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Review

The converging roles of Batten disease proteins in neurodegeneration and cancer

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SUMMARY

Epidemiological studies have reported an inverse correlation between cancer and neurodegenerative disorders, and increasing evidence shows that similar genes and pathways are dysregulated in both diseases but in a contrasting manner. Given the genetic convergence of the neuronal ceroid lipofuscinoses (NCLs), a family of rare neurodegenerative disorders commonly known as Batten disease, and other neurodegenerative diseases, we sought to explore the relationship between cancer and the NCLs. In this review, we survey data from The Cancer Genome Atlas and available literature on the roles of NCL genes in different oncogenic processes to reveal links between all the NCL genes and cancer-related processes. We also discuss the potential contributions of NCL genes to cancer immunology. Based on our findings, we propose that further research on the relationship between cancer and the NCLs may help shed light on the roles of NCL genes in both diseases and possibly guide therapy development.

OVERVIEW OF NEURODEGENERATION AND CANCER

Neurons are terminally differentiated cells that are relatively quiescent and non-replicative (Houck et al., 2018). An accumulation of misfolded proteins within neurons causes cellular toxicity and contributes to premature neuronal death (i.e., neurodegeneration) as seen in diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD). In contrast, cancer is characterized by rapid cell proliferation and the avoidance of cell death (Hanahan and Weinberg, 2017). In accordance with their distinct characteristics, epidemiological data show an inverse relationship between cancer and neurodegeneration, although there are some exceptions (e.g., PD with malignant melanoma) (Houck et al., 2018). Nevertheless, there is mounting evidence suggesting that common genes and pathways are dysregulated in both diseases but in a contrasting manner (Houck et al., 2018; Klus et al., 2015). Causative genes in neurodegenerative diseases, such as *PARK2*, are aberrantly expressed or mutated in cancer (Houck et al., 2018). In addition, meta-analyses from genome-wide association studies show that the genetic overlap between AD and cancers occurs due to the regulation of gene expression with respect to enhancer activity (Feng et al., 2017). Interestingly, more than 60% of AD-associated genes are linked to cancer, with the intersecting genes regulating cell growth, innate immunity, and detoxification (Houck et al., 2018). Consistent with these findings, the physico-chemical properties of the overlapping cancer and neurodegenerative proteins are altered dissimilarly, whereby genes upregulated in AD encode more structurally disordered proteins compared to cancer genes (Klus et al., 2015). In total, these studies reinforce a shared gene network in neurodegeneration and cancer, indicating the importance of understanding how the shared genes are dysregulated in both diseases.

THE NEURONAL CEROID LIPOFUSCINOSES

The neuronal ceroid lipofuscinoses (NCLs), commonly known as Batten disease, are a family of neurodegenerative lysosomal storage disorders that affect all ethnicities and ages (Mole and Cotman, 2015). Batten disease has a worldwide distribution with estimated incidence rates ranging from 2 to 13 of 100,000 live births (Williams, 2011). Patients suffer from progressive vision loss, mental deterioration, seizures, motor deficits, and a shortened life span (Schulz et al., 2013). The pathological cellular hallmarks of Batten disease include neuronal degeneration and the accumulation of autofluorescent lipofuscin in the lysosomes of neurons, especially in the cerebral cortex, cerebellum, and retina (Radke et al., 2015).

As of 2020, a total of 493 germline mutations in 13 distinct genes (*CLN1-CLN8, CLN10-CLN14*) have been reported in the NCL mutation database (https://www.ucl.ac.uk/drupal/site_ncl-disease/mutation-and-

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patient-database). Each gene is associated with a different subtype of NCL (Mole and Cotman, 2015). A recent study showed that mutations in the *TBCK* (TBC1 domain-containing kinase) gene present characteristics and clinical pathology that resemble other NCL subtypes, and thus, may be classified as a new NCL subtype, CLN15 disease (Beck-Wödl et al., 2018). The NCL family of proteins comprises soluble lysosomal enzymes (CLN1/PPT1, palmitoyl protein thioesterase 1; CLN2/TPP1, tripeptidyl peptidase 1; CLN5, ceroid lipofuscinosis neuronal 5; CLN10/CTSD, cathepsin D; CLN13/CTSF, cathepsin F), lysosomal transmembrane proteins (CLN3, ceroid lipofuscinosis neuronal 3; CLN7/MFSD8, major facilitator superfamily domain-containing 8; CLN12/ATP13A2, ATPase 13A2), proteins associated with vesicular membranes (CLN4/DNAJC5, DnaJ heat shock protein family member C5; CLN14/KCTD7, potassium channel tetramerization domain-containing 7), membrane proteins that reside in the endoplasmic reticulum (ER) (CLN6, ceroid lipofuscinosis neuronal 6; CLN8, ceroid lipofuscinosis neuronal 8) and a secreted glycoprotein (CLN11/PGRN, progranulin) (Cárcel-Trullols et al., 2015). Despite the molecular genetic heterogeneity of these proteins, research in non-mammalian and mammalian models suggests that the NCL proteins may participate in shared or converging pathways (Huber, 2020; Persaud-Sawin et al., 2007). However, the precise functions of NCL proteins, their interactions with one another, and the underlying mechanisms that lead to NCL pathology are poorly understood, which has severely hindered therapy development.

No previous studies have examined the relationship between cancer and the NCLs despite the genetic convergence of the NCLs and other neurodegenerative diseases (e.g., AD and PD) (Benes et al., 2008; Kao et al., 2017). In this review, we explore the roles of NCL genes in different oncogenic processes and identify similarities between cancer and the NCLs by examining the underlying genes and pathways. Next, we discuss the potential roles of NCL genes in cancer immunology. In total, this review aims to provide a better understanding of the genetic similarities shared by neurodegeneration and cancer, which may aid in the usage of NCL genes as potential biomarkers and prognostic indicators.

ROLES OF NCL GENES IN CANCER

Surveying cancer patients for perturbations in the NCL pathway

Cancer is a genetic disease that is a consequence of genetic abnormalities in somatic cells (e.g., abnormal chromosomal rearrangements, copy number changes, and gene mutations). Large-scale banking of tumors and sequencing approaches have improved our understanding of the perturbed genes in different malignancies. Using The Cancer Genome Atlas (TCGA), we surveyed the NCL genes for abnormalities (e.g., mutations, deletions, or amplifications) across various tumors. Over 32 Pan-Cancer studies that characterize genomic and cellular alterations in a diverse set of tumors were incorporated into this analysis via cBioPortal, encompassing a total of 10,967 samples (Cerami et al., 2012; Ellrott et al., 2018; Gao et al., 2018; Hoadley et al., 2018; Liu et al., 2018; Sanchez-Vega et al., 2018; Taylor et al., 2018) (Figure 1A). Our analysis revealed that ∼20% of all tumor samples have perturbations in the NCL pathway (i.e., the 13 NCL genes as a collective) (Figure 1A). When we looked at the stratification of these tumors, the most affected tumor was uterine carcinosarcoma (40%), a type 2 endometrial carcinoma (Figure 1B). Similarly, over 30% of tumor samples from ovarian, esophagus, bladder, stomach, and melanoma cancers had perturbations in the NCL pathway. The complexity of this stratification extends to the type of alteration that occurs in different cancers, such as gene amplifications being most common in uterine carcinosarcoma and gene mutations being more common in melanomas (Figure 1B). In line with these analyses, clinical data show differential expression of NCL genes between tumor and normal tissue samples in a variety of cancers, except for *CLN3* (Figure 2). Collectively, these analyses reveal that the NCL pathway is commonly altered in various cancers, with different genomic alterations driving oncogenesis.

Since the NCLs are neurodegenerative diseases, it is not surprising that brain cancers are influenced by altered NCL gene expression (Figure 3). An analysis of TCGA data from two brain cancers (338 patients total), low-grade gliomas (LGG) and glioblastoma multiform (GBM) tumors, revealed that 12 of the 13 NCL genes, except *CLN3*, influence patient prognosis (Figure 3). *PGRN* expression had the most dramatic effect on patient prognosis (hazard ratio of 3.6) with problematic increases in expression (Figures 3 and 4A). In contrast, some of the NCL genes have tumor suppressive effects on patient survival, such as *DNAJC5*, *CLN8*, *CTSF*, and *KCTD7* (Figure 3). Taken together, these findings suggest that the NCL pathway and its role in cancer is complex, thus warranting further examination. In support of our analyses, there is evidence in the literature linking 9 of the 13 NCL genes to cancer (*PPT1, TPP1, CLN3, DNAJC5, CLN5, CTSD, PGRN, ATP13A2, CTSF*). The associations of each of these genes with cancer-related processes
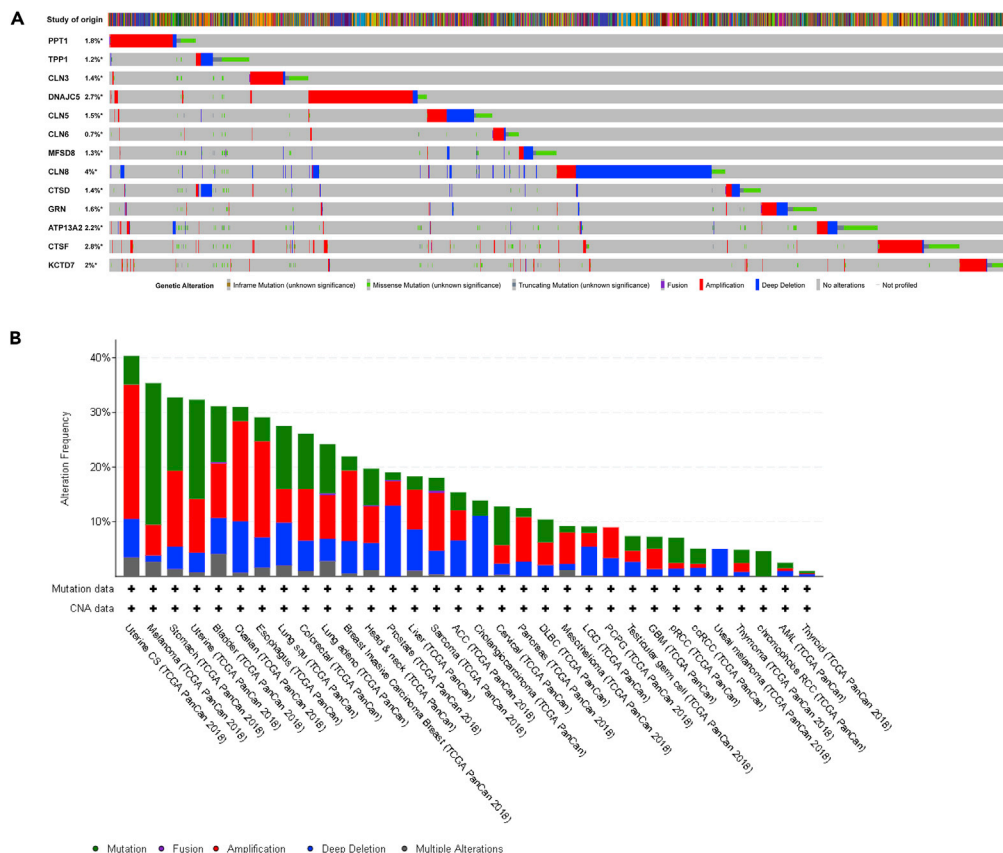
Figure 1. The links between NCL genes and cancer

