middle East (Saudi Arabia, Turkey, and Iran) [2, 83, 92], and the black South African community [73]. Other common variants are also prevalent in some people.

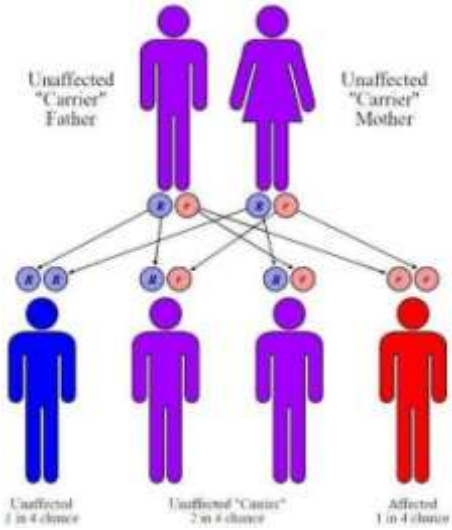

FIG.1:CYSTINOSIS

The molecular pathophysiology of cystitis;

The lysosome's ability to transport cystines is compromised by a malfunctioning cystinosin transporter, which raises intralysosomal cystine levels [93]. Cystinosis causes abnormalities in the process of protein breakdown, which is mostly dependent on lysosomes [75]. Further supporting the idea that malfunctioning lysosomes play a role in the pathophysiology of cystinosis is the employment of small Rab GTPases, which enhance cellular function by upregulating lysosomal trafficking [52]. Numerous downstream effects of elevated lysosomal cystine contribute to the molecular pathophysiology of cystinosis. Proximal tubular epithelial cell (PTEC) and podocyte dysfunction, inflammation, autophagy, oxidative stress, changed cellular energy metabolism, altered calcium signaling, and apoptosis are all factors in the multifactorial pathophysiology of cystinosis.

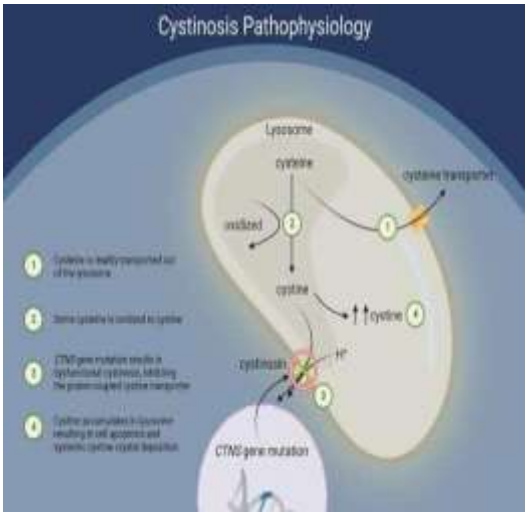

FIG.2:CYSTINOSIS PATHOPHYSIOLOGY

Podocyte dysfunction and PTEC:

The of nephropathic cystinosis is characterized by PTEC and podocyte dysfunction. Cystinosin plays a key role in the function of PTECs and podocytes; in proximal renal tubular cells, ctns−/− zebrafsh exhibit increased lysosomes, slit membrane stenosis, and partial podocyte disappearance [27]. Cystinosis can harm podocytes, which can lead to giant cell transformation [84] and mult- inucleation [14] because of a lack of cytokinesis. The actual damage to podocytes is probably complex, arising from multinucleation, altered cytoskeleton, and increased podocyte motility [46]. It has been shown that AKT kinase is at the core of the intricate signaling cascade that controls podocyte adhesion and motility; inhibition of AKT kinase causes the hypermobile podocytes observed in cystinosis to return to normal [47, 49]. Patients with cystitis have higher levels of podocytes and PTECs in their urine than do controls.Nevertheless, there is no known relationship between podocyturia and proteinuria, age, or estimated glomerular filtration rate [47, 49]. Because of their hypermobile nature, compromised cell adhesion sites, and altered cytoskeleton, podocytes in cystinosis are more likely to be lost in the urine [47, 49]. The aberrant transport of endolysosomal vesicles contributes to the loss of PTECs in the urine. This is explained by delayed

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lysosomal cargo processing and a reduction in multiligand receptor surface expression [48].

