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Review

Cell biology of the NCL proteins: What they do and don't do☆

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ABSTRACT

The fatal, primarily childhood neurodegenerative disorders, neuronal ceroid lipofuscinoses (NCLs), are currently associated with mutations in 13 genes. The protein products of these genes (CLN1 to CLN14) differ in their function and their intracellular localization. NCL-associated proteins have been localized mostly in lysosomes (CLN1, CLN2, CLN3, CLN5, CLN7, CLN10, CLN12 and CLN13) but also in the Endoplasmic Reticulum (CLN6 and CLN8), or in the cytosol associated to vesicular membranes (CLN4 and CLN14). Some of them such as CLN1 (palmitoyl protein thioesterase 1), CLN2 (tripeptidyl-peptidase 1), CLN5, CLN10 (cathepsin D), and CLN13 (cathepsin F), are lysosomal soluble proteins; others like CLN3, CLN7, and CLN12, have been proposed to be lysosomal transmembrane proteins. In this review, we give our views and attempt to summarize the proposed and confirmed functions of each NCL protein and describe and discuss research results published since the last review on NCL proteins. This article is part of a Special Issue entitled: "Current Research on the Neuronal Ceroid Lipofuscinoses (Batten Disease)".

1. Introduction

Neuronal ceroid lipofuscinoses (NCLs), also known as Batten disease, make up the most common group of inherited neurodegenerative disorders of childhood, with selective destruction and loss of neurons in the cerebral, cerebellar cortex and retina. Most NCLs show an autosomal recessive mode of inheritance, and are classified according to the severity of the resulting mutations and the ages of onset such as congenital, infantile, late infantile, juvenile, adult or even late adult onset. They share clinical features such as progressive loss of vision as well as mental and motor deterioration, epileptic seizures, and eventually premature death.

NCLs are considered lysosomal storage diseases (LSD) characterized by a heterogeneous origin of the storage material. This material consists mostly of accumulation of ceroid-lipopigments, subunit c of mitochondrial ATP synthase or sphingolipid activator proteins A and D in lysosomes. Commonly, the accumulated ceroid-lipopigments are autofluorescent and are positive for periodic acid–Schiff (PAS), which stains polysaccharides, glycoproteins and glycolipids, Luxol fast blue (LFB), which stains lipoproteins in the myelin sheath, Sudan black B, which stains neutral triglycerides and lipoproteins, and the Ziehl-Neelsen acid fast stain, which stains mycolic acids [1]. The nature of the storage material accumulation in NCLs might be a result of an ancillary process and may not necessarily lead to clarifying the functions of NCL-causing gene products. Nevertheless, the elucidation of the nature and cell location of the involved proteins underlying such common clinical and pathological features is crucial to disentangle the affected pathways and to ascertain common processes.

NCL-associated proteins (CLN1 to CLN14) differ in their function and their intracellular localization (see Table 1). NCL proteins have been localized mostly in lysosomes (CLN1, CLN2, CLN3, CLN5, CLN7, CLN10, CLN12 and CLN13) but also in the Endoplasmic Reticulum (ER) (CLN6 and CLN8), or in the cytosol associated to vesicular membranes (CLN4 and CLN14). Some of them such as CLN1, which is palmitoyl protein thioesterase 1 (PPT1), CLN2, which is tripeptidyl-peptidase 1 (TPP1), CLN5 with unknown function, CLN10, which is cathepsin D, and CLN13, which is cathepsin F, are lysosomal soluble proteins; some other like CLN3, CLN7, and CLN12, have been proposed to be lysosomal transmembrane proteins.

Mutations in these NCL proteins cause the different forms of NCL disease and the potential interactions between proteins affecting different NCL pathways have been studied. In this review, we summarize the proposed and confirmed functions of each NCL protein and describe and discuss research results published since the last review on NCL proteins [2]. Despite the research efforts, a definitive function has not been established for the majority of NCL proteins.

2. NCL proteins

2.1. CLN1 (palmitoyl protein thioesterase 1)

Mutations of the *CLN1* gene cause infantile CLN1 disease, which is the most severe form of NCLs, presents in children at 1–2 years of age,

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Table 1
NCL proteins and their subcellular localization and function.

NCL gene	Protein	Subcellular localization	Function
CLN1	CLN1/Palmitoyl protein thioesterase 1 (PPT1) 306 aa, soluble protein	Lysosomal matrix, extralysosomal vesicles, lipid rafts, ER and presynaptic areas in neurons	Palmitoyl thioesterase; associated to endo/exocytosis in synaptic vesicle recycling, to cholesterol metabolism and to apoptosis
CLN2	CLN2/Tripeptidyl-peptidase 1 (TPP1) 563 aa, soluble protein	Lysosomal matrix and ER	Serine protease; associated to macroautophagy, endocytosis and TNF-α-induced apoptosis
CLN3	CLN3 438 aa, transmembrane protein, (6 transmembrane domains)	Late endosomal/lysosomal membrane	Unknown function; postulated to have a role in endocytosis, autophagy, maintenance of vacuolar/lysosomal pH, anterograde/retrograde transport of lysosomal enzyme transporters, osmoregulation, apoptosis and cell cycle control
CLN4	CLN4/Cysteine-string protein alpha (CSPα)/DNAJC5 198 aa, soluble protein	Cytosolic, associated to vesicular membranes, to synaptic vesicles in neurons, and to secretory granules in endo/exo/neurocrine cells	Hsc70 co-chaperone; involved in presynaptic endo/exocytosis; function is fully rescued by α-synuclein
CLN5	CLN5 407 aa, soluble protein	Lysosomal matrix	Unknown function; involved in sphingolipid transport and synthesis, myelination, cell, growth, apoptosis, and retrograde transport of the lysosomal enzyme transporter, CIMPR
CLN6	CLN6 311 aa, transmembrane protein (7 transmembrane domains)	ER membrane	Unknown function; associated to autophagy, endocytosis, regulation of pH and biometal metabolism
CLN7	CLN7/MFSD8 518 aa, transmembrane protein (12 transmembrane domains)	Lysosomal membrane	Unknown function; predicted to have a role in the transport of small substrates across cellular membranes
CLN8	CLN8 286 aa, transmembrane protein (5 transmembrane domains)	ER/ ER-Golgi intermediate compartment membrane	Unknown function; postulated to have a central role in the regulation of sphingolipid transport and synthesis; also related to oxidative and ER stresses, mitochondrial function, calcium homeostasis, inflammation and apoptosis
CLN9	CLN9 Unknown protein	Unknown localization	Unknown function
CLN10	CLN10/Cathepsin D (CTSD) 412 aa, soluble protein	Lysosomal matrix and extracellular	Aspartyl endopeptidase; have major roles in apoptosis and autophagy; in cancer cells has major roles in proliferation, angiogenesis, invasion and metastasis
CLN 11	CLN11/Progranulin/ Proepithelin/Acrogranin 593 aa, soluble protein	Extracellular	Unknown function; main role associated to autophagy but also reported roles in inflammation, embryogenesis, cell motility and tumorigenesis
CLN 12	CLN12/ATPase 13A2/KRPPD/PARK9/HSA9947/ RP-37C10.4 1180 aa, transmembrane protein (10 transmembrane domains)	Lysosomal membrane and multivesicular bodies.	Unknown function; predicted to shuttle cations, heavy metals and lipids across cell membranes; also postulated to be involved in pH homeostasis, lysosomal degradation, biometal homeostasis, and protection against α-synuclein toxicity
CLN 13	CLN13/Cathepsin F 484 aa, soluble protein	Lysosomal matrix	Cysteine protease; has been mainly associated to proteasome degradation and autophagy; also related to cell immunity and lipoprotein degradation
CLN 14	CLN14/Potassium channel tetramerization domain-containing protein 7 (KCTD7) 289 aa, soluble protein	Cytosolic and also partially associated to the plasma membrane	Unknown function; predicted to be involved in the hyperpolarization of the neuronal cell membrane; also associated to proteasome degradation

aa: amino acid.

and typically leads to death by ages 8–11 [3]. *CLN1* mutations causing milder disease forms including late infantile, juvenile, or adult phenotype have also been reported [4,5]. The *CLN1* gene encodes palmitoyl protein thioesterase 1 (PPT1), a soluble lysosomal enzyme involved in lysosomal degradation of S-fatty acylated proteins [6–8]. Low or inexistent levels of palmitoyl protein thioesterase 1 (PPT1) and granular osmiophilic deposits (GRODs) in leukocytes are the distinctive hallmarks of infantile CLN1 disease.