(A) Survey of genomic alterations across Pan-Cancer studies in the NCL pathway. In total, 13 genetically distinct genes cause different subtypes of NCL (*PPT1, TPP1, CLN3, DNAJC5, CLN5, CLN6, MFSD8, CLN8, CTSD, PGRN, ATP13A2, CTSF, KCTD7*). NCL genes are altered in ~20% of the cancers examined by 32 Pan-Cancer studies that comprise The Cancer Genome Atlas (TCGA) dataset. Using cBioPortal (https://www.cbioportal.org/), we assessed the occurrence of gene duplication, deletion, fusion, and mutation (inframe, missense, and truncating) events with each of the NCL genes.
(B) Genetic alterations in NCL genes across different forms of cancer. The gene alterations occur more frequently in certain cancer types in the TCGA dataset than in others including uterine carcinosarcomas, melanomas, stomach, and uterine cancers. The frequency of gene alterations is based on the frequency of mutations, copy number alterations, and fusion genes. cBioPortal (https://www.cbioportal.org/) was used to analyze the TCGA dataset and generate the plot. "+" indicates samples examined with the presence of mutation or CNA data.

will be described, in turn, in the sections to follow. While targeted studies have not yet been performed to examine the impact of mutations in *CLN6*, *MFSD8*, *CLN8*, and *KCTD7* on oncogenesis, our findings described in Figures 1-3 should spur future research in this area.

CLN1/PPT1

The function of PPT1 and its association with NCL and cancer

PPT1 encodes a lysosomal enzyme, PPT1, that removes fatty acids from fatty-acylated cysteine residues in proteins prior to their degradation in lysosomes (Verkruyse and Hofmann, 1996) (Table 1). Protein depalmitoylation by PPT1 is important for maintaining neuronal health and mutations in *PPT1* cause CLN1 disease, an infantile form of NCL (Koster and Yoshii, 2019; Mole and Cotman, 2015). Studies have linked PPT1 to neuronal growth and survival, apoptosis, autophagy, endocytosis and the regulation of synaptic vesicles (Aby et al., 2013; Cho and Dawson, 2000; Kim et al., 2008; Rebecca et al., 2019; Sapir et al., 2019) (Table 1). The modification of several well-studied cancer proteins via palmitoylation has also been implicated in cancer (Ko and Dixon, 2018).
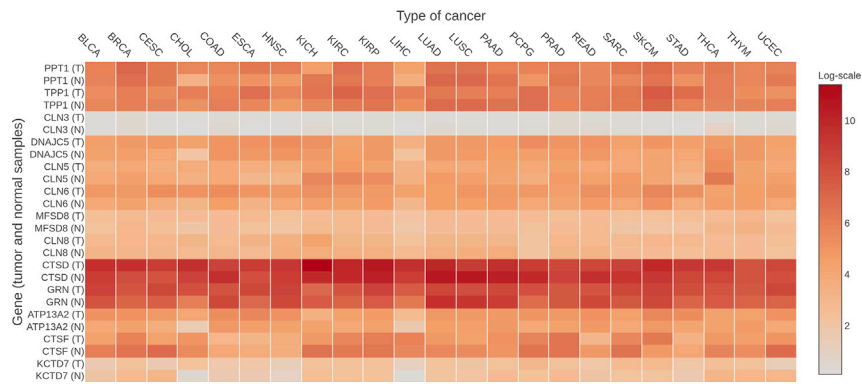
Figure 2. The expression of NCL genes in TCGA cancer types

The expression of NCL genes in different TCGA tumor samples (labeled with T) and the associated normal tissue (labeled with N) differs across cancer types. Each NCL gene shows a unique expression profile in different cancer types. The expression of the genes is shown in terms of the log-scale and determined using the $log_2(TPM +1)$ equation. The cancer types have been abbreviated as follows: BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangio carcinoma; COAD, colon adenocarcinoma; ESCA, esophageal carcinoma; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; PRAD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; THCA, thyroid carcinoma; THYM, thymoma; UCEC, uterine corpus endometrial carcinoma.

Clinical data collected from match-paired tumor and normal tissue samples (i.e., derived from the same patient) revealed elevated *PPT1* mRNA expression in breast cancer, clear cell renal cell carcinoma (ccRCC), head and neck squamous cell carcinoma, thyroid cancer, colon adenocarcinoma, esophageal adenocarcinoma, and colorectal carcinoma tumor samples, with the exception of non-small cell lung cancer (NSCLC), where expression was reduced (Rebecca et al., 2019; Tsukamoto et al., 2006) (Table 1). *PPT1* mRNA expression was also elevated in metastatic tumors compared to primary tumors, suggesting a role for PPT1 in metastasis (Rebecca et al., 2019; Tsukamoto et al., 2006). Increased levels of *PPT1* mRNA have also been linked to poor prognoses for malignancies of the liver, esophagus, kidney, and head and neck (Rebecca et al., 2019). Together, these observations indicate that *PPT1* mRNA levels are correlated with oncogenesis and contribute to poor patient prognosis.

The mechanism underlying PPT1 function

PPT1 depalmitoylates the V_0 sector isoform a1 (V_0a1) subunit of the vacuolar H^+-adenosine triphosphatase (v-ATPase) (Bagh et al., 2017). Depalmitoylation of this subunit facilitates the reversible assembly of V_1/V_0 domains on the lysosomal membrane. In $Ppt1^{-/-}$ mice, misrouted V_0a1 causes a reduction in V_1 sector subunit A (V_1A) protein, which leads to lysosomal deacidification and autophagy impairment (Bagh et al., 2017) (Table 1). Besides regulating lysosomal pH, v-ATPase also facilitates the docking of mTORC1 on the lysosome by interacting with Ragulator, a scaffolding complex (Sancak et al., 2010). Consequently, loss of *PPT1* in A375P melanoma cells disrupts the interaction between the V_1A subunit and the p18 subunit of Ragulator (Rebecca et al., 2019). Loss of the V_1A-p18 interaction leads to the displacement of mTORC1 from the lysosomal membrane and inhibits mTORC1 signaling pathways, which blocks protein translation and halts cancer cell proliferation (Figure 5). Therefore, inhibiting the depalmitoylating activity of PPT1 impairs autophagy and mTORC1-regulated signal transduction (Table 1).

The anti-apoptotic role of PPT1 is well established. Overexpression of *PPT1* in LA-N-5 neuroblastoma cells causes resistance to two inducers of apoptosis, C_2-ceramide and the phosphoinositide-3-kinase (PI3K) inhibitor LY294002 (Cho and Dawson, 2000). Cells overexpressing *PPT1* oppose the actions of ceramide by increasing the activation of an anti-apoptotic protein kinase, Akt, and reducing the membrane association of Ras, thereby inhibiting apoptosis (Cho and Dawson, 2000) (Table 1). These findings in neuroblastoma cells are consistent with our analysis of TCGA data from patients with brain cancer, where high *PPT1* expression was associated with poor prognosis (Figure 3). Follow-up studies showed that *PPT1* inhibition through
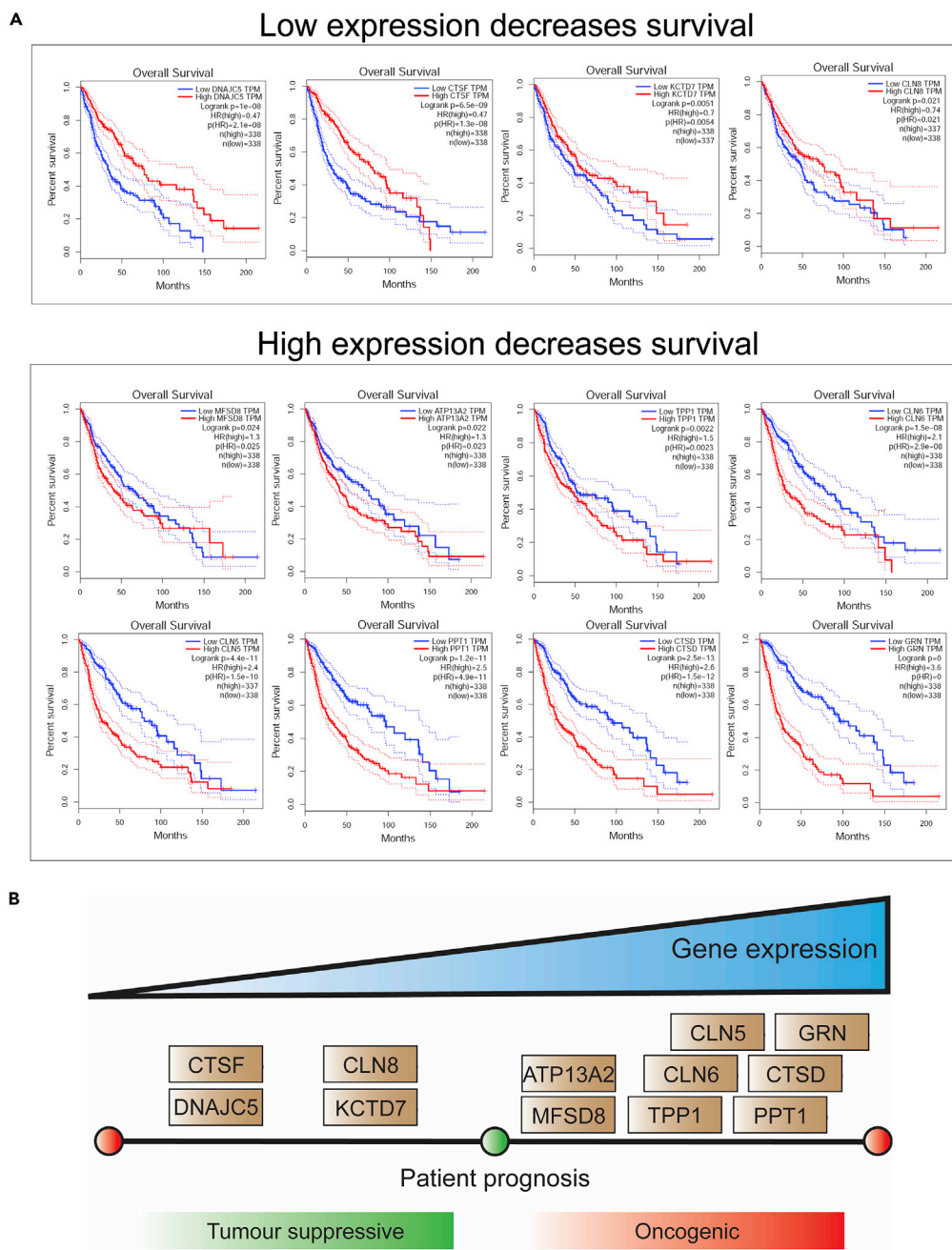
A