Inflammation:

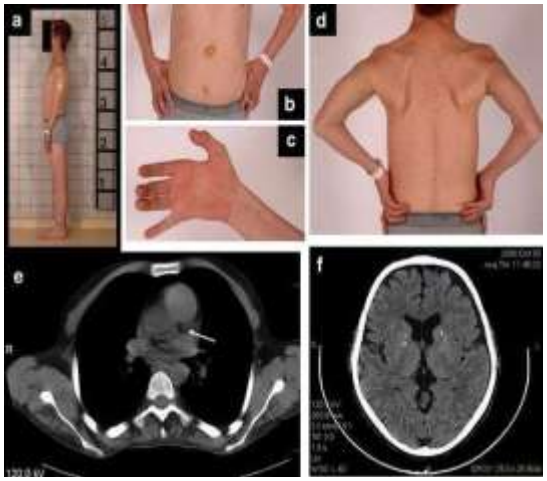

FIG.3:CYSTINE BUILDUP

Cystinosis etiology is significantly influenced by inflammation. Galectin 3, the NLRP2/3 infammasome, and the enzyme chitotriosidase are some of the main inflammatory mediators in this process. NLRP3 infam-masome activation can result from cystine buildup, and individuals with cystinosis had greater serum levels of I-1β 18 than controls. In response to cystine crystal stimulation, these cytokines are released in a dose-dependent manner [74]. Reactive oxygen species are produced concurrently by the NLRP3 inflammation, which also plays a role in the pathophysiology of cystitis [74]. Furthermore, there is high expression of NLRP2.exerts a significant proinfamatory and probrotic role in cystinosis and in cystinotic PTECs [79]. This inflammatory process also involves IL-6, which functions as an independent predictor of leukocyte cystine levels in addition to IL-1β and IL-18.[99].Additionally, it has been shown that anakinra-induced IL-1 suppression can lessen cachexia in individuals with cystinosis [17]. In cystinosis, the chitotriosidase enzyme activity is elevated [28]. An indicator of macrophage activity, chitotriosidase is an enzyme that breaks down chitin and is expressed by active macrophages [28]. Gaucher disease and other lysosomal illnesses also exhibit increased chitotriosidase activity [41]. Interestingly, a prospective multicenter investigation found a significant relationship between the quantity of chitotriosidase and problems outside the kidneys [99]. Chitotriosidase activity may be used as a new biomarker for therapeutic monitoring and the degree of cystinosis [28, 99]. It is known that galectin 3 has a role in the inflammatory process that leads to the development of chronic kidney disease [64]. Compared to Ctns−/−mice, Ctns−/−Gal3−/−mice have better renal function and lower macrophage infiltration into the kidney due to the overexpression of Galec-tin 3 [64].

Oxidative stress:

It has been suggested that the pathogenesis of renal Fanconi syndrome in cystinosis is related to altered glutathione metabolism and elevated oxidative stress [16]. Oxidative stress is facilitated by cystinotic cells' elevated superoxide dismutase synthesis and decreased glutathione concentration [19]. Urinary shed PTECs from patients with cystinosis have also been shown to have increased levels of cellular oxidative stress [102]. According to research, cystinotic cells are more susceptible to oxidative stress because of reduced glutathione synthesis and a weakened gamma glutamyl cycle, which may be brought on by changed ATP levels and mitochondrial dysfunction [67, 103, 104].