The crystal structure of PPT1 revealed a soluble, globular monomer with an α/β hydrolase fold and a catalytic triad (S115, D233, H289) [8]. Ohno et al. postulated that there is a structural basis for the effect of PPT1 mutants showing that mutations which exhibited a total loss of enzymatic activity affected the core region of the enzyme [9]. Despite not knowing precisely neither the *in vivo* substrates of PPT1-mediated depalmitoylation activity nor its precise physiological role, several reports have shown the association of PPT1 to the F1 complex of mitochondrial ATP synthase, H-Ras, palmitoyl-CoA, α subunits of heterotrimeric G proteins or neuron-specific GAP43 and rhodopsin [10–13]. Experiments showing depalmitoylation of GAP-43 and rhodopsin peptides by PPT1 *in vitro* demonstrated that the enzyme was more efficient at neutral pH (7.4) than at acidic pH (4.0) [13]. This could be considered as potential evidence for a possible extralysosomal function of PPT1. Besides lysosomes PPT1 has also been found in lipid rafts with a suggested role in regulating lipid content in CHO cells as overexpression of PPT1 resulted in decreased ceramide contents relative to cholesterol and sphingomyelin [14]. In neurons, the localization and functional activity of PPT1 is not limited to lysosomes, PPT1 is also found in the presynaptic area [15–17], suggesting a neuron-specific function of PPT1. Supporting this notion, the expression of PPT1 in human and mouse brain is developmentally regulated and coincides with cortical synaptogenesis [18–20].

Studies in *Drosophila* have indicated that PPT1 is involved in endocytosis. In *Ppt1* loss-of-function *Drosophila* mutants, Garland cells, a small group of nephrocytes that take up waste materials from the hemolymph by endocytosis, had defects in endocytic trafficking [21]. Endocytic tracer uptake and ultrastructural analysis of these Garland cells indicated that PPT1 plays a role in modulating the early stages of vesicle formation [21]. A recent study by Aby et al. examined the consequences of *Ppt1* mutations at the *Drosophila* larval neuromuscular junction, a very well-characterized synapse. They showed changes in synaptic vesicle

exo- and endocytosis proved by a reduced ability of nerve terminals to recover from repetitive stimulation and by reductions in FM1-43 uptake in the *Ppt1*-mutant larval nerve terminals [22]. The authors' findings highlight the importance of PPT1 and palmitoylation in general, in synaptic vesicle exo- and endocytosis and neuromuscular function [22]. A previous study by Kim et al. using postmortem brain tissues from a patient with infantile CLN1 disease and tissue from *Ppt1*-knockout (*Ppt1*$^{-/-}$) mice that mimic infantile CLN1 disease, had corroborated the *Drosophila* studies [23]. Neuronal communication relies on repeated cycles of exo- and endocytosis of the neurotransmitter-laden synaptic vesicles (SVs) at the nerve terminals [24–27], and Kim et al. reported that PPT1 deficiency causes persistent membrane anchorage of the palmitoylated SV proteins VAMP2 and SNAP25, impairing, subsequently, the regeneration of fresh SVs, an essential process for maintaining the SV pool size at the synapses [23].

In most NCL diseases the storage material consists mainly of subunit c of ATP synthase, while in infantile CLN1 and congenital CLN10 diseases the main components of storage material are sphingolipid activator proteins (SAPs) A and D [28,29]. Examining the possible implications of PPT1 in lipid accumulation Lyly et al. showed that in PPT1-deficient mouse primary neurons, there is an increased amount of subunits of the F1 complex of mitochondrial ATP-synthase in the plasma membrane and increased uptake of apolipoprotein A (apoA-1) by this complex, therefore postulating a role for PPT1 in cholesterol metabolism [10].

Recent therapeutic approaches also provided some insights into the function of PPT1. Treatment of *Ppt1*$^{-/-}$ mice with a non-toxic hydroxylamine derivative, N-(tert-Butyl) hydroxylamine (NtBuHA) known to cleave thioester linkage in palmitoylated proteins depleted lysosomal ceroid, suppressed neuronal apoptosis, slowed neurological deterioration and extended lifespan [30]. In cultured fibroblasts and lymphoblasts from infantile CLN1 disease patients with nonsense *CLN1* mutations, PTC124, a read-through drug that promotes translation through premature stop codons, increased PPT1 enzyme activity [31,32] and slightly affected apoptosis [31]. Kim et al. reported that neuronal apoptosis in infantile CLN1 disease is caused by caspase-4 activation leading to caspase-3 effector activation, and that inhibition of caspase-4 activity is cytoprotective in lymphoblasts from infantile CLN1 disease patients [33]. They confirmed that the PPT1-targeted protein, GAP43 is accumulated in the ER in the affected lymphoblasts and suggested that ER stress-induced activation of the unfolded protein response (UPR) mediates caspase-4 and caspase-3 activation, and apoptosis [33]. Finally, the same group reported that the use of antioxidant drugs such as omega-3 and omega-6 fatty acids [34] and resveratrol [35], reduces oxidative stress and suppresses apoptosis in *Ppt1*$^{-/-}$ mice, resulting in a very modest increase in life span [35].

A potential link between PPT1 and another soluble lysosomal NCL protein, CLN5 has also been found: GST-CLN5 pulled down endogenous PPT1 from both mouse brain extract and HeLa cell lysates, and overexpressed PPT1 and CLN5 colocalized in cultured cells as shown by confocal microscopy [36]. In the same study, when CLN5 with the most common Finnish variant late infantile NCL-causing mutation (p.Y392X) was expressed in HeLa cells and in neuroblastoma cells (SH-SY5Y), the mutant CLN5 was retained in the ER and did not colocalize with the lysosomal marker LAMP-1. Interestingly, simultaneous overexpression of wild type PPT1 with mutated CLN5 in both cell lines resulted in co-localization of the two proteins in LAMP-1 positive lysosomes [36].

All in all, the synapse-specific role of PPT1, regulating synaptic vesicle exo- and endocytosis [22,23] and thus, neurotransmission and synaptic integrity, is the most likely explanation for the rapid neurodegeneration occurring in infantile CLN1 disease. Further studies are required to clarify how exactly PPT1 deficiency leads to neuronal death.

2.2. CLN2 (tripeptidyl-peptidase 1)

Mutations in *CLN2*, which encodes tripeptidyl-peptidase 1 (TPP1), cause late infantile CLN2 disease, which presents in children at 2–4 years of age, and typically leads to death by 6–15 years of age [37]. *TPP1* has also been identified as the causative gene for autosomal recessive spinocerebellar ataxia 7 (SCAR7) by exome sequencing. [38]. TPP1 is a serine protease that is active at an acidic pH optimum to remove tripeptides from the amino terminus of proteins but its *in vivo* substrates are unknown. TPP1 is synthesized as an inactive proenzyme (pro-TPP1) that is proteolytically processed into the active enzyme after exposure to low pH *in vitro* or targeting to the lysosome *in vivo* [39]. Transfection experiments have indicated that TPP1 mutants have delayed processing and are retained in the ER rather than transported to lysosomes [40]. The same studies also showed that Ca^{2+} is necessary for the autocatalytic processing of the precursor protein into the mature TPP1 [40]. Several studies have confirmed that the *CLN2*/*Cln2* gene is ubiquitously expressed in human, rat and mouse tissues and it is developmentally regulated [41–44]. Koike et al. measured TPP1 (CLN2) protein levels in various tissues from adult rats and mice and found that TPP1 was highly expressed in the brain [41]. Another study in human subjects showed that the expression of TPP1 in the cerebral cortex increased with development, and reached adult levels after the age of 2 [42].