Low expression decreases survival

High expression decreases survival

B

Figure 3. NCL gene expression influences the survival of patients with brain cancer

(A) Low expression of *CLN4/DNAJC5*, *CLN8*, *CLN13/CTSF*, and *CLN14/KCTD7* and high expression of *CLN1/PPT1*, *CLN2/TPP1*, *CLN5*, *CLN6*, *CLN7/MFSD8*, *CLN10/CTSD*, *CLN11/PGRN*, and *CLN12/ATP13A2* lead to poor prognosis in overall survival for patients with brain cancer. *CLN3* has no effect. The genes are ordered in terms of the cox proportional hazard ratio (HR) value in relation to the survival of patients. HR values are derived from expression cohorts that were determined for the median group, with 50% used as the cutoff for high and low expression (50% higher or lower expression in samples). The brain cancer samples incorporated in this analysis include both lower grade gliomas and glioblastomas. The HR values for the NCL genes were determined using the TCGA dataset.

(B) Summary of the relationship between NCL gene expression and the prognoses of patients with brain cancer. The effect of NCL genes on brain cancer prognosis is a spectrum, with *CLN4/DNAJC5*, *CLN8*, *CLN13CTSF*, and *CLN14/KCTD7* acting as tumor suppressors and the other NCL genes functioning as oncogenes when they are highly expressed in tumors. Genes with identical HR values (from A) are stacked together. Good and poor prognoses are indicated by green and red, respectively.
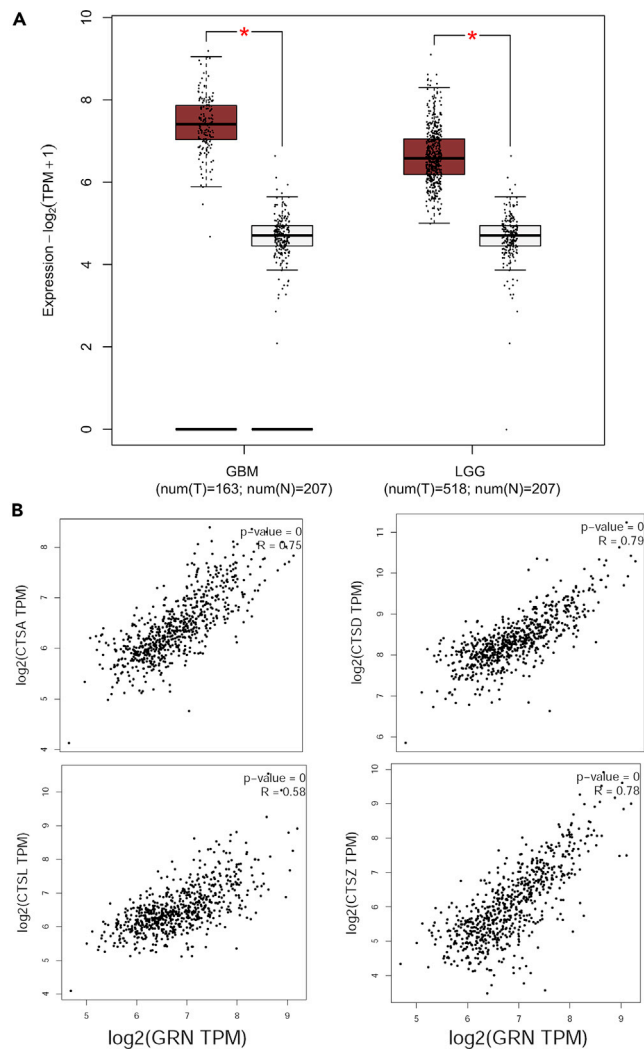
Figure 4. *GRN* expression is high in gliomas and correlates with the expression of cathepsin family genes

(A) Expression of *GRN* in gliomas (shown in red) differs from normal tissue samples (shown in white). Significance was determined using one-way analysis of variance (ANOVA). *p < 0.05. Cancer types examined include low-grade gliomas (LGGs) and glioblastoma multiform (GBM) tumors.

(B) Expression of cathepsin family genes (*CTSA, CTSD, CTSL,* and *CTSZ*) is correlated with the expression of *GRN* in brain cancer samples. A Pearson correlation was used to assess the trend in expression between *GRN* and the cathepsin family genes. The plots were generated with the GEPIA 2 tool, using TCGA data.

antisense *PPT1* and a PPT1 inhibitor DAPKA, increases apoptosis in these cells and enhances the effect of chemotherapeutic agents such as Vepesid and Adriamycin (Cho et al., 2000; Dawson et al., 2002). Therefore, inhibiting PPT1 appears to be a valid approach for treating malignancies of the central and peripheral nervous systems.

PPT1 as a therapeutic target in cancer

Recent studies have proposed that PPT1 may be an effective therapeutic target in cancer (Potts et al., 2015; Rebecca et al., 2017, Rebecca et al., 2019). The mechanistic insight into targeting PPT1 in cancer is based on its depalmitoylating activity. Chloroquine (CQ) derivatives are anti-malarial drugs that have since been repurposed as anti-cancer drugs. The dimerization of CQ produces a small molecule capable of inhibiting both lysosomal catabolism and the mTORC1-dependent anabolism pathway in cancer cell lines and mouse models (Rebecca et al., 2017, Rebecca et al., 2019). Rebecca et al., 2019 developed a potent lysosomal-specific dimeric CQ known as DC661 and revealed that PPT1 was the molecular target of DC661 and two other

Table 1. Summary table of genes implicated in both NCL and cancer and their putative roles in both diseases

NCL protein	Alternate name; function	Putative roles in NCL	Gene expression in cancer	Putative roles in cancer	References
CLN1	PPT1; Palmitoyl thioesterase	Synaptogenesis, Neuronal apoptosis, Axonal outgrowth, Neurite extension, Lysosomal pH regulation	Upregulated in breast cancer, clear cell renal cell carcinoma, head and neck squamous cell carcinoma, thyroid cancer, colon adenocarcinoma, esophageal adenocarcinoma, and colorectal carcinoma. Downregulated in non-small cell lung cancer	mTOR pathway, Autophagy, Proliferation, Apoptosis, Lysosomal pH regulation, Cancer immunoevasion	Bagh et al. (2017); Cho and Dawson (2000); Kim et al. (2008); Rebecca et al., 2017, Rebecca et al., 2019; Sapir et al. (2019); Sharma et al., 2020; Tsukamoto et al. (2006); Verkruyse and Hofmann (1996)
CLN2	TPP1; Serine protease	Macroautophagy, Endocytosis, TNF-α-induced apoptosis	Upregulated in hepatocellular carcinoma, colorectal carcinomas, and gastric tumors	Metastasis	Autefage et al. (2009); Kuizon et al. (2010); Micsenyi et al. (2013); Zhao et al. (2017)
CLN3	Transmembrane protein	Neuronal apoptosis, Lysosomal pH regulation, Autophagy, Endocytosis, Osmoregulation, Proliferation, Apoptosis, Cell motility, Cell cycle regulation, Ceramide pathway	Upregulated in prostate, cancer, ovarian cancer, colon cancer, breast cancer, neuroblastoma, glioblastoma, and hepatocellular carcinoma. No effect in lung and pancreas cancer	Apoptosis, Proliferation, Metastasis, Cell migration, Ceramide pathway	Nugent et al. (2008); Cao et al. (2006); Getty et al. (2011); Golabek et al. (2000); Mathavarajah et al. (2018); Rusyn et al. (2008); Rylova et al. (2002); Xu et al., 2019; Zhu et al., 2014
CLN4	DNAJC5/CSPα; Hsc70 co-chaperone	Synaptic transmission, Endocytosis and exocytosis of synaptic vesicles, Synaptic and neuronal viability	Downregulated in multiple myeloma via circ-*DNAJC5*	Extracellular vesicle secretion?	Nosková et al., 2011; Sharma et al. (2011); Su et al., 2019; Zhou et al. (2020)
CLN5	Glycoside hydrolase	Cell growth, Apoptosis, Lipid metabolism, Retromer recruitment, Regulation of sphingolipid levels and transport	No evidence in literature	Apoptosis	Haddad et al. (2012); Huber and Mathavarajah (2018); Mamo et al. (2012); Potts et al. (2015); Schmiedt et al., 2012
CLN10	CTSD; aspartic protease	Neural growth, Tissue remodeling, Apoptosis, Autophagy	Upregulated in breast and metastatic melanomas	Proliferation, Apoptosis, Cell migration, Invasion, Angiogenesis, Metastasis, Cytokine release	Boonen et al. (2016); Fusek et al. (2007); Hah et al. (2012); Koike et al., 2003; Podhajcer et al. (1995); Scott and Pearson (1981); Shacka et al. (2007); Tan et al. (2013)