Alter cellular energy metabolism:

Modified metabolism of cellular energy Reduced intracellular ATP levels are frequently reported in cystinosis, which is characterized by altered cellular energy homeostasis [61]. According to studies, while Na+ K+ ATPase pump activity is maintained, the intracellular drop in ATP may be caused by a decrease in cellular glutathione [61] or a decrease in apical reabsorption of phosphate [89]. Additionally, a conditionally immortalized PTEC line has shown much lower levels of cAMP, mitochondrial potential, and complex I and IV activation [5]. The activation of the cytosolic fuel sensor AMPK in rabbit renal proximal tubule cells with a cystinosin knockdown [88] further supports the existence of an energy imbalance. Signaling by calcium Since calcium signaling is disrupted in other lysosomal disorders such Gaucher and Niemann-Pick type C disease, it has been hypothesized that altered calcium signaling plays a part in cystinosis [56]. Furthermore, in a cellular model of cystinosis, it has been shown that the calcium sensor UNC13D controls autophagy and endolysosomal trafficking [105, 106]. ATP-induced calcium release appears to be slightly sensitized in cystinosis cells compared to control, despite the fact that no significant dysregulation of intracellular calcium dynamics has been observed in cystinosis [47, 49]. Since lysosomal calcium release triggers downstream calcineurin activation and

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TFEB dephosphorylation, which in turn trigger the expression of lysosomal and autophagy genes, a connection between lysosomal calcium signaling and autophagy has been demonstrated [70].

Clinical manifestation:

Nephropathic cystinosis, juvenile cystinosis, and ocular cystinosis are the three clinical types of cystinosis. The degree of kidney involvement and the age at which the disease first manifests are what define them. With up to 95% of cases, nephropathic cystinosis, sometimes referred to as infantile nephropathic cystinosis, is the most prevalent type of cystinosis [30]. The most severe kind of the illness typically results in renal Fanconi syndrome and kidney failure in the first ten years of life if treatment is not received [37]. Five percent of cases are juvenile cystinosis, also referred to as late-onset cystinosis. Typically, juvenile cystinosis manifests between the ages of [10 and 12]. Compared to nephropathic cystinosis, it is thought to be less severe, and people are more likely to experience a lesser form of renal Fanconi syndrome within the first ten years of life without treatment [37]. Five percent of occurrences of cystinosis are in children, commonly referred to as late-onset cystinosis. The typical age range for juvenile cystinosis development is [10 to 12.] In addition to having significant glomerular involvement and proteinuria, people with this condition are likely to have a milder type of renal Fan-coni syndrome, making it less severe than nephropathic cystinosis [30]. The type of cystinosis that is not nephropathic is called ocular cystinosis. It is seldom identified before maturity and typically manifests as cystine buildups within the cornea [37, 90]. At the age of one year, children with nephropathic cystinosis start exhibiting signs of renal Fanconi syndrome. This includes rickets, growth retardation, constipation, failure to thrive, polyuria, polydipsia, dehydration, and vomiting. Acidosis, hypokalemia, proteinuria, hypophosphatemia, and aminoaciduria can all be found in laboratory results [90]. Physical changes in the kidney's structure do not show up until the second year of life, despite the fact that these symptoms start to show around one year. This suggests a potential window of opportunity to offer disease- curing treatment in the future before the kidney's proximal tubules undergo permanent physical changes [13, 16].Renal transplantation is the best course of action for people who reach stage 5 renal failure. At the age of one year, children with nephropathic cystinosis start exhibiting signs of renal Fanconi syndrome. This includes rickets, growth retardation, constipation, failure to thrive, polyuria, polydipsia, dehydration, and vomiting. Acidosis, hypokalemia, proteinuria, hypophosphatemia, and aminoaciduria can all be found in laboratory results [90]. Physical changes in the kidney's structure do not show up until the second year of life, despite the fact that these symptoms start to show around one year. This suggests a potential window of opportunity to offer disease-curing treatment in the future before the kidney's proximal tubules undergo permanent physical changes [13, 16]. renal transplantation is the best course of action for people who reach stage 5 renal failure. Early cysteamine treatment increases the linear growth of cystinosis patients, according to a 20-year longitudinal research [40]. Cysteine crystal deposits in the cornea are a symptom of ocular cystinosis. These cystine crystals, which appear in the cornea after 16 months of age, are indicative of cystinosis [36]. Later in life, progressive retinopathy and band keratopathy may develop if therapy is not received [30], with retinopathy resulting in blindness in 10–15% of cases [36].