Although the knowledge of the *in vivo* interacting partners of TTP1 could give us key information regarding its function, the native substrates of TPP1 and its exact physiological roles are not known. Nevertheless, several studies *in vitro* have described distinct interactions of TPP1 with different substrates [45–48]. Peptide hormones such as angiotensin II [45], glucagon [46], substance P [45], cholecystokinin and neuromedin [46,47], as well as synthetic amyloid-β-peptides and the mitochondrial ATP synthase subunit c [48], were cleaved by TPP1 *in vitro*.

Late infantile CLN2 disease has been lately associated with macroautophagy and with defective endosomal/lysosomal cell processes [49,50]. Micsenyi et al. described significantly increased levels of microtubule-associated protein 1 light chain 3 (LC3-II), an autophagy marker, in cerebrum and cerebellum extracts in 13-week-old TPP1-deficient mice, consistent with defective macroautophagosome maturation in the last stages of the disease [49]. Vidal-Donet et al. showed upregulated Akt-mTOR signaling pathway in late infantile CLN2 disease fibroblasts and a reduced formation of autophagosomes. This study also indicated that the observed accumulation of higher amounts of Radical Oxygen Species (ROS) in late infantile CLN2 disease fibroblasts and a decrease in catalase activity could both increase the accumulation rate of peroxidized lipids and lipofuscin in late infantile CLN2 disease [50].

Generation of induced pluripotent stem cells (iPSCs) from patient's fibroblasts and subsequent differentiation of the iPSCs to specific cell types of interest has become a powerful tool for human disease modeling and therapeutic screening [51,52]. Lojewski et al. generated iPSCs from late infantile CLN2 disease and juvenile CLN3 disease patients' fibroblasts and also generated neural progenitor cell lines (NPC) from the iPSCs [52]. Despite the reported changes in macroautophagy and defective endosomal/lysosomal cell processes found in late infantile CLN2 disease fibroblasts [50] Lojewski et al. found no changes in the area of the autophagic degradative vacuoles in late infantile CLN2 disease iPSCs [52]. When TPP1 expression was measured in juvenile CLN3 disease iPSCs and neural progenitor cells, interesting results were obtained. TPP1 expression in the iPSCs derived from juvenile CLN3 disease patients was significantly lower than in non-affected, control iPSCs, whereas in neural progenitor cells derived from juvenile CLN3 disease iPSCs, TPP1 expression was significantly higher than those derived from non-affected, control iPSCs [52]. This might be due to a cell-type specific compensatory response to the CLN3 deficiency. Previous studies have also shown increased TPP1 activity in the brain of *Cln3*$^{-/-}$ mice and juvenile CLN3 disease patients [53–55].

TPP1 has also been proposed to play a central role in TNFα-induced apoptosis [56]. According to this study, fibroblasts from late infantile CLN2 disease patients are resistant to TNFα-induced apoptosis and

TPP1 can catalyze the cleavage of Bid, a Bcl-2 interacting protein *in vitro*. Nevertheless, a month later, a paper by Kim et al. showed that in the *Tpp1*$^{-/-}$ mouse model of late infantile CLN2 disease, genetic modulation of p53 or Bcl-2 expression did not affect neurodegeneration, tremor onset or frequency, and the characteristic shortened life-span [57]. The authors also suggested that neuronal death in late infantile CLN2 disease either does not occur via apoptosis or it occurs via apoptotic pathways not involving p53 or Bcl-2 [57].

In conclusion, the involvement of TPP1 in macroautophagy and TNFα-induced apoptosis indicates that this lysosomal serine protease affects cell viability. It is still unknown, however, how TPP1-deficiency causes selective neurodegeneration.

2.3. CLN3

Recessive mutations in the *CLN3* gene cause juvenile CLN3 disease, the most common subtype of NCLs [58]. Although, *CLN3* mutations primarily affect neurological processes causing vision loss, seizures, and progressive motor and cognitive decline, there is also evidence of pathology outside of the central nervous system, more specifically in the cardiac and immune systems [59–62]. *CLN3* encodes a 438-amino acid putative lysosomal transmembrane protein with 6 transmembrane domains, with both N- and C-termini in the cytosol [63,64]. The most frequent disease-causing mutation of the *CLN*3 gene is a 1 kb deletion, which removes exons 7 and 8 and creates a premature stop codon. This mutation results in a substantial decrease in mRNA expression and stability, so most likely the mutant, truncated protein is not expressed at all [65]. Expression analyses indicate that the *CLN3*/*Cln3* gene and CLN3 protein is ubiquitously expressed in various human and mouse tissues [58,66–69]. Tissue expression pattern and intracellular localization of CLN3 has not been completely elucidated mainly because of low endogenous CLN3 levels and the lack of suitable, specific antibodies. The precise cellular function of CLN3 is not completely known. CLN3 has been primarily found in endosomes and lysosomes with a suggested involvement in endocytosis and endocytic trafficking [50,70–74]. The yeast ortholog of CLN3, Btn1p, has been shown to play an important role in the transport of a subset of proteins between the vacuole (the yeast equivalent of the lysosome) and the trans-Golgi network [75,76]. Using small interfering RNA (siRNA)-mediated ablation of CLN3 in HeLa cells expressing the Cation-Independent Mannose 6-Phosphate Receptor (CI-MPR) reporter, it was found that CLN3 plays a key role in the exit of CI-MPR (CD8-CI-MPR) from the trans-Golgi network [77]. CLN3 has also been linked to autophagy [78]. Vidal-Donet et al. have reported a clear impairment of macroautophagy maturation in juvenile CLN3 disease patients' fibroblasts alongside a 0.6 increase in lysosomal pH in these fibroblasts, which could be a causal or contributive factor of altered macroautophagy [50]. Lojewski et al. also observed abnormalities of autophagy in juvenile CLN3 disease patient-derived iPS cells and in neural progenitor cells derived from juvenile CLN3 disease iPSCs [52]. Although the average number of autophagic vacuoles per cell (normalized to total cell area) did not differ significantly in comparison with the control cell line, the average area of the identified autophagic vacuoles in juvenile CLN3 disease patient-derived iPS cells was significantly larger than in control cells as observed by transmission electron microscopy. In juvenile CLN3 disease iPSCs-derived neural progenitor cells, ultrastructural analysis revealed a significantly higher number of empty vacuoles and a marked depletion of multivesicular bodies [52]. The observed abnormalities could be the result of defective fusion events such as those previously observed in cerebrum and cerebellum extracts [49]. Other studies in yeast lacking Btn1p, the ortholog protein of CLN3, as well as subsequent analyses in patients' fibroblasts and human embryonic kidney cells with mutated CLN3 have shown disturbances in the maintenance of the vacuolar/lysosomal pH [50,79–81].

A recent study using *Amoeba Dictyostelium* localized CLN3 fused to GFP in the contractile vacuole system that acts as an osmoregulatory organelle and controls the intracellular water balance by collecting and expelling excess water out of the cell [82]. In spite of the lack of kidney-related clinical symptoms in juvenile CLN3 disease patients, findings by Stein et al. suggest an osmoregulated role for CLN3 in renal control of water and K^+ balance. This group used a *Cln3* reporter mouse harboring a nuclear-localized bacterial β-galactosidase (β-Gal) gene driven by the native *Cln3* promoter and detected β-Gal most prominently in epithelial cells of skin, colon, lung, and kidney [83]. In the kidney, β-Gal-positive nuclei were predominant in medullary collecting duct principal cells, with increased expression along the medullary osmotic gradient, and reporter mouse-derived renal epithelial cultures demonstrated an increase in β-Gal expression that was dependent on tonicity [83]. Following this report, Getty et al. tested if human CLN3 expression and localization is affected by osmotic changes in a stably transfected BHK (baby hamster kidney) cell line that expresses a moderate level of myc-tagged human CLN3 under the control of the human ubiquitin C promoter [84]. Hyperosmolarity (800 mOsm), achieved by either NaCl/urea or sucrose, dramatically increased the mRNA and protein levels of CLN3 as determined by quantitative real-time PCR and Western blotting. The subcellular localization of myc-tagged CLN3 also changed dramatically: under isotonic conditions (300 mOsm), human CLN3 was found in a punctate vesicular pattern surrounding the nucleus with prominent Golgi and lysosomal localizations, and hyperosmolarity (800 mOsm) extended CLN3 distribution away from the perinuclear region and enhanced its lysosomal localization [84].