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Table 1. *Continued*

| NCL protein	Alternate name; function	Putative roles in NCL	Gene expression in cancer	Putative roles in cancer	References
CLN11	PGRN; secreted glycoprotein	Neuroinflammation, Glial activation, Autophagy, Cell migration, Regulation of lysosomal function and homeostasis	Upregulated in breast cancer, liver cancer, ovarian cancer, brain tumors, and laryngeal squamous cell carcinomas	Proliferation, Cell cycle regulation, Cell migration, Invasion, Angiogenesis, Metastasis, Chemoresistance, Cancer immunoevasion	Cheung et al. (2004); He and Bateman (2003); He et al. (2002); Kao et al. (2017); Kessenbrock et al., 2008; Kong et al. (2007); Monami et al. (2006); Monami et al., 2009; Liu et al., 2007; Tangkeangsirisin et al. (2004); Tangkeangsirisin and Serrero (2004)
CLN12	ATP13A2; transmembrane protein	Autophagy, Neuronal signaling, Vesicular transport, Regulation of ion homeostasis, Regulation of lysosomal function and pH	Upregulated in non-small cell lung cancer	Nanovesicle secretion, Protein homeostasis	Covy et al. (2012); Dehay et al. (2012); Demirsoy et al. (2017); Gitler et al., 2009; Liu et al. (2015); Tsunemi et al. (2014); Usenovic et al., 2012
CLN13	CTSF; cysteine protease	Proteasome degradation, Lipoprotein degradation, MHC class II maturation and peptide loading in antigen-presenting cells, Autophagy	Upregulated in ovarian cancer Downregulated in melanoma, chronic myelogenous leukemia, lung carcinoma, ependimoma, glioblastoma, medulloblastoma, and gastric cancer	Proliferation, Apoptosis	Di Rosa et al. (2015); Janic et al., 2018; Jerič et al. (2013); Lindstedt et al. (2003); Santamaría et al. (1999); Shi et al. (2000); Smith et al., 2013

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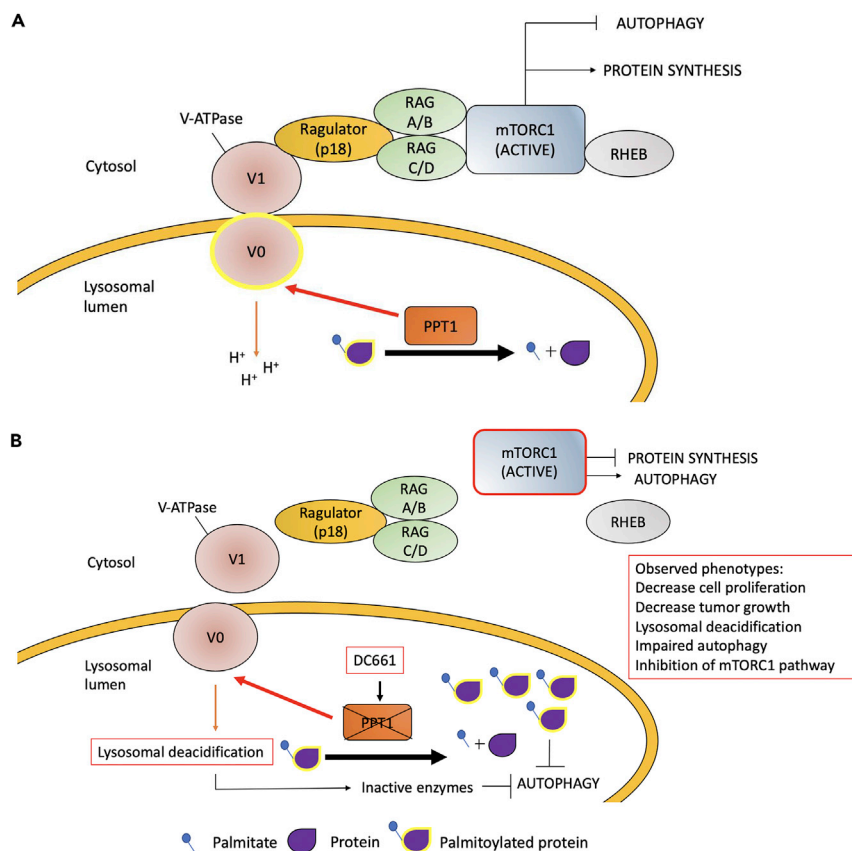
Figure 5. PPT1 activity in cancer cells

(A) PPT1 depalmitoylates the V0a1 subunit of v-ATPase and facilitates v-ATPase assembly on the lysosomal membrane. The V1 subunit of v-ATPase interacts with Ragulator and facilitates the formation of the mTORC1 complex on the lysosome, which activates mTORC1. Active mTORC1 promotes protein synthesis and inhibits autophagy. PPT1 also removes palmitate from palmitoylated proteins prior to their degradation in the lysosome.

(B) DC661 targets PPT1 and inhibits its function. The V0a1 subunit of v-ATPase is not depalmitoylated, thus disrupting the assembly of v-ATPase and leading to lysosomal deacidification. The interaction between the V0a1 subunit of v-ATPase and Ragulator is lost, leading to the displacement of mTORC1 from lysosomal membrane and mTORC1 inhibition. Protein synthesis is inhibited and halts cell proliferation and tumor growth. Impaired autophagy observed in cancer cells treated with DC661 may be due to lysosomal deacidification, accumulation of palmitoylated proteins in the lysosomes, or both. Substrates highlighted in yellow are PPT1 substrates.

CQ derivatives. PPT1 depalmitoylation activity was inhibited, and there was a consequent accumulation of palmitoylated CD44 in A375P melanoma cells treated with CQ derivatives. Treatment of cells with DC661 reduced proliferation, deacidified lysosomes, impaired autophagy, induced apoptosis, and inhibited the mTORC1 pathway (Figure 5). Similarly, silencing of *PPT1* caused A375P melanoma cells to phenocopy these effects, which further supports that *PPT1* inhibition impairs lysosomal function (Table 1). The feasibility of targeting *PPT1* genetically or pharmacologically was demonstrated using xenograft mouse models, where loss of *PPT1* decreased tumor growth by impairing autophagic flux. Cumulatively, genetic and pharmacological inhibition of *PPT1* has anti-tumor effects, demonstrating PPT1 as a potential new target for drug development and DC661 as a promising therapeutic option for cancer.

Overall, loss of *PPT1* exerts anti-tumor effects by impairing lysosomal function and promoting apoptosis in cancer cells (Table 1). Although the mechanism underlying the regulation of apoptosis by PPT1 via Akt activation is unknown, it is likely that PPT1 depalmitoylates proteins in the PI3K/Akt and apoptotic signaling pathways (e.g., Ras). Thus, the identification of PPT1 substrates in these two pathways should be further explored to elucidate the mechanism that regulates the role of *PPT1* in oncogenesis.

CLN2/TPP1

The function of TPP1 and its association with NCL and cancer

TPP1 encodes a serine protease, TPP1, that cleaves tripeptides from the N-terminus of proteins (Kuizon et al., 2010) (Table 1). TPP1 is synthesized as an inactive pro-enzyme in the ER and is activated in the presence of calcium and the acidic environment of the lysosome. TPP1 is associated with macroautophagy and tumor necrosis factor (TNF)-induced apoptosis (Autefage et al., 2009; Micsenyi et al., 2013) (Table 1). Mutations in *TPP1* cause CLN2 disease, a late infantile form of NCL (Mole and Cotman, 2015). Several studies have also examined the role of TPP1 in cancer.

Higher levels of *TPP1* mRNA and protein were observed in hepatocellular carcinoma (HCC) and gastric tumors compared to matched normal tissue (Zhao et al., 2017) (Table 1). In HCC tumors, the level of *TPP1* mRNA is positively modulated by a transcription factor called regulatory factor X5, which is also overexpressed in HCC (Zhao et al., 2017). High expression of *TPP1* is associated with low overall survival for patients with HCC (Zhao et al., 2017). Similarly, the same relationship is observed in patients with brain cancer (Figure 3). However, follow-up work showed that TPP1 did not play a role in HCC cell proliferation, apoptosis, and tumor growth, suggesting that other yet to be identified mechanisms underlie the low survival of patients (Chen et al., 2019).

Tsukamoto et al. (2006) reported that the expression of *TPP1* mRNA was significantly higher in colorectal carcinomas and distant metastases. Consistent with this result, strong TPP1 immunoreactivity was observed at the invasive front of primary colorectal carcinomas, infiltrating carcinoma cells in the subserosa, as well as metastatic carcinoma cells in the lymph node and liver (Tsukamoto et al., 2006). Likewise, Junaid et al. (2000) demonstrated that TPP1 enzymatic activity was 2 to 7-fold higher in breast tumor samples compared to normal tissue. Work done *in vitro* showed that an increase in the secretion and activity of TPP1 in the conditioned media was observed when *TPP1* was overexpressed (Haskell et al., 2003; Lin and Lobel, 2001). Collectively, the increased activity of TPP1 in tumor samples suggests that TPP1 is involved in tumor progression and metastasis . Although no studies have described the functional consequences of elevated TPP1 levels in metastasis, it is plausible that, like other serine proteases, TPP1 is active in the acidic tumor microenvironment (TME) and promotes metastasis through the proteolysis of the extracellular matrix (ECM) and basement membrane (BM) (Table 1). Thus, the putative role of TPP1 in the TME may explain how it can promote oncogenesis without contributing to the tumor-promoting phenotypes observed in HCC (Chen et al., 2019). Hence, future work to explore the potential role of extracellular TPP1 in metastasis is warranted.

CLN3

The function of CLN3 and its association with NCL and cancer

CLN3 encodes an integral membrane protein of unknown function (Nugent et al., 2008). Mutations in *CLN3* cause CLN3 disease, a juvenile form of NCL (Mole and Cotman, 2015) (Table 1). CLN3 is postulated to be involved in a variety of biological processes including osmoregulation, autophagy, apoptosis, lysosomal pH regulation, ceramide metabolism, cell cycle control, cell migration, and proliferation (Cao et al., 2006; Getty et al., 2011; Golabek et al., 2000; Mathavarajah et al., 2018; Rusyn et al., 2008; Zhu et al., 2014) (Table 1).