Diagnosis:

There are three primary ways to diagnose cystinosis. This includes the detection of corneal cystine crystals, genetic analysis, and the assessment of leukocyte cystine levels [91]. The gold standard is the measurement of leukocyte cystine levels. High-performance liquid chromatography or liquid chromatography-tandem mass spectrometry are used to perform it [37]. Cystinosis should always be regarded as a differential diagnosis because it is the most frequent cause of renal Fanconi syndrome in infants [30].

Treatment:

The few available treatments for cystinosis are not curative. To minimize renal damage and the disease's progression, early diagnosis and treatment are essential [34]. Treatment for cystitis can be divided into three categories: symptom relief, lifestyle changes, and cystine-targeted therapy. Avoiding extended sun and heat exposure can reduce the risk of heatstroke due to decreased sweating [35]. Additionally, patients who suffer from significant polyuria and polydipsia should have unrestricted access to water and bathrooms [103,104]. The primary goal of symptomatic therapy is to manage the adverse effects of renal impairment. This include preventing keeping proper fluid and electrolyte

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balance, and eating a healthy, balanced diet. The three electrolytes that are most crucial are sodium, potassium, and bicarbonate; these are routinely checked [103, 104]. Unrestricted consumption of salt and water is crucial because poor renal function causes a significant loss of fluids and electrolytes [37]. In order to avoid rickets, vitamin D supplements are frequently administered to patients. In an experimental investigation using Ctns−/−mice, 25(OH)D3 showed an advantage over 1,25(OH)2D3 by avoiding adipose tissue browning and muscle atrophy [108]. Additionally, an experimental investigation has shown that IL 1 has a function in cystinosis metabolic bone disease, which may help explain the impact of immunosuppressive medication. Pediatric patients frequently experience severe failure to thrive [26]. For individuals who are unable to maintain a nutritious diet, nasogastric tubes and gastrostomy tube feeding are keeping proper fluid and electrolyte balance, and eating a healthy, balanced diet. The three electrolytes that are most crucial are sodium, potassium, and bicarbonate; these are routinely checked [103,104]. Unrestricted consumption of salt and water is crucial because poor renal function causes a significant loss of fluids and electrolytes.[37]. In order to avoid rickets, vitamin D supplements are frequently administered to patients. In an experimental investigation using Ctns−/−mice, 25(OH)D3 showed an advantage over 1,25(OH)2D3 by avoiding adipose tissue browning and muscle atrophy [108]. Additionally, an experimental investigation has shown that IL 1 has a function in cystinosis metabolic bone disease, which may help explain the impact of immunosuppressive medication Pediatric patients frequently experience severe failure to thrive [26]. For individuals who are unable to maintain a nutritious diet, nasogastric tubes and gastrostomy tube feeding are advised [31]. Proton-pump inhibitors may also be helpful for people who experience frequent vomiting and reflux [25]