CLN3 has also been associated with cell migration, cell morphology, and myosin distribution [85,86]. Getty et al. reported an interaction between myosin IIB and CLN3, and suggested that the observed migration defect in *Cln3*$^{-/-}$ mouse embryonic fibroblasts results, in part, from the loss of the CLN3-myosin-IIB interaction [85].

Besides the attributed roles in lysosomes, CLN3 has been widely associated with cell proliferation, apoptosis and control of cell cycle. A recent study reported increased rates of proliferation in *Cln3*$^{-/-}$ *Amoeba Dictyostelium* [82]. Cell cycle arrest has been detected in the G1/G0 phase in *CLN3*-silenced colorectal cancer cells [87] and in lymphoblast cells from juvenile CLN3 disease patients [88]. The later study also indicated an accumulation of p21, sphingosine, glucosylceramide, and sulfatide as possible cell cycle regulators [88]. Overexpressed p21 might be involved in cell cycle arrest and induction of apoptosis but the group showed very scarcely apoptosis-indicating results [88]. The same group also reported enhanced levels of gangliosides and α-synuclein oligomers, and reduced levels of sphingomyelin and autophagy in juvenile CLN3 disease lymphoblast cells [89], providing a possible explanation for the higher rate of cell death typically found in juvenile CLN3 disease lymphoblast cells. Rusyn et al. reported that wild type CLN3, but not mutant CLN3, binds galactosylceramide, and suggested that wild type CLN3 may function as a galactosylceramide transporter [90]. The same study also indicated that inhibition of galactosylceramide synthesis in normal cells by galactosylceramide synthase siRNA negatively affects cell growth and induces apoptosis, suggesting that galactosylceramide could be a center piece in the reported alterations in cell growth or apoptosis in juvenile CLN3 disease cells [90]. Apoptosis specifically, however, was not measured by Rusyn et al. [90]: to detect apoptosis they used propidium iodide uptake, which detects cells dying by necrosis (primary necrosis or secondary necrosis ~24-48 h after apoptosis). Zhu et al. also reported that silencing of *CLN3* by siRNA in HCT116 colorectal cancer cells inhibited proliferation, promoted apoptosis and induced G0/G1 cell cycle arrest [87]. Wu et al. showed that CLN3 overexpression increased the proliferation and conferred resistance to tunicamycin induced apoptosis in neuroblastoma SH-SY5Y cells [91].

All in all, CLN3 affects a number of cellular processes including lysosmal pH regulation, autophagy, endocytosis, protein transport from the trans-Golgi, proliferation and apoptosis. It is unclear, however, in which process CLN3 plays a real functional role and which process is affected as a secondary consequence of its primary function. As regards the selective neurodegeneration in juvenile CLN3 disease, loss of any of

the proposed function of CLN3 may cause or contribute to it. For instance, the endocytic defect caused by *CLN3* mutations can change neurotransmitter release and surface expression of receptors and ion channels in neurons, leading to impaired neurotransmission and eventually neuronal cell death. A few studies in mouse models of juvenile CLN3 disease provide supporting evidence for this scenario [92–94].

2.4. CLN4 (Cysteine-string protein α)

Mutations in the *CLN4* gene cause some adult onset forms of NCL under the name of Kufs disease. Kufs disease is the least frequent among NCL types and the most difficult to diagnose [95,96]. Two clinical variants of Kufs disease exist: type A, characterized by progressive myoclonus epilepsy and cognitive decline, and type B, characterized by movement and behavioral abnormalities and dementia [97].

Identifying the molecular basis of the dominant form of adult NCL, Kufs Disease type A, it turned out that *CLN4* is the *DNAJC5* gene encoding cysteine-string protein α (CSPα), [98,99]. CSPα is a chaperone to ensure protein folding and it has been found on synaptic vesicles in neurons accounting for 1% of total vesicle proteins [100], and also on secretory granules in various endocrine, neurocrine and exocrine cells [101]. The disease-causing mutations occur within the highly conserved cysteine-string region that is responsible for membrane binding/targeting and oligomerization [98]. A recent study in *Caenorhabditis elegans* showed that mutating *dnj-14*, the ortholog of *DNAJC5*, results in shortened lifespan and a small impairment of locomotion and neurotransmission. Worms with mutant *dnj-14* also presented age-dependent neurodegeneration of sensory neurons [102].

Several studies have confirmed that the lack of CSPα in mice produces progressive defects in neurotransmission, synapse loss, neurodegeneration, and early lethality, whereas the moderate overexpression of wild-type α-synuclein, a small presynaptic protein linked to Parkinson disease, fully rescues the CSPα-null phenotype [103,104]. In spite of the lack of interaction between the two proteins [103], these studies suggest that α-synuclein is in the same biochemical pathway as CSPα [103,104]. It has been shown that CSPα forms a chaperone complex with Hsc70 (heat shock cognate protein of 70 kDa) and SGT (Small Glutamine-rich Tetratricopeptide repeat-containing protein) on synaptic vesicles and does not participate directly in exocytosis by binding calcium channels [105–107]. Research by Garcia-Junco-Clemente et al. using primary hippocampal neurons from CSPα-deficient mice indicates that CSPα may regulate the synaptic vesicle cycle through refolding or switching the conformation of proteins necessary for the cycle and that with repeated firing and multiple rounds of the synaptic vesicle cycle, CSPα-deficient synapses likely accumulate incorrect conformations of CSPα-interacting proteins, eventually leading to synaptic dysfunction and loss [108].

In order to clarify what are the actual interacting partners of CSPα, Zhang et al. screened over 1500 unique synaptic proteins and found that the levels of 22 proteins were selectively decreased in CSPα-deficient synapses [109]. Two of these putative CSPα interacting partners, SNAP-25 (synaptosomal-associated protein, 25 kDa) and the GTPase dynamin 1, which are necessary for synaptic vesicle fusion and fission, respectively, directly bound to the CSPα-Hsc70-SGT chaperone complex [109]. Sharma et al. also found that the CSPα-Hsc70-SGT complex binds directly to monomeric SNAP-25 to prevent its aggregation enabling it to function in synaptic vesicle exocytosis [110]. A recent study by Chiang et al. indicates that in PC12 cells CSPα regulates the exocytosis of synaptic vesicle-like microvesicles by modulating fusion pore dynamics in a phosphorylation-dependent (at Ser10 of CSPα) manner [111].

In conclusion, CSPα plays an important role in synaptic vesicle exo- and endocytosis, maintaining normal neurotransmission and synaptic stability, and thereby, overall neuronal viability. Neurodegeneration in CSPα-deficient mice is primarily produced by defective SNAP-25 function, which impairs SNARE (Soluble N-ethylmaleimide sensitive factor Attachment protein REceptors) complex assembly and prevents synaptic vesicle exocytosis [112].

2.5. CLN5

Defects in the *CLN5* gene were originally identified as causing a so-called Finnish variant of late infantile NCL. Nevertheless, nowadays, this variant has also been described in NCL patients of broad ethnicity, and early juvenile and adult cases caused by *CLN5* mutations have recently been reported [113–115].

CLN5/*Cln5* mRNA has been detected mostly in human and mouse brain but also in peripheral organs [116,117]. *Cln5* mRNA expression is particularly high in the cerebral cortex, cerebellum, and in the ganglionic eminence of the embryonic mouse brain. In the postnatal mouse brain, expression of the CLN5 protein is prominent in cerebellar Purkinje cells, cortical neurons, hippocampal pyramidal neurons, and hypothalamic neurons [117]. Recently, Schmiedt et al. reported that the *Cln5* gene in mice is developmentally regulated, and its highest expression in microglial cells within the brain and a very early activation of microglia in *Cln5*-knockout (*Cln5*$^{-/-}$) mice suggest a role for CLN5 in regulating microglial function [118].