CLN3 mRNA and protein are abundant in many forms of cancer including prostate, ovarian, colon, breast, neuroblastoma, GBM, and HCC-derived cancer cell lines (Mao et al., 2015; Rylova et al., 2002; Xu et al., 2019) (Table 1). These findings extend to patient samples, where *CLN3* mRNA expression is higher in colon tumors compared to normal colon tissue (Rylova et al., 2002) (Table 1). Similarly, CLN3 protein amounts are also elevated in HCC tissue (Xu et al., 2019). However, *CLN3* expression is not increased in cancer cell lines derived from the lung or pancreas (Rylova et al., 2002) (Table 1). Additionally, in our survey of NCL genes in brain cancer patients, *CLN3* was the only gene that did not significantly influence patient prognosis (Figure 3). Thus, *CLN3* appears to play a role in some, but not all, forms of cancer. In patients with HCC, high *CLN3* mRNA levels correlate with larger tumor sizes, increased vascular invasion, and an absence of tumor encapsulation; *CLN3* expression is therefore connected to HCC tumor invasion and metastasis (Xu et al., 2019). Furthermore, high *CLN3* mRNA levels correlate with reduced overall and recurrence-free survival in patients with HCC (Xu et al., 2019). Apart from metastasis, different regions of the CLN3 protein are associated with regulating cell growth and death. Persaud-Sawin et al. (2002) identified stretches of
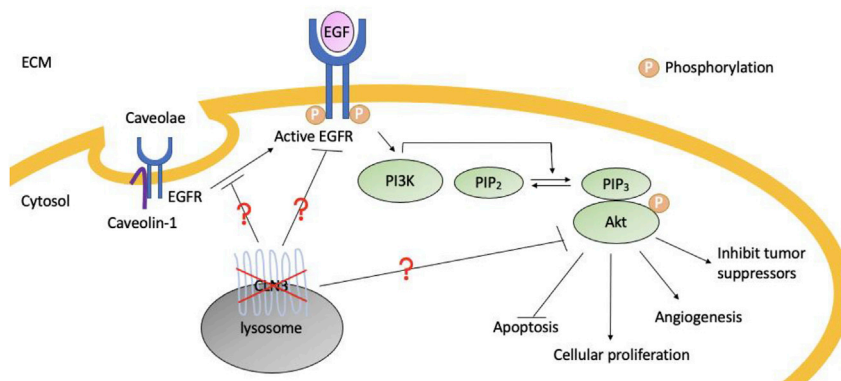
Figure 6. The effect of *CLN3* inhibition in cancer cells

When *CLN3* is inhibited in liver cancer cells, activation of EGFR and Akt is suppressed through an unknown mechanism. Inactivation of the EGFR/PI3K/Akt pathway reduces the proliferation and invasiveness of cancer cells. CLN3 may regulate the trafficking and/or degradation of EGFR through caveolin-1.

highly conserved residues responsible for modulating cell growth and apoptosis between exons 11 and 13 of *CLN3*. Based on Figure 1, it is plausible that these regions are amplified in cancer and more work should be carried out to explore the involvement of the genomic region between exons 11 and 13 in the context of cancer.

Examining CLN3-dependent pathways for cancer therapy development

Many studies have explored the functions of *CLN3* in cancer cells. Tumor growth, proliferation, and viability of prostate, HCC, neuroblastoma, breast, ovarian, and colorectal cancer cell lines decrease significantly when *CLN3* is knocked down (Mao et al., 2015; Rylova et al., 2002; Xu et al., 2019; Zhu et al., 2014) (Table 1). *CLN3* knockdown in DU145 prostate cancer cells causes a dramatic increase in endogenous ceramide levels, which consequently promotes apoptosis (Rylova et al., 2002). In contrast, the overexpression of *CLN3* in NT2 human teratocarcinoma-derived progenitor cells reduces ceramide levels, resulting in increased cell growth and reduced apoptosis (Puranam et al., 1999). Aligning with a central role in ceramide regulation, cells overexpressing *CLN3* cannot rescue cells from apoptosis when treated with exogenous ceramides (Puranam et al., 1999; Rylova et al., 2002) (Table 1). Therefore, inhibiting the amount of CLN3 protein and increasing ceramide levels may be useful therapeutic strategies in cancer cells that overexpress *CLN3*. Furthermore, this therapeutic strategy may be effective for other oncogenic NCL genes since most of them have also been associated with ceramide dysregulation (Rusyn et al., 2008).

The knockdown of *CLN3* also reduces the migration, invasive and metastatic potential of HCC, and human tumor xenografts in mice (Xu et al., 2019) (Table 1). The mechanism underlying these phenotypes is related to how CLN3 attenuates the epidermal growth factor receptor (EGFR)/PI3K/Akt signaling pathway. EGFR and Akt activation were significantly reduced in SMMC7721 and HCCLM3 liver cancer cell lines when *CLN3* was knocked down (Xu et al., 2019). Cells treated with EGFR and PI3K inhibitors (AG1478 and LY294002, respectively) phenocopied *CLN3* knockdown phenotypes and displayed reduced proliferation and invasiveness (Xu et al., 2019). The ectopic expression of the constitutively active form of Akt (myr-Akt) reversed the effect of *CLN3* depletion on cancer cell growth and invasiveness, thus supporting that CLN3 promotes these aggressive phenotypes in cancer cells through the EGFR pathway (Figure 6). However, the mechanism by which CLN3 activates the EGFR pathway and promotes oncogenesis is still unknown.

The function of CLN3 has been linked to the trafficking and/or degradation of EGFR through caveolin-1, a protein that is required for the vesicular invagination of plasma membrane caveolae (Tecedor et al., 2013; Yasa et al., 2020) (Figure 6). *CLN3*-deficient brain endothelial cells display reduced plasma membrane-associated caveolin-1, which decreases caveolae formation and caveolae-dependent endocytosis (Tecedor et al., 2013). Since EGFR maintains an inactive state in caveolae when it is bound to caveolin-1, it is possible that the changes in caveolae and the trafficking of caveolin-1 with *CLN3* mutation, alter EGFR trafficking and signaling (Couet et al., 1997). Thus, future studies on *CLN3* should explore this pathway to validate the postulated interactions between CLN3, EGFR, and caveolin-1 in cancer cells.

Overall, *CLN3* promotes malignant cell growth and viability through the dysregulation of ceramide production (Table 1). CLN3 also plays a role in metastasis through the EGFR/PI3K/Akt pathway (Table 1). These studies reveal that CLN3 may be a molecular contributor to cancer progression and that assessing *CLN3* expression and function could be used to not only predict patient prognoses in the cancers described above but also be of therapeutic significance.

CLN4/DNAJC5/CSPα

The function of DNAJC5 and its association with NCL and cancer

CLN4 disease, also known as autosomal dominant adult-onset NCL, is caused by mutations in *DNAJC5* (Mole and Cotman, 2015; Nosková et al., 2011). The DNAJC5 protein, also known as cysteine string protein α (CSPα), functions as a co-chaperone that regulates the ATPase activity of Hsc70/Hsp70 and assists in the proper folding of proteins in synaptic vesicles (Nosková et al., 2011) (Table 1). The co-chaperone function of DNAJC5 has been associated with synaptic transmission and neuroprotection, which could explain why high *DNAJC5* expression improves the prognoses of patients with brain cancer (Figure 3) and (Nosková et al., 2011; Sharma et al., 2011) (Table 1). It also suggests that DNAJC5 may function as a tumor suppressor.

The role of DNAJC5 in exosome release

DNAJC5 is secreted via extracellular vesicles (EVs) in catecholaminergic-derived central nervous system (CNS) cells, mouse brain tissue, and human GBM (Deng et al., 2017) (Table 1). DNAJC5 facilitates the export and elimination of toxic misfolded proteins linked to neurodegeneration, such as α-synuclein, through EVs (Deng et al., 2017). On the other hand, the release of these aggregation-prone proteins also facilitates the propagation of proteotoxic stress with neighboring neurons and may alternatively promote neurodegeneration (Deng et al., 2017). Thus, further work is required to determine the fate of misfolded proteins exported by DNAJC5 and whether they are detrimental or beneficial in different contexts.

EVs, such as exosomes, are critical mediators of cell-to-cell communication and can promote the remodeling of the TME to support tumor cell metastasis (Colombo et al., 2019). Malignant cells in multiple myeloma (MM) rely on the TME of the bone marrow for their progression and dissemination (Colombo et al., 2019). Roccaro et al., 2013 demonstrated that exosomes released from MM mesenchymal stromal cells in the bone marrow promote the growth and spread of tumors in severe combined immunodeficient mouse models. Thus, it is possible that, through its role in regulating exosome release, DNAJC5 exerts tumor suppressive effects in MM.

The links between DNAJC5, non-coding RNAs, and cancer

The relationship between *DNAJC5* and MM extends to the realm of non-coding RNAs, specifically the recently discovered circular RNAs (circRNAs). circRNAs regulate transcription and translation, and their altered expression have been associated with tumor progression (Su et al., 2019). Zhou et al. (2020) reported that circ-*DNAJC5* is downregulated in MM and is associated with lower MM risk and disease progression after treatment (Table 1). These results suggest that circ-*DNAJC5* could be utilized as a biomarker for MM prognosis. The findings also align with our analysis showing that over 30% of patients with MM have gene mutations associated with the NCL pathway (Figure 1B). Although the mechanistic details on how circ-*DNAJC5* contributes to MM progression remain elusive, the studies discussed above support the link between DNAJC5 and MM through its role in exosome secretion (Table 1). Thus, future studies should investigate the role of DNAJC5 in different cancers and the mechanism underlying the association of circ-*DNAJC5* with MM risk.