One clinical consequence of cystitis is growth retardation. While growth hormone treatment can also be started to improve final height [8, 40], cytosteamine medication alone will improve statural growth [96]. Diabetes, hypothyroidism, and hypogonadism are fewer common consequences of cystinosis that are treated with insulin, levothyroxine, and testosterone, respectively [103,104]. Before the age of 20, 90% of people with cystinosis develop renal failure [20]. Dialysis and kidney transplantation are the only remaining therapy alternatives at this time [50]. The initial illness does not affect the donor kidney after transplantation. Despite having a good prognosis for individuals with cystinosis, kidney transplants are not risk-free [57]. Transplant recipients face a number of difficulties, including significant rehabilitation, lifelong immunotherapy, and surgical complications. Ocular cysteamine levels are unaffected by oral administration of cysteamine [94]. The treatment for ocular cystinosis involves applying topical 0.5% cysteamine eye drops 10–12 times daily. Photophobia and ocular discomfort can be significantly reduced by topical cysteamine, which enhances quality of life [95]. Sustained release cysteamine eyedrops have been the subject of numerous research with the goal of enhancing medication stability, enabling a once-daily dosage schedule, and lowering patient disease burden [51, 78]. Furthermore, a drugless treatment for ocular cystinosis using gold nanoparticle contact lenses has been developed and evaluated in vitro; the gold nanoparticles remove cysteine from the surrounding tissue [63]

Cysteamine:

The cornerstone of treatment for individuals with cystinosis is cysteamine. One medication that depletes cystines is cysteamine. Because cysteamine causes a disulphide exchange reaction that produces both cysteine and cystine-cysteamine mixed disulphide, it reduces intra-lysosomal cystine levels. A "system c" transporter allows cystine to exit the lysosome in the form of cysteine-cysteamine-mixed disulphide, while the cysteine carrier allows the remaining cystine to exit [103, 104]. Cysteamine enhances overall prognosis and postpones the onset of extrarenal problems, the necessity for kidney transplantation, and the progression of kidney failure [34]. Cysteine therapy should be continued in patients undergoing kidney transplantation in order to prevent harm to extrarenal organs [103,104]. Proton pump inhibitors help lessen the gastrointestinal distress and disturbance that are the primary side effects of cysteamine [25]. At first, the patient's quality of life was continuously disrupted by the four times a day that cysteamine was administered. Because of its brief half-life, the quick release formulation of cysteamine limits the user to taking it once every six hours, including at night [103,104]. There have been recent attempts to extend the half-life of cysteamine. In 2013 and 2014, respectively, the USA and Europe authorized the use of a delayed release version of cysteam-ine [4]. This permit dosing twice a day, at 12-hour intervals [60]. By

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avoiding the stomach and preventing severe gastrointestinal effects, delayed release cysteamine lessens the necessity for concurrent gastro-protection [31]. Compared to immediate release cysteamine, it has been demonstrated to enhance renal function, leukocyte cystine levels, and quality of life [58, 96]. The possibility of once-daily dosage has been raised by attempts to find cysteamine pro-drugs such esterifed gamma-glutamyl-cysteamine, which may maintain cysteamine levels above the threshold of efficacy for at least 24 hours [33]. To lessen the burden of sickness on patients, more study is required to examine prodrugs and cysteamine analogues. The management of this illness depends on early diagnosis and therapy [34]. Veys et al.'s multicenter sibling cohort study found that presymptomatic cysteamine treatment was more beneficial than treatment started at the onset of symptoms [98]. Furthermore, when diagnosed before the age of 18 months, kidney transplantation is necessary at a significantly later age [72]. Despite recent improvements in cystinosis therapy, there is still a significant gap: 7% of patients in impoverished nations die at age 5, compared to 0% in industrialized nations [7]. Notably, there are significant differences in the availability of cysteamine around the globe; in developing and developed economies, 74% and 7% of patients, respectively, have access to delayed release cysteamine. Furthermore, third-world countries have fewer diagnostic capacities than developed ones; in developing economies, genetic testing and intra-lysosomal cystine level measurements are available in 63% and 30% of cases, respectively, whereas in developed economies, they are 100% and 94% available [77]. As could be expected, the mean age of illness and mortality is lower in emerging nations [7]. Notably, there are significant differences in the availability of cysteamine around the globe; in developing and developed economies, 74% and 7% of patients, respectively, have access to delayed release cysteamine. Furthermore, third-world countries have fewer diagnostic capacities than developed ones; in developing economies, genetic testing and ntra-lysosomal cystine level measurements are available in 63% and 30% of cases, respectively, whereas in developed economies, they are 100% and 94% available [77]. As could be expected, the mean age of illness and mortality is lower in emerging nations [7]