Human CLN5 consists of 407 amino acids with an N-terminal signal sequence that is cleaved after entering the Endoplasmic Reticulum. Another major modification in CLN5 is N-glycosylation. It has been shown that there are eight putative N-glycosylation sites of human CLN5 that are utilized *in vivo* and that mutations in these sites could affect folding, trafficking or lysosomal function [119]. CLN5 is a soluble protein that localizes to the lysosomal compartment [120,121]. Its localization has been confirmed by several colocalization studies using anti-lysosome-associated membrane protein 1 (LAMP1) antibodies in cells overexpressing CLN5 [36,117,122,123]. CLN5 has been suggested to interact with other NCL proteins in COS-1 cells overexpressing PPT1, CLN3, CLN6 and CLN8 and in the same cells with endogenously expressed TPP1 [36,122].

In *Cln5*$^{-/-}$ mice, alterations in serum lipid profiles, defective lipid transport and hypomyelination were found, indicating the involvement of CLN5 in lipid metabolism [118]. CLN5 has also been suggested to function as a modulator of dihydroceramide synthase (CerS) and also of cell growth and apoptosis [124,125]. It was found that sphingolipids downstream of CerS, namely ceramide and dihydroceramide were diminished in fibroblasts from CLN5-deficient patients [125], first described as CLN9 variant [124]. Haddad et al. hypothesized that CLN5 and CLN8 are functionally related as CLN8 corrects CLN5 defects and altogether modulate dihydroceramide synthase 1 and 2 [125]. Nevertheless, they did not prove that both CLN5 and CerS or both CLN5 and CLN8 coimmunoprecipitated in either the normal fibroblasts or in fibroblasts from CLN5-deficient patients [125].

A recent study reported that CLN5 is essential for the recruitment of retromer, which is responsible for the sorting and recycling of lysosomal receptors [126]. In this article, the authors showed that in HeLa cells overexpressing HA-tagged CLN5 and myc-tagged sortilin, a lysosomal enzyme transporter, both proteins coimmunoprecipitate. Once they knock down the *CLN5* gene by RNA interference, they show that the stability of sortilin and Cation-Independent Mannose 6-Phosphate Receptor (CIMPR) diminishes, but they also show that mature cathepsin D levels do increase, which is not inconsistent since alternative lysosomal targeting pathways exist for cathepsin D [127]. This study also claims that defects in the recruitment of the retromer is responsible for the loss of the function of the CIMPR transporter. Such function for CLN5 is inconsistent with its properties as a soluble lysosomal protein. Also a very modest reduction in the retromer subunits VPS35 and VPS26 is presented [126]. Moreover, the obtained results also contradict to a previous study. Seaman used siRNA to knock down VPS26 in HeLa cells, and reported increased expression of CIMPR [128]. In the same report, using a pulse-chase experiment it was confirmed that there is no increased turnover of the CIMPR in the VPS26 knock-down cells [128].

All in all, the exact cellular function of CLN5 is still unknown. Nevertheless, the high relative expression level of CLN5 in CNS neurons and microglial cells [117,118] as well as the defective myelination in the brain of *Cln5*$^{-/-}$ mice and late infantile CLN5 disease patients [118] indicate the particular importance of CLN5 function in the brain. Loss of CLN5 function can lead to selective neurodegeneration in multiple ways: it may directly affect neuronal viability, it could cause abnormal microglial activation leading to neurotoxicity, and finally it definitely causes dysfunction of oligodendrocytes resulting in hypomyelination that can disrupt axonal signal propagation leading to synapse loss and eventually axonal and neuronal degeneration.

2.6. CLN6

Up-to-date there is little understanding of how mutations of the *CLN6* gene cause late infantile CLN6 disease [129]. CLN6 is a transmembrane Endoplasmic Reticulum (ER) protein without any posttranslational modifications reported to date in its 311 amino acids (27 kDa) and without any known function or homologous proteins in NCBI, Ensembl or other protein databases [130,131]. Northern blot analysis in different human and murine tissues has revealed that the *CLN6*/*Cln6* transcripts are ubiquitously present in different tissues [132]. *Cln6* expression is developmentally regulated in murine brain with greatest expression in the cerebellum and hypothalamus. From a cellular perspective, from P14 onward in mice, *Cln6* mRNA expression is the highest in cells of cortical layers II-VI, Purkinje cells in the cerebellum, and the dentate gyrus and CA1 region in the hippocampus [133].

CLN6 has been associated with autophagy, regulation of pH and endocytosis [134–136]. Thelen et al. claimed that they found age-dependent increases in the autophagosomal marker, LC3-II, in the brain of *Cln6* mutant (*nclf*) mice as compared to wild type mice by Western blot [134]. The obtained results are not conclusive in our opinion, as they show very slight differences in the densitometric band analysis of LC3-II expression and show no differences as compared to LC3-I bands, that correspond to the protein not associated to autophagosomes. The tubulin bands seem to be overexposed, so the shown ratio of LC3-II to tubulin seems not reliable for comparisons [134]. The authors also claim that p62 protein, known to recognize toxic cellular waste to be processed by autophagy, is accumulated in the brain of *nclf* mice, but there is an issue with the amount of protein loaded and it is difficult to ascertain differences between *nclf* and wild type mice [134].

Mutant CLN6 leads to the common phenotype in NCL cells such as accumulation of autofluorescent lipopigments, subunit c of mitochondrial ATP synthase, free cholesterol and phospho- and glycosphingolipids in lysosome-derived storage bodies [134,136–140]. It is remarkable, though, that CLN6 is known to be retained in the Endoplasmic Reticulum (ER) with no colocalization with lysosomal markers and also neither the synthesis, sorting nor the proteolytic processing of the lysosomal enzyme, cathepsin D is affected in fibroblasts from patients with CLN6 disease, in sheep (OCL6) and mouse (*nclf*) models [141]. However, arylsulfatase A, responsible for the lysosomal hydrolysis of sulfatides, was strongly reduced in all of the mutant CLN6 cell lines compared with controls [141]. Nevertheless, Lobel and colleagues have shown that there are no differences in the total mannose 6-phosphate proteome of brain material between CLN6 disease patients and healthy controls [142].

Recently, a new role for CLN6 in biometal metabolism was proposed. Aberrant biometal metabolism has been studied in other neurodegenerative disorders such as Alzheimer's and Parkinson's diseases [143]. The accumulation of zinc, copper, manganese and cobalt has been shown in *CLN6* mutant Merino and South Hampshire sheep at the age of symptom onset [144]. A recent report by Kanninen et al. [145] also demonstrated the accumulation of these biometals in the spinal cord, cortex, heart and liver of *Cln6* mutant (*nclf*) mice. At 12 weeks of age, the most pronounced alterations in the levels of both *Cln6* transcript and tissue biometals were observed in the spinal cord and heart, whereas at 24 weeks of age, both *Cln6* transcript and biometal changes were detected in the cerebellum and heart. At this age it is also remarkable that an inverse relationship between regional *Cln6* mRNA expression and accumulation of biometals was found [145]. Accumulation of these 4 biometals and sustained reduction in *Cln6* mRNA in the mice hearts was evident by 32 weeks of age. Biometal disregulation seems to result as CLN6 failure as the accumulation occurs specifically when significant loss of *Cln6* transcript is detected in each respective tissue. In the same study [145] the authors related the loss of proper CLN6 function and the accumulation of zinc to Zip7 expression, a zinc/manganese transporter that they found overly expressed in cerebellar Purkinje cells of *Cln6* mutant (*nclf*) mice. Their data though do not support this hypothesis as the ratio of zinc in *nclf* compared to control brain fractions does not correlate with the expression of Zip7 in the same cell subfractions [145]. In a later report from the same group, Grubman et al. claim that CLN6 colocalizes with Zip7 in primary mouse cortical neurons using antibodies against the respective endogenous proteins coupled to secondary antibodies detected by fluorescence confocal microscopy [146]. However, the results show very unspecific binding of both markers and no reliable colocalization results should be derived from the presented photos. Also, in this report the authors claim again that zinc accumulates in subcellular fractions that display Zip7 loss in the occipital lobe of presymptomatic *CLN6* mutant sheep. The displayed results, consisting of the analysis of zinc contents in control and *CLN6* mutant subfractions, however, do not correlate with the shown expression of Zip7 [146].