CLN5

The function of CLN5 and its association with NCL and cancer

Mutations in *CLN5* cause variant late-infantile CLN5 disease; however, juvenile and adult cases of CLN5 disease have also been reported (Mole and Cotman, 2015; Xin et al., 2010). CLN5 is a soluble glycoside hydrolase that localizes to the lysosome and extracellularly (Huber and Mathavarajah, 2018) (Table 1). CLN5 plays a role in many biological processes including cell growth, apoptosis, lipid metabolism, the recruitment of retromer, and the regulation of sphingolipid levels and transport (Haddad et al., 2012; Mamo et al., 2012; Schmiedt et al., 2012) (Table 1). Furthermore, co-immunoprecipitation revealed that CLN5 interacts with other NCL proteins that have been associated with cancer including PPT1, TPP1, and CLN3 (Lyly et al., 2009).
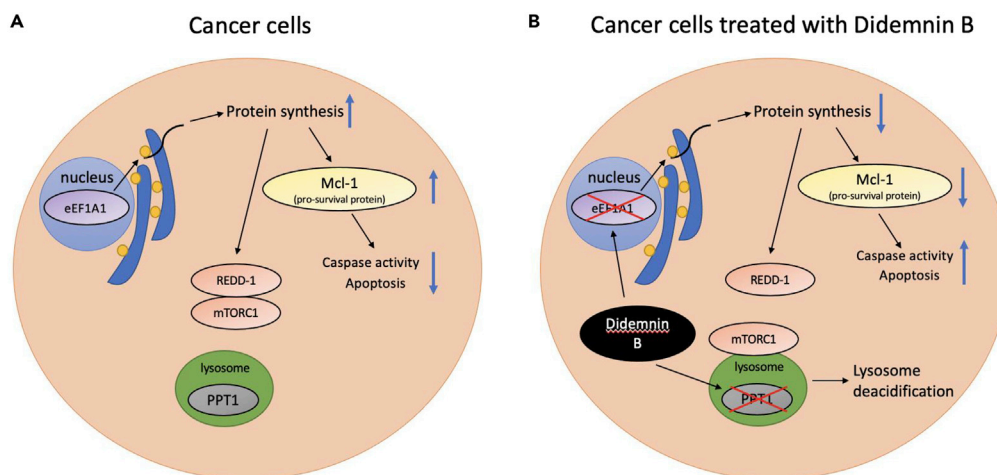
Figure 7. Didemnin B induces apoptosis in selective cancer cells through combinatorial inhibition of PPT1 and eEF1A1

(A) In cancer cells, eEF1A1 promotes protein translation and synthesis of pro-survival Mcl-1, which inhibits apoptosis. The increase in protein synthesis causes REDD-1 (regulated in development and DNA damage responses 1) to bind to mTORC1 and block the docking of mTORC1 on the lysosomal membrane.

(B) Didemnin B targets eEF1A1 which leads to translational inhibition and decreases protein synthesis of Mcl-1 in cancer cell. In response to translational inhibition, REDD-1 relieves its inhibition on mTORC1, thereby activating mTORC1. Didemnin B also targets PPT1, causing lysosomal deacidification. Combinatorial depletion of Mcl-1 and PPT1 increases caspase activation and induces apoptosis in cancer cells.

Cyclic depsipeptide didemnin B is an anti-proliferative agent that induces apoptosis in selective cancer cell lines by targeting both eukaryotic translation elongation factor 1 alpha 1 (eEF1A1) and PPT1 (Figure 7). The sensitivity of these cancer cell lines to apoptosis was associated with the reduced expression of *CLN5* (Potts et al., 2015) (Table 1). These findings were corroborated in a recent study that showed that the viability of primary hemangioblastoma and ccRCC was reduced when *CLN5* expression was silenced (de Rojas-P et al., 2020). They also described how deleterious mutations in *CLN5* protect patients against tumor development in Von Hippel-Lindau syndrome, another rare disease of dominant inheritance where patients display an increased susceptibility to tumor development. The protective effect offered by mutations in *CLN5* may be related to how CLN5 is involved in retromer recruitment, since retromer mediates apoptosis by facilitating the transport of the anti-apoptotic Bcl-xL to mitochondria, thus linking CLN5 to the regulation of cell death (Farmer et al., 2019; Mamo et al., 2012) (Table 1). Together, these studies indicate a possible role of *CLN5* in cancer development. Hence, inhibiting *CLN5* in neoplastic cells through novel small molecules could be a future therapeutic strategy to induce apoptosis in tumor cells.

CLN10/CTSD

The function of CTSD and its association with NCL and cancer

CTSD encodes a soluble lysosomal aspartic protease, CTSD, and mutations in *CTSD* cause CLN10 disease, or congenital NCL (Mole and Cotman, 2015; Steinfeld et al., 2006) (Table 1). CTSD is synthesized as an inactive pro-enzyme (hereafter referred to as pro-CTSD) that is released into the ER lumen (Vetvicka et al., 2010). pro-CTSD is then tagged with mannose-6-phosphate (M6P) in the Golgi complex and targeted to the lysosome (Vetvicka et al., 2010). The M6P and the pro-fragment/activation peptide (AP) are cleaved off in the endosome, and the product is further processed into enzymatically active CTSD in the lysosome (Vetvicka et al., 2010) (Figure 8A). The function of CTSD has been linked to neural growth, tissue remodeling, apoptosis, and autophagy (Boonen et al., 2016; Hah et al., 2012; Koike et al., 2003; Shacka et al., 2007) (Table 1). In addition to NCL, CTSD has been investigated extensively in the context of cancer.

Elevated expression of *CTSD* mRNA is detected in breast cancer and metastatic melanoma cell lines (Podhajcer et al., 1995; Tan et al., 2013) (Table 1). High levels of CTSD protein are also found in various cancers and metastatic tumors, supporting its involvement in metastasis (Tan et al., 2013). Indeed, numerous *in vitro*
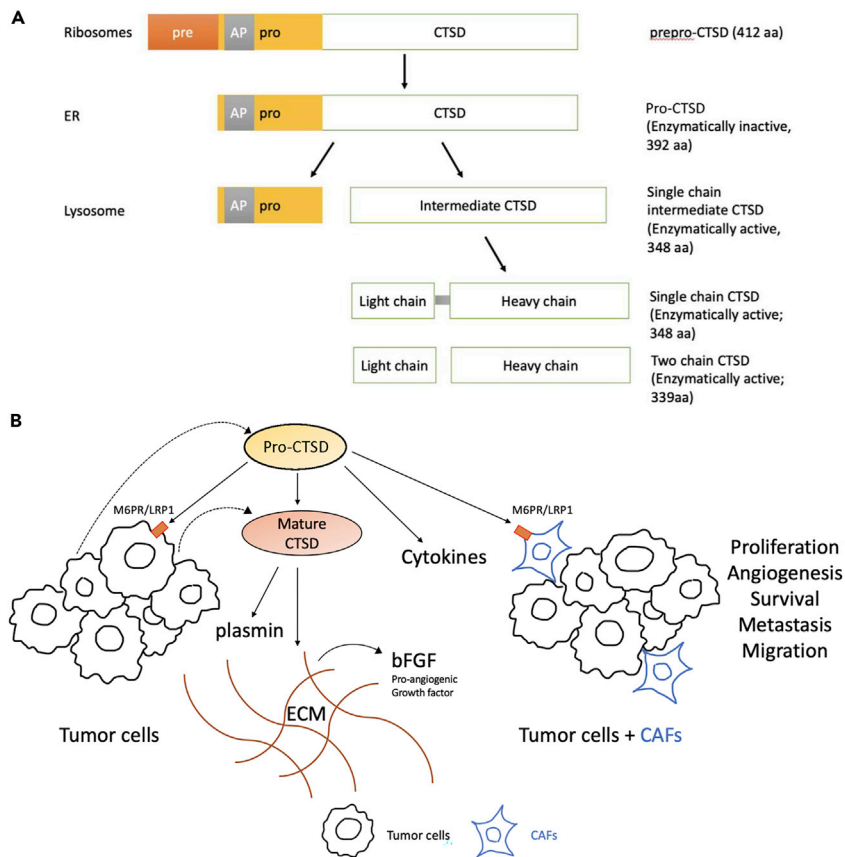
Figure 8. CTSD activity in cancer

(A) Synthesis and maturation of CTSD. CTSD is synthesized as a prepro-enzyme on the ribosome (prepro-CTSD). Upon entering the ER lumen, the pre-fragment is cleaved off and pro-CTSD is tagged with M6P residues that ensure the trafficking of pro-CTSD to the lysosome. The pro-fragment is cleaved off in the acidic environment of the endosome and lysosome, resulting in the single chain intermediate CTSD. Further processing of CTSD occurs in the lysosome yielding the enzymatically active CTSD. The activation peptide (AP) region of pro-CTSD, pro-CTSD, and enzymatically active CTSD have all been implicated in cancer.

(B) Role of pro-CTSD/CTSD in cancer. pro-CTSD/CTSD is secreted by cancer cells (indicated by the dashed lines). pro-CTSD promotes proliferation in an autocrine and paracrine manner by binding to M6PR and LRP1 in both cancer cells and fibroblast cells. pro-CTSD also stimulates the secretion of cytokines. Enzymatically active CTSD degrades the ECM by indirectly activating plasmin. Pro-angiogenic factors and growth factors such as bFGF are released when the ECM is degraded. All these mechanisms ultimately contribute to tumor-promoting effects.

studies have reported that *CTSD* overexpression leads to mislocalization of CTSD and causes hypersecretion of pro-CTSD in breast, endometrial, prostate, lung and ovarian cancer cell lines (Chen et al., 2011; Heylen et al., 2002; Vetvicka2004; Winiarski et al., 2013). The secretion of CTSD is also supported by stromal staining in immunohistochemistry analyses and its detection and activity outside the cell (Abbott et al., 2010; Guszcz et al., 2014; Tan et al., 2016). In addition, increased *CTSD* expression and sera activity correlates with larger tumor size, more advanced clinical staging, a higher risk of lymph node metastasis, increased distant metastasis, an elevated risk for relapse, and shorter survival (Cheng et al., 2008; Guszcz et al., 2014; Tan et al., 2016). Collectively, these studies indicate that CTSD promotes oncogenesis, and it can serve as a useful biomarker in a clinical setting.