Options for future therapy:

Many studies have been conducted in recent years to develop a more effective treatment for cystinosis. Since bone marrow and hematopoietic stem/progenitor cell (HSPC) transplants have been successful in Ctns-/- mice, there has been interest in them. In Ctns−/−mice, transplanting syngeneic wild-type murine hematopoietic stem and progenitor cells led to up to 97% intra- lysosomal cystine clearance, which also decreased illness systemic symptoms [87]. Following this, a 16-year-old male patient with cystinosis underwent an allogenic HSPC transplant. Unfortunately, graft-versus-host disease claimed the patient's life 35 months after the transplant [29]. Additionally, studies have looked into downstream molecular targets that could help with cystinosis. These targets consist of LAMP2A and mTOR. Preclinical studies have shown that inhibition of mTOR/mTORC1 can reverse the downstream effects of intra-lysosomal cystine buildup on lysosomal function and cell differentiation, indicating a significant potential therapeutic target [65]. When combined with cysteamine treatment [45] and dietary protein restriction [6], mTOR inhibition represents more choices to alleviate cellular dysfunction brought on by cystinosis. A potential point of intervention to ameliorate the condition is the disruption of chaperone-mediated autophagy (CMA), which is also present in cystinosis. Increased LAMP2A localization is facilitated by CMA activation in vitro, which raises murine Ctns-/-cell survival [107]. In a human proximal tubule cell line created using CRISPR-Cas9 CTNS KO, it has similarly, been demonstrated that CMA overexpression causes proximal tubule cell dysfunction [105, 106] Members of the flavonoid family, such as genistein and luteolin, have potential medicinal uses. Through activation of transcription factor EB (TFEB), in vitro studies showed that genistein, an isoflavone abundant in soy, could recover the cystinotic cellular phenotype in a mechanism independent of cystinosin [76]. In animal models of nephropathic cystinosis, additional research demonstrated that genistein could ameliorate kidney disease [24]. Additionally, genistein has a bone-protective effect [24]. Furthermore, it has been shown that luteolin can target illness components that are resistant to cysteamine therapy [23]. When combined, these findings suggest that a treatment using genistein/luteolin and cysteamine may target distinct pathways in the pathophysiology of cystinosis for enhanced therapeutic benefit. ACE-tRNA, as opposed to gene therapy, minimizes the possible toxicity linked to overexpression or off-target expression of cDNA by enabling endogenous

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transcription. Furthermore, it eliminates the issues related to delivering full-length cDNA, which might exceed AAVs' packaging threshold [100]. ACE-tRNAs present a potential novel therapeutic strategy to target disorders like Duchenne muscular dystrophy, cystinosis, and cystic fibrosis that are mediated by nonsense variants The unique difficulties that RNA- and molecular-based therapy encounters in cystinosis should not be overlooked. Targeting the kidney presents additional challenges for RNA-based therapeutics because of the intricate renal architecture and the wide range of cell types found there [10]. Peptide ligands, antibody-like molecules, and aptamers are RNA delivery systems that may be useful in cystinosis because they enable treatments to target the kidney directly [10].

Conclusion:

The intra lysosomal buildup of cysteine is the cause of cystinosis, a rare autosomal recessive genetic disorder. There aren't many curative therapeutic options for it. The goals of treatment are to reduce symptoms, postpone renal failure, and limit the progression of the illness. The majority of patients undergoing cysteamine treatment now reach adulthood, indicating significant progress in the treatment of cystinosis. Improving morbidity and mortality rates requires early intervention and ongoing cysteamine therapy for the rest of one's life [44]. Numerous intriguing studies are being conducted in this area, offering patients with cystinosis a number of novel and promising treatment possibilities.

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