In conclusion, further research efforts are needed to clarify the precise function of CLN6. Nevertheless, the selective neurodegeneration in CLN6 deficiency could be easily linked to the observed accumulation of biometals, especially to zinc. Zinc is a key modulator of intracellular and intercellular neuronal signaling, and zinc dyshomeostasis can cause neuronal cell death [147]

2.7. CLN7

CLN7 disease, a variant late infantile phenotype, is caused by defects in the *MFSD8* gene. Analysis of RNA expression by Northern blot in a Turkish family that harbored different *MFSD8* mutations showed ubiquitous *MFSD8* expression at very low levels with higher amounts in heart, liver and pancreas [148]. Analyses of rat neuronal, astroglial and microglial cultures using real-time RT–PCR showed that *Mfsd8* mRNA was 12 and 6.4 times more abundant in neurons than in astrocytes and microglial cells, respectively [149]. The same study showed that rat *Mfsd8* transcripts were 2.4 and 5 times more abundant in the hippocampus than in the cortex and midbrain, respectively [149].

MFSD8 is a multispanning integral lysosomal membrane protein. Not too much is known about it apart from being a member of the major facilitator superfamily (MFS) of secondary active permeases, which are proteins that transport small substrates (inorganic and organic cations, sugars and sugar phosphates, drugs, neurotransmitters, and amino acids) across membranes [150]. The substrates of MFSD8, its mode of transport, and physiological function, however, are unknown. Several biochemical studies have shown colocalization of MFSD8 (CLN7) with different lysosomal markers [148,149,151–153]. Shariffi et al. showed colocalization of endogenously expressed CLN7 and LAMP1 in mouse hippocampal neurons [149]. Siintola et al. proved colocalization of HA-tagged wild type and mutant CLN7 with LAMP-1 in transiently transfected COS-1 cells [148]. More recently, Steenhuis et al. showed colocalization of lysotracker red and LAMP1 with overexpressed GFP-tagged CLN7 in HeLa cells [153]. None of the expressed pathogenic mutations identified in patients with CLN7 disease altered the protein trafficking and lysosomal localization [148,149,154]. Upon arrival in lysosomes, CLN7 is cleaved twice by lysosomal cysteine proteases releasing N- and C-terminal fragments [154].

In conclusion, future research has to identify the transported substrate(s) of CLN7 and if CLN7 has a neuron-specific function, which

could explain the neurodegenerative feature of late infantile CLN7 disease.

2.8. CLN8

The *CLN8* gene is mutated in two distinct clinical NCL phenotypes: the progressive epilepsy with mental retardation (EPMR) also known as Northern Epilepsy, a juvenile-onset phenotypic variant, and a more severe late-infantile NCL variant [155]. A naturally-occurring *Cln8* mutant, *mnd* (motor neuron degeneration) mouse model exhibiting a disease phenotype similar to that of late-infantile CLN8 disease patients [155–157] has been used to study the disease. Several studies using analysis of human autopsy or mouse tissues have concluded that RNA transcripts of the *CLN8*/*Cln8* gene are ubiquitously expressed but are highest in the human heart, liver, pancreas and kidney, and within the mouse brain, cortex and hippocampus are predominant locations [155,158].

CLN8 is an ER-resident transmembrane protein of predicted 286 amino acid (aa) residues that contains 5 hydrophobic regions including a TLC (TRAM-LAG1-CLN8) domain, and recycles between ER and ER-Golgi intermediate compartment (ERGIC) using an ER-retrieval signal (KKRP) in its cytoplasmic C-terminus in nonneuronal cells [155,157,159].

CLN8 mutations do not affect the protein localization at the ER but CLN8 has also been located outside the ER in a specialized subcompartment of the polarized epithelial Caco-2 cells [160], in the Golgi, endosomes and lipid rafts of mouse fibroblasts [161], in light membrane fraction different from ER after fractionation of mouse brain [160] as well as in the proximity of plasma membrane in hippocampal neurons [160,162].

The 200 aa (62–262 aa) TLC (TRAM-LAG1-CLN8) domain of CLN8 has been proposed to play a role in ceramide synthesis and glycosphingolipid trafficking, and also in catalyzing the synthesis of ceramide-like moieties and/or stimulate lipid synthesis [159]. In spite of being unknown, the function of CLN8 has been tightly related to lipid homeostasis [125,163–168]. Recently an induction of *CLN8* mRNA expression was found in a model of chemically induced Gaucher disease, a sphingolipid degradation disorder caused by the deficiency of lysosomal β-glucosidase [168]. In the same study, the level of *CLN8* mRNA was further increased in the presence of Lyso-GL1, a potent bioactive lipid substrate of acid β-glucosidase. The study by Zhang et al. also indicated that in cells derived from Gaucher disease patients, there was an increased basal expression of *CLN8* mRNA relative to control cells [168]. Another study linked ceramide levels and their synthesis to CLN8 activity. Haddad et al. found that *mnd* mouse-derived fibroblasts presented a decreased generation of ceramide measured by mass spectrometry in comparison to normal controls [125]. More importantly, the levels of ceramide were increased when CLN8 was overexpressed in human fibroblasts [125]. Prior studies by Hermansson et al. in brains from EPMR patients are in accordance with the results obtained by Haddad and colleagues, as the lipidomic analysis of the samples showed reduced levels of ceramide, galactosyl- and lactosylceramide and sulfatide as well as a decrease in long fatty acyl chain-containing molecular species within the sphingolipids [165]. Another study by Kuronen et al. used mass spectrometric analysis to reveal reduced levels of galactolipids in cerebral cortical tissue from *mnd* mice, which correlated with the subsequent diminished myelin maturation [164].

Other studies have pointed to other possible functions for CLN8 such as in oxidative and ER stresses, mitochondrial function, calcium homeostasis, inflammation and apoptosis [167,169–172]. Overexpression of wild type, but not mutant, CLN8 has also been found to induce cell proliferation and protection against NMDA-induced apoptosis in human neuroblastoma cell lines [162].

All in all, further studies are needed to determine the exact role of CLN8 in lipid homeostasis to better understand the link between CLN8 deficiency and neurodegeneration. Lipid homeostasis is particularly important for the CNS, as this organ has a high concentration of lipids, second only to adipose tissue, and it has been shown that lipid deficits in the brain cause dendritic spine degeneration, synapse loss, neuroinflammation, and eventual neurodegeneration [173].

2.9. CLN9

The scarce reports about CLN9 have erroneously attributed CLN5 disease to CLN9 phenotype [124,174]. CLN9 disease was first described to have a similar clinical presentation as CLN3 disease [174]. Fibroblasts from CLN9-deficient patients were characterized by rounded cell bodies and prominent nucleoli, poor cell attachment, increased cell proliferation rate and increased sensitivity to etoposide-induced apoptosis [174]. The authors also suggested that the *CLN9* gene might have an impact on sphingolipid metabolism as they showed that the activity of the key enzyme of the ceramide de novo synthesis pathway, serine palmitoyl transferase, is increased by more than 100% but also observed a strong decrease of ceramide and sphingomyelin and the glycosphingolipids lactosylceramide, ceramide trihexoside, and globoside levels in CLN9-deficient fibroblasts [174]. Nevertheless, a novel mutation in the *CLN5* gene (p.Gln232X) was lately identified as causative for the wrongly assumed CLN9 variant and Western blotting proved the presence of a truncated CLN5 protein in patient fibroblasts [125].

2.10. CLN10 (cathepsin D)

CLN10 disease is an autosomal recessive congenital disorder caused by mutations in the *Cathepsin D* gene encoding the lysosomal enzyme cathepsin D (CTSD) [29,175]. It is characterized as congenital NCL and survival is a matter of hours or days but juvenile onset forms of CLN10 disease have also been reported in the literature [175].