Secreted CTSD and its association with cancer

Extracellular pro-CTSD and CTSD participate in carcinogenesis in both a catalytic-dependent and independent manner (Benes et al., 2008; Vetvicka et al., 2010). Secreted pro-CTSD can be either auto-activated in the acidic tumor-conditioned media or activated by other proteinases (Briozzo et al., 1991; Maynadier

et al., 2013; Wittlin et al., 1999). Intriguingly, Butler et al. (2019) discovered that PGRN, another NCL protein, interacts with pro-CTSD to stimulate its maturation to CTSD *in vitro*. Coupled with our finding from Figure 4B showing *CTSD* to be one of the most highly correlated genes in terms of expression to *PGRN* in glioma tumor samples, these results suggest that PGRN facilitates the maturation of CTSD, which can promote oncogenesis through its enzymatic activity. Studies have revealed that the AP region of pro-CTSD has mitogenic effects and pro-CTSD can bind to the M6P receptor and low-density lipoprotein (LDL) receptor-related protein 1 (LRP1) in both cancer cells and fibroblasts to promote oncogenesis (Beaujouin et al., 2010; Laurent-Matha et al., 1998). The pleotropic effects of pro-CTSD on cancer have been reviewed extensively and are depicted in Figure 8 (Benes et al., 2008; Vetvicka et al., 2010).

The link between CTSD enzymatic activity and cancer

In NCL, the functions of CTSD have been linked to apoptosis and autophagy. Similarly, CTSD dysregulates these two processes during oncogenesis. Berchem et al. (2002) showed that cells overexpressing *CTSD* significantly inhibited tumor apoptosis in cancer xenografts, while cells lacking CTSD proteolytic activity did not. In different malignancies, CTSD can promote cell survival through the induction of autophagy as well as other mechanisms. Based on work in *HeLa* cells, CTSD activity appears to prevent oxidative stress-induced cell death by inducing autophagy (Hah et al., 2012). However, its activity was also shown to enhance the survival of colorectal cancer cells undergoing acetate-induced mitochondrial apoptotic death through an autophagy-independent process (Oliveira et al., 2015). In total, CTSD appears to promote the survival of tumor cells by preventing apoptosis (Table 1).

The proteolytic activity of CTSD also stimulates angiogenesis, invasion, and tumor metastasis (Table 1). Secreted CTSD from MCF7 breast cancer cells cleaves the ECM-bound pro-angiogenic basic fibroblast growth factor (bFGF), which also possesses mitogenic activity (Briozzo et al., 1991). Furthermore, Maynadier et al. (2013) demonstrated that CTSD indirectly activates plasmin by degrading plasminogen activator inhibitor-1. Consequently, plasmin can activate matrix metalloproteinases (MMPs) and degrade components of the ECM including fibrin, fibronectin, proteoglycans, and laminin at increased levels (Lu et al., 2011). CTSD can also directly degrade these ECM proteins, in addition to collagen, to facilitate metastasis (Benes et al., 2008; Scott and Pearson, 1981). Moreover, CTSD mediates its action by degrading transforming growth factor β (TGF-β) from its latent complex, stimulating the activation of the TGF-β signaling pathway which further drives metastasis (Pruitt et al., 2013). These studies collectively suggest an oncogenic role for enzymatic CTSD in promoting metastasis through the degradation of ECM proteins and the activation of TGF-β signaling.

Overall, CTSD increases tumor cell proliferation, survival, and invasion through the ECM and BM (Figure 8B) (Table 1). Additionally, pro-CTSD and CTSD in the TME may contribute synergistically to cancer progression through unique mechanisms. Thus, targeting both the receptor-binding and catalytically active regions of CTSD may be effective in suppressing tumor development. Future clinical work should explore the use of pro-CTSD and CTSD as biomarkers, as well as the therapeutic effects of inhibiting CTSD in cancer treatment.

CLN11/PGRN

The function of PGRN and its association with NCL and cancer

PGRN is a highly glycosylated protein that contains 7 full and 1 half granulin (GRN) domains (Arechavaleta-Velasco et al., 2017) (Table 1). PGRN is secreted and participates in multiple physiological processes including growth, inflammation, wound repair, cell motility, and the regulation of lysosomal function (He and Bateman, 2003; Kao et al., 2017; Kessenbrock et al., 2008; Monami et al., 2006) (Table 1). In addition, it exerts neurotrophic and neuroprotective properties (Kao et al., 2017) (Table 1). Thus, the loss of a single *PGRN* allele leads to frontotemporal dementia, while loss of both alleles causes CLN11 disease (Kao et al., 2017; Mole and Cotman, 2015). Due to its diverse physiological roles, altered expression of *PGRN* has also been linked to cancer (Arechavaleta-Velasco et al., 2017).

A recent review has thoroughly described the oncogenic role of PRGN in cancer (Arechavaleta-Velasco et al., 2017). Only a handful of studies relating to its role in cancer have emerged since. Here, we further supplement and solidify the evidence. *PGRN* is overexpressed in many cancers including breast, liver, ovarian, brain tumors, and laryngeal squamous cell carcinomas (Cheung et al., 2004; He and Bateman, 2003; Kong et al., 2007) (Table 1). A similar trend is observed in several human cancer cell lines (Frampton

et al., 2012; Lu and Serrero, 2000). Consistent with these results, our TCGA data analysis showed that LGG and GBM tumors have higher *PGRN* mRNA expression (Figure 4A). Based on these findings, an increase in the amount of PGRN appears to promote oncogenesis.

The changes in *PGRN* mRNA have implications for patient prognosis. Higher amounts of *PGRN* mRNA were found in metastatic cancers compared to non-metastatic cancers, suggesting a more prevalent role in metastasis (Cuevas-Antonio et al., 2010; Donald et al., 2001). Indeed, clinical data show a similar association where *PGRN* expression is positively correlated to aggressive tumor phenotypes such as size, stage, and lymph node metastases in various cancers (Chen et al., 2008; Cheung et al., 2004; Kong et al., 2007). Futhermore, high *PGRN* expression is associated with poorer patient prognosis and increased risk of recurrence (Cuevas-Antonio et al., 2010; Kong et al., 2007). In our analysis, elevated expression of *PGRN* in patients with brain cancer was also associated with the greatest hazard ratio of all the NCL genes, leading to poor survival outcomes (Figure 3). Finally, PGRN is elevated in the sera of patients with different malignancies and is associated with reduced overall survival (Arechava-leta-Velasco et al., 2017). Therefore, PGRN appears to have prominent role in cancer progression and patient prognosis.

PGRN is an oncogene

PGRN is an autocrine growth factor that can stimulate proliferation and anchorage-independent growth in cancer cell lines (Cheung et al., 2004; Monami et al., 2009) (Table 1). However, PGRN can only stimulate cell proliferation on collagen gel substratum in the presence of serum, suggesting that PGRN acts in concert with other extracellular signals to overcome the growth inhibitory effects of collagen (He et al., 2002). The molecular mechanisms behind PGRN-induced cell proliferation appear to be tied to its role in cell cycle regulation. Studies have revealed that *PGRN* overexpression increases the expression of cyclin D1 and cyclin-dependent kinase 4, thereby facilitating entry into the S-phase via the G1/S checkpoint (Liu et al., 2007). Together, these results suggest that PGRN may function as a growth factor to promote cell cycle progression past the G1/S checkpoint, thus contributing to tumor growth (Table 1).

PGRN also promotes migration and invasion in many forms of cancer including breast, colorectal, bladder, ovarian, prostate, HCC, and human epithelial adrenal carcinoma (Cheung et al., 2004; He et al., 2002; Liu et al., 2007; Monami et al., 2006, Monami et al., 2009; Tangkeangsirisin and Serrero, 2004). *PGRN* overexpression increases the expression of mesenchymal marker genes (e.g, vimentin) and decreases the expression of epithelial marker genes (e.g., E-cadherin) in cancer cells and cancer-associated fibroblasts, suggesting that it favors epithelial-mesenchymal transition (Dong et al., 2016). In addition, PGRN modulates the expression and activation of pro-invasive enzymes that degrade the ECM such as MMP-2, MMP-9, MMP-13, and MMP-17 (He et al., 2002; Kong et al., 2007; Liu et al., 2007; Tangkeangsirisin and Serrero, 2004). Upon ECM and BM degradation, PGRN promotes cancer cell migration through cytoskeletal remodeling. In bladder cancer cells, PGRN binds to drebrin, an actin-binding protein, and stimulates the formation of paxillin-ERK-focal adhesion kinase (FAK) complex (Monami et al., 2006; Xu et al., 2015) (Figure 9A). These two complexes promote metastasis by inducing actin cytoskeleton remodeling (Monami et al., 2006; Xu et al., 2015). Collectively, PGRN appears to play an additional role in determining the invasiveness of tumors through its oncogenic actions (Table 1).

Within the TME, PGRN is also involved in angiogenesis. Clinical reports revealed that elevated expression of *PGRN* is associated with denser micro-vessels in malignant tissues and the increased expression of angiogenic factors, namely vascular endothelial growth factor (VEGF) (Chen et al., 2008; Tangkeangsirisin and Serrero, 2004; Yang et al., 2015). Upregulation of *PGRN* significantly elevated the expression of *VEGF-A* in colorectal and breast cancer cell lines (Yang et al., 2015). These findings indicate that cancer cells in the TME rely on PGRN for VEGF-induced angiogenesis, possibly through its interaction with midkine (MDK) growth factor in the ECM. Consistent with this idea, secreted MDK growth factor induces lymphangiogenesis through mTOR pathway and its inhibition significantly abrogates VEGF-induced capillary formation (Filippou et al., 2020). Overall, it appears that PGRN and MDK growth factors interact extracellularly to enhance tumor angiogenesis (Table 1).