The CTSD protein is ubiquitously expressed in most mammalian tissues whereas in the retina it is mostly expressed in the pigment epithelium, ganglion cells, and Müller cells [176]. CTSD is a lysosomal enzyme belonging to the pepsin family of proteases and is one of the most studied aspartic proteases [177]. Human CTSD is synthesized and translocated into the Endoplasmic Reticulum (ER) as an inactive precursor proenzyme (53 kDa), processed into a proteolytically active, intermediate proenzyme (48 kDa), and finally transported through the endosomes into the lysosomes [178,179]. The mature form of human CTSD is composed of two polypeptides interlinked by disulphide bridges [180]. Aspartic acid residues contained on both polypeptides are essential for the enzymatic activity of the protein [177,180]. The consequences of CTSD mutation on the expression, proteolytic activity or cell processing of the enzyme in the development of CLN10 disease have been largely discussed. In the first reported clinical case of juvenile CLN10 disease variant, two missense mutations in the CTSD gene (p.Phe229Ile and p.Trp383Cys) were found that caused reduced proteolytic activity and diminished amount of CTSD in patient fibroblasts [175] but activity was not completely abrogated as in the congenital case, and this fact might have been key in determining a less severe clinical phenotype. In the same study it was found that in mouse 3T3 cells transfected with either human wild type or p.Phe229Ile mutant *CTSD*, human and mouse endogenous CTSD colocalize. However, when 3T3 cells were transfected with human p.Trp383Cys mutant *CTSD*, only a small amount of the mutant human protein colocalized with mouse CTSD, whereas most of p.Trp383Cys CTSD was detected in non-lysosomal compartments, in particular within the ER [175]. In a patient of Pakistani origin with congenital CLN10 disease, immunohistochemistry of brain sections revealed the absence of the CTSD protein but when this mutated CTSD was transiently expressed in BHK cells, a truncated form of CTSD was produced and appeared stable, but was enzymatically inactive [29]. Fritchie et al. published a study on fibroblasts from another congenital *CLN10* disease patient harboring a mutation in exon 3 of the *Cathepsin D* gene (p.Ser100Phe), showing that cathepsin D activity was marginal, but the protein appeared stable and normally processed [181].

CTSD has been tightly related to apoptosis and autophagy [182–192], two cell processes that are extensively discussed in this review regarding most of the NCL types. CTSD is considered as a central player in the apoptotic response, but its importance is cell type dependent [193]. For instance, CTSD mediates cytochrome c release and caspase activation during staurosporine-induced apoptosis in human fibroblasts [187]. CTSD is a major component of lysosomes and functions as a highly active endopeptidase with an optimum pH between 3.0 and 5.0, playing an obvious role in the degradation and turnover of cellular components under nutrient-deficient conditions [177]. Several studies have reported dysfunctions in macroautophagy in CTSD deficiency, showing accumulation of autophagosomes [190] or accumulation of autofluorescent storage material and increased levels of LC3-II [194] in neurons of CTSD-deficient mice. These two major functions of CTSD in apoptosis and macroautophagy are closely related as it has been shown that lucanthone, an autophagic inhibitor drug induces apoptosis via CTSD accumulation in different breast cancer cells [192]. CTSD is supposed to have activity at physiologic pH and it has been suggested to promote apoptosis upon its translocation to the cytosol [195–197].

In conclusion, the strong involvement of CTSD in autophagy and apoptosis, two processes heavily utilized during brain development [198, 199], can explain the extremely short disease course of congenital CLN10 disease.

2.11. CLN11 (progranulin)

The first report of homozygous mutations in the progranulin gene (*PGRN*) in two siblings suffering from a newly described type of adult onset neuronal ceroid lipofuscinosis was published in 2012 [200]. Progranulin gene expression was detected in epithelial cells, bone marrow, spleen, lymph nodes, and cells of the innate immune system [201, 202]. In the CNS, gene expression and protein analysis have revealed that progranulin is mainly expressed in neuroinflammatory microglia and neocortical neurons, pyramidal and granule cells of the hippocampus, cerebellar Purkinje cells, in the ventromedial hypothalamus, and in motor neurons [202–205]. Progranulin is a 68.5-kDa secretory protein that works as a growth factor. It is a multidomain protein linked by six disulphide bridges that is proteolytically cleaved in the linking regions by matrix (MMP) and disintegrin metalloproteases (ADAM), and neutrophil secreted serine proteases to generate individual 6-kDa cleavage products that are called granulins A-G [206–209]. Progranulin is involved in multiple physiological processes and distinct pathologies, such as tumorigenesis, inflammation, autoimmune disorders and neurodegenerative diseases [206,208–214]. Along with lipofuscin accumulation reduced synaptic connectivity and plasticity, altered ubiquitination and myelin formation have been found in the brain of progranulin-deficient mice [200,210,215].

Progranulin has been suggested to play a role in lysosomes. Progranulin could be transported into lysosomes by sortilin receptor [216] as it binds to this protein. Sortilin has been shown to be an alternative to CIMPR into lysosomal sorting [217]. Also, granulins cleaved from progranulin bind to CpG oligodeoxynucleotides at lysosomes in macrophages, enabling Toll-like receptor 9 signaling [218]. Furthermore, in progranulin-deficient mice, accumulation of the autophagy-related receptor, p62 and the lysosomal protease cathepsin D was increased in the cerebral cortex, and p62 and LAMP1 were found to be accumulated in the ventral posteromedial nucleus/ventral posterolateral nucleus of thalamus [215,219]. A recent study by Tanaka et al. examining traumatic brain injury in progranulin-deficient mice suggests that progranulin has a central role in preventing lysosomal dysfunction [220]. Using confocal microscopy it was demonstrated that after traumatic brain injury in wild type mice LAMP1 and progranulin colocalize in activated microglia of the cerebral cortex [220]. Most importantly, it was also shown that the production of progranulin is increased in activated microglia after traumatic brain injury, and that progranulin deficiency leads to decreased mammalian target of rapamycin complex 1 (mTORC1) activity with a resultant increase of lysosomal biogenesis in activated microglia and exacerbated neuronal damage in the cerebral cortex [220]. mTORC1 negatively regulates transcription factor EB (TFEB), which is a master regulator of lysosomal genes and its nuclear translocation induces lysosomal biogenesis [221,222].

All in all, the role of progranulin in autophagy and lysosomal homeostasis, especially in microglial cells, seems to be relevant to the neuropathological changes in CLN11 disease. Further studies are needed, however, to determine how exactly progranulin deficiency leads to selective, late-onset neurodegeneration.

2.12. CLN12

Mutations in the *ATP13A2* (*CLN12*) gene are a known cause of Kufor-Rakeb syndrome, a rare form of autosomal recessive juvenile or early-onset, levodopa-responsive Parkinsonism with dementia [223,224]. Kufor-Rakeb syndrome-affected individuals show not only typical NCL symptoms but also extrapyramidal involvement. A recent study using postmortem pathological analysis in a Kufor-Rakeb syndrome patient with a homozygous missense mutation in the *ATP13A2* gene confirmed extensive lipofuscin deposits in the cortex, basal nuclei, cerebellum, and retina [224]. Several studies have also linked a single base deletion in the *ATP13A2* gene to NCL in Tibetan Terriers [225,226].

CLN12 (*ATP13A2*) mRNA transcripts are ubiquitously expressed in most human tissues, with particularly high levels in the brain, and also but to a lesser extent in skeletal muscle and in kidney. Within the brain, the highest expression is in the ventral midbrain containing substantia nigra [223].

The *CLN12* (*ATP13A2*) gene, also known as *KRPPD*, *PARK9*, *HSA9947*, *RP-37C10.4*, encodes a lysosomal transmembrane protein of 36 kDa containing 10 predicted transmembrane domains [223,227,228]. Several homozygous and compound heterozygous mutations are known to result in truncation of the ATP13A2 protein leading to a loss of function [229–231].

ATP13A2 belongs to the family of P-Type ATPases as a type 5. P-Type ATPases use the energy derived from ATP hydrolysis to shuttle various substrates, ranging from cations and heavy metals to lipids, across biological membranes against their concentration gradients (reviewed in [232]). Wild type ATP13A2 is known to be targeted to acidic compartments, such as the late endosomes and lysosomes, as showed by co-localization with LAMP1/2a and lysotracker [223,233]. Recent studies in Kufor-Rakeb syndrome patient-derived fibroblasts and ATP13A2-deficient cell lines have shown that the loss of the protein increases the size and number of lysosomes and dramatically perturbs lysosomal function by impairing pH homeostasis, lysosomal enzyme proteolytic processing, lysosomal degradation and lysosome-mediated clearance of autophagosomes [223,234,235]. Lately, in both differentiated SH-SY5Y cells and rat primary neurons, the endogenous ATP13A2 was shown to localize to multi-vesicular bodies, a late endosomal compartment that also plays a key role in the autophagic pathway [236].

It has also been observed that loss of ATP13A2 function impairs oxidative stress response in human neuroblastoma cells [233] and human ATP13A2 expression is upregulated under this cell event [237]. Furthermore, patient-derived ATP13A2-deficient olfactory neurospheres show increased sensitivity toward Zn^{2+} toxicity [238]. Defective autophagy and accumulation of defective proteins might account for the observed alterations in oxidative stress response.

ATP13A2 has also been shown to protect against α-synuclein toxicity in several model systems including yeast, *C. elegans* and mammalian cells [239]. α-Synuclein is a small presynaptic protein linked to Parkinson disease. ATP13A2 could protect against α-synuclein toxicity by any of the following mechanisms: enhancing lysosomal degradation of protein aggregates [234,235,240], regulating the autophagic delivery of the protein into lysosomes [234,235], promoting the removal of the protein from the cell via exosomes reducing the α-synuclein stress [236] or by

affecting α-synuclein membrane interactions thus reducing its degree of toxicity [241,242].

Other proposed functions for ATP132, recently reviewed by Van Veen et al. [243], are linked to its role as a cation transporter and involvement in the regulation of Mn^{2+}, Zn^{2+}, Mg^{2+}, and H^{+} homeostasis. Also, a role as flipase in lipid transport across membranes is proposed due to its close phylogenetic relation to the type 4 P-Type ATPases [243].

In conclusion, the protection by ATP13A2 against α-synuclein toxicity is the strongest functional link to Parkinsonism in CLN12 disease. Moreover, since normal neuronal function depends on tightly regulated Mg^{2+} and Zn^{2+} homeostasis, Mg^{2+} voltage-dependently blocks NMDA-type glutamate receptors [244] and Zn^{2+} is a key modulator of intracellular and intercellular neuronal signaling [147], loss of the cation transporter function of ATP13A2 can cause dysregulated neurotransmission and eventually dementia characteristic for CLN12 disease.

2.13. CLN13 (cathepsin F)

Mutations in the *Cathepsin F* (*CTSF*, *CLN13*) gene were originally described in mice. Cathepsin F-deficient mice develop neurological disease beginning at 12–16 months of age with lack of coordination, weakness and premature death. They also display excess accumulation of autofluorescent granules in the cerebral cortex, hypothalamus, cerebellar Purkinje cells and anterior horn cells of the spinal cord, and cortical atrophy and glial activation [245]. Lately, rare mutations in *CTSF*, after genomic analysis by linkage mapping followed by exome sequencing, have been described in 3 families with adult-onset NCL with predominant dementia and motor disturbances, rather than epilepsy [246].

Immunohistochemical analysis has determined that cathepsin F is strongly expressed in neuronal cells, mainly in the cerebral cortex, cerebellum and hippocampus, and in hepatocytes and Leydig cells in testis [247]. Cathepsin F is a cysteine protease consisting of 484 amino acids and contains a 251 amino acid propeptide encoding an N-terminal cystatin-like proregion that can work as a cysteine protease inhibitor [248–251]. Cathepsin F is tagged with mannose 6-phosphate residues in the cis-Golgi network and targeted to the lysosomes by the CIMPR transporter [252].

Besides its role as a lysosomal enzyme, cathepsin F has been recently associated to proteasome degradation and autophagy. Confocal microscopy in HEK 293T cells overexpressing either wild type or N-terminally truncated forms of cathepsin F revealed that mutants accumulated in perinuclear aggresome-like inclusions, and were confirmed as p62-positive aggregates [253]. The p62 protein recognizes toxic cellular waste to be processed by autophagy. Interestingly, Jeri et al. suggested a compensatory role of autophagy as the evaluated mutants colocalized in a much more defined pattern with the autophagy marker, microtubule-associated protein 1A/1B-light chain 3 (LC3B) [253]. The same study also found that the truncated forms of cathepsin F caused a 2–3 fold increase in caspase activation [253].

Other functions of cathepsin F have been linked to MHC class II maturation and peptide loading in antigen-presenting cells [254], and lipoprotein degradation [255].

All in all, it is completely unclear how mutations of *cathepsin F* cause adult-onset NCL with predominant dementia and motor disturbances. However, the slow development of the disease indicates that either the function of cathepsin F is mildly affected or the loss of its function is partly compensated, and long time is needed until the accumulated damages, due to lysosomal/autophagic defects, reaches a threshold and the disease symptoms appear.

2.14. CLN14 (Potassium channel tetramerization domain-containing protein 7)

Potassium channel tetramerization domain-containing protein 7 (KCTD7) has been extensively linked to progressive myoclonic epilepsy [256,257] and also to ataxia [258]. A missense homozygous mutation of *KCTD7* was recently found to cause a NCL subtype in a Mexican family affected by infantile-onset progressive myoclonic epilepsy, vision loss, cognitive and motor regression, premature death, and prominent NCL-type storage material [259].

KCTD7 is a highly conserved protein consisting of 289 amino acids, and in mouse it is mainly expressed in the brain and more specifically in cortical neurons, in granular and pyramidal cell layers of the hippocampus, and in cerebellar Purkinje cells [259,260]. When GFP-tagged KCTD7 was expressed in a *Cln3* mutant cerebellar cell line it showed broad, somewhat punctate cytoplasmic localization and distinct signal at the plasma membrane [259]. The studies by Kousi et al. in BHK cells transfected with HA-tagged wild type and mutant KCTD7 indicated that KCTD7 is a soluble cytosolic protein [261].

KCTD7 is a member of the KCTD protein family [262]. This family of proteins shares an N-terminal BTB/POZ domain that shows sequence homology to the T1 tetramerization domain found in voltage-gated potassium channels [262]. The structure and organ localization of KCTD7 suggests that it is involved in hyperpolarization of the cell membrane via interaction with a component of the ubiquitin ligase complex. In fact, overexpression of KCTD7 in murine neurons hyperpolarizes the cell membrane and decreases the excitability of transfected neurons in patch clamp experiments [260].

KCTD7 has been shown to directly interact with Cullin-3, a component of E3 ubiquitin-protein ligases that selectively tag proteins for degradation by the proteasome [260]. Staropoli et al. determined that the KCTD7 mutation originally described for CLN14 disease by them, which is not in the N-terminal BTB/POZ domain, abolished the interaction of KCTD7 with Cullin-3 [259]. They suggested that the abolished interaction between KCTD7 and Cullin-7 could be tilting the balance of degradation versus accumulation of substrate proteins towards the second event, and that could in turn elicit a toxic response within the cell [259].

In conclusion, KCTD7, as a regulator of K^{+} conductance in neurons, clearly affects neuronal excitability [260] providing a direct link to progressive myoclonic epilepsy in CLN14 disease. Further studies are needed, however, to determine if the membrane potential-affecting role of KCTD7 is specific to glutamatergic or GABAergic neurons, or restricted to certain neuronal subtypes.

Conflict of interest

None of the authors of this paper has any conflict of interest relating to the publication.

Transparency document

The Transparency document associated with this article can be found, in the online version.

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