The resistance to anti-cancer drugs is one of the major challenges in developing treatments for many types of cancers. PGRN has been implicated in conferring resistance to various anti-neoplastic drugs in several
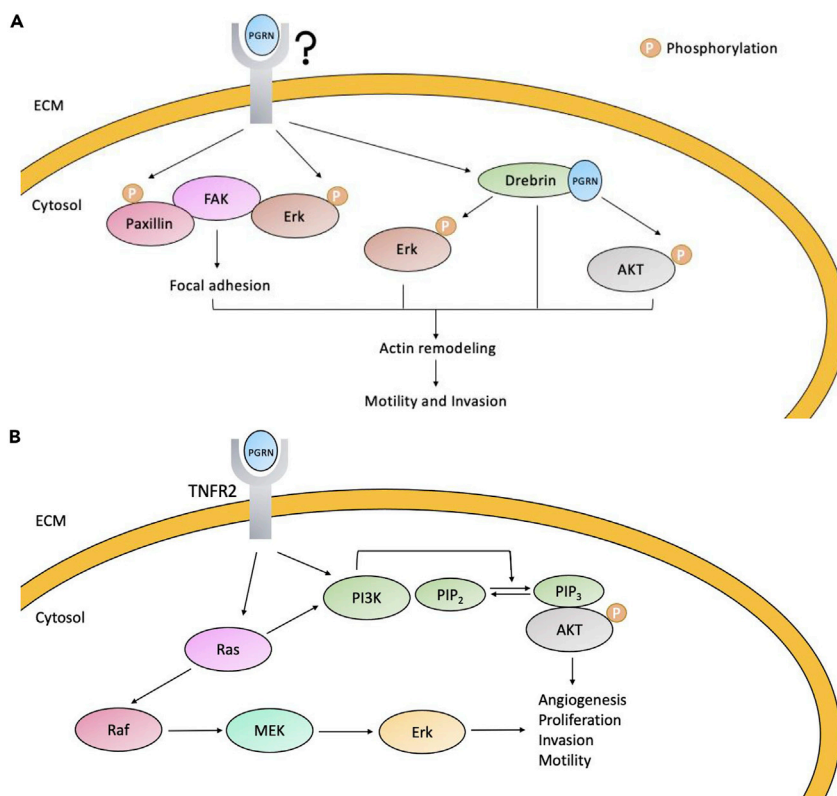
Figure 9. The effects of PGRN vary dependent on cancer cell type
(A) In bladder cancer, PGRN binds to an unknown receptor and stimulates the formation of paxillin/FAK/ERK complex. PGRN also binds to an actin-binding protein, drebrin. These two complexes promote invasion and motility of cancer cells through actin cytoskeleton remodeling (modified from Tanimoto et al., 2016).
(B) In cervical and colorectal cancer cells, PGRN binds to TNFR2 and activates PI3K/Akt and Ras/ERK signaling pathways, thereby promoting tumorigenesis and metastasis.

cancer cell lines (e.g., breast cancer cell lines toward tamoxifen) (Pizarro et al., 2007; Tangkeangsirisin et al., 2004) (Table 1). Conversely, PGRN depletion enhances the vulnerability of the above-mentioned cells to chemotherapeutic drugs (Abrhale et al., 2011). Overall, these findings demonstrate the pleiotropic role of PGRN in promoting oncogenesis.

PGRN-mediated signal transduction

The aggressive phenotypes in cancer cells that overexpress *PGRN* involve Ras, PI3K, mTOR, and FAK signaling pathways (Cuevas-Antonio et al., 2010; Monami et al., 2006). Significant efforts have been made to identify PGRN receptors that are responsible for activating the signal transduction. In cervical and colorectal cancer cells, PGRN binds to TNF receptor 2 (TNFR2) and activates Ras and PI3K signaling pathways (Feng et al., 2016; Yang et al., 2015) (Figure 9B). Accumulated evidence indicates that PGRN is upstream of many growth-promoting pathways and the broad nature of its functions in these pathways suggests that its inhibition may be beneficial for many malignancies where these pathways are upregulated or hyperactive. Thus, PGRN should be considered as an important molecular candidate to pursue therapeutically.

CLN12/ATP13A2/PARK9n detailn detailn n

The function of ATP13A2 and its association with NCL and cancer

ATP13A2 encodes a P5B-type ATPase transmembrane protein, ATP13A2, that localizes to endo-lysosomal compartments (Dehay et al., 2012) (Table 1). ATP13A2 has been linked to the regulation of ion homeostasis, which is critical for maintaining lysosomal pH and function, as well as neuronal signaling (Dehay et al., 2012;

Gitler et al., 2009; Usenovic et al., 2012) (Table 1). Furthermore, ATP13A2 functions as a stress-response protein, protecting neurons from oxidative stress and α-synuclein toxicity (Covy et al., 2012; Gitler et al., 2009) (Table 1). Studies have also tied ATP13A2 to the regulation of autophagy and vesicular transport (Dehay et al., 2012; Usenovic et al., 2012) (Table 1). Mutations in *ATP13A2* cause CLN12 disease and Kufor-Rakeb syndrome, which is an early-onset autosomal recessive form of PD with dementia (Dehay et al., 2012; Farias et al., 2011; Mole and Cotman, 2015).

Liu et al. (2015) reported a ~1.5-fold relative increase in *ATP13A2* mRNA levels in match-paired tumor and tumor-adjacent tissues from patients with NSCLC (Table 1). However, *ATP13A2* expression did not correlate with tumor staging in patients with NSCLC. In contrast, increased expression of *ATP13A2* is associated with reduced survival in patients with acute myeloid leukemia (AML) and brain cancer (Li et al., 2020) (Figure 3). Further functional analysis linked the elevated expression to oncogenic signaling pathways such as Wnt and Notch signaling, as well as fatty acid metabolism in AML (Li et al., 2020). These findings indicate that *ATP13A2* expression may play an important role in some forms of cancer.

The role of ATP13A2 in cellular proteostasis and its link to cancer

Protein synthesis is hyperactivated in cancer cells, thus making them more prone to proteotoxicity and reliant on proteolytic systems (e.g., proteasome and the lysosomes) (Guang et al., 2019). Demirsoy et al. (2017) linked the function of ATP13A2 to the regulation of cellular proteostasis via the lysosome when the proteasome is inhibited. They treated cells with the proteasome inhibitors, MG132 and bortezomib, to induce proteotoxic stress, which is marked by the intracellular accumulation of ubiquitinated proteins (Ub-proteins). Ub-proteins are either degraded in the lysosome or exported via nanovesicles such as exosomes during endosomal sorting (Demirsoy et al., 2017). A375P melanoma cells overexpressing *ATP13A2* showed a reduced intracellular accumulation of Ub-proteins and an increased secretion of nanovesicles, while *ATP13A2*-silenced cells showed an increase in Ub-proteins and no effect on nanovesicle secretion (Demirsoy et al., 2017). These findings were consistent with studies showing that *ATP13A2* overexpression promotes the secretion of exosomes (Tsunemi et al., 2014). Together, these data indicate that ATP13A2 may play an important role in regulating the turnover of Ub-proteins and promoting nanovesicle secretion (e.g., exosomes) in response to proteotoxic stress (Table 1). Since ATP13A2 is involved in regulating exosome secretion, it is possible that overexpression of *ATP13A2* in cancer cells increases the export of exosomes, thereby creating a favorable TME for tumorigenesis. Future work should explore this pathway in malignancies and examine how changes in the TME relate to ATP13A2. Collectively, it appears that ATP13A2 could confer cancer resistance to proteasome inhibitors by re-routing these intracellular cargos and facilitating the export of exosomes through the endo-lysosomal network.

CLN13/CTSF

The function of CTSF and its association with NCL and cancer

CTSF encodes a lysosomal cysteine proteinase, CTSF, that causes CLN13 disease when mutated (Mole and Cotman, 2015; Smith et al., 2013) (Table 1). Like CTSD, CTSF is synthesized as a pro-enzyme and activated in the acidic lysosome (Santamaría et al., 1999). Within the lysosome, CTSF has many functions including proteasome degradation, lipoprotein degradation, autophagy, MHC class II maturation, and peptide loading in antigen-presenting cells (Jerič et al., 2013; Lindstedt et al., 2003; Shi et al., 2000) (Table 1).

CTSF mRNA is altered in several cancer cell lines. *CTSF* expression is low in melanoma, chronic myelogenous leukemia, and lung carcinoma cells, while its expression is high in ovarian cancer cells (Santamaría et al., 1999) (Table 1). Most cell lines show reduced expression of *CTSF*, and this reduction leads to poor prognosis in patients with brain cancer (Figure 3). Our analyses in Figure 3 corroborate with previous work showing that *CTSF* expression was reduced in several pediatric brain tumors including ependimoma, GBM, and medulloblastoma (Di Rosa et al., 2015). Similarly, in tissues of patients with gastric cancer (GC), *CTSF* expression and protein amounts are significantly reduced (Ji et al., 2018) (Table 1). In addition, the presence of CTSF and three other auto-antibodies was found to be specific to the sera of patients with GC compared to other gastric diseases, which can be used to delineate GC from other disorders (Yang et al., 2016). Furthermore, the low serum auto-antibody levels against CTSF were associated with poor survival (Yang et al., 2016). These findings support the possible use of CTSF as a diagnostic and prognostic marker for patients with GC.

The potential role of CTSF as a tumor suppressor protein

Only a handful of studies have assessed the role of CTSF in cancer. However, there is evidence supporting a tumor suppressive role for CTSF in p53-regulated pathways. Tumor suppressor p53 is a nuclear transcription factor that regulates DNA repair, apoptosis, and cellular senescence in response to DNA damage (Ozaki and Nakagawara, 2011). *p53* is mutated in about 50% of cancers (Ozaki and Nakagawara, 2011). p53 modulates the expression of critical mediators of apoptosis and cell cycle arrest such as p53-upregulated modulator of apoptosis (PUMA), NOXA, and p21 (Janic et al., 2018). Janic et al., 2018 revealed that the combined loss of *Ctsf, Puma*, and *p21* in hematopoietic stem/progenitor cells resulted in the development of leukemia/lymphoma when these cells were transplanted into mice (C57BL/6-Ly5.1). In contrast, this result was not observed when *Ctsf, Puma*, and *Myc* were lost (Janic et al., 2018). CTSF appears to function within the context of the p53-p21 axis in a tumor-suppressive manner. Consistent with the previous study, p53 can bind to the regulatory regions of CTSF, and *CTSF* expression was shown to be p53-dependent (Brady et al., 2011). The knockdown of *CTSF* significantly enhanced GC tumor cell proliferation and reduced apoptosis, a p53-regulated pathway (Table 1). These results suggest that CTSF is an effector of p53-dependent tumor suppressive functions, and future work should explore the mechanisms by which CTSF acts as a tumor suppressor.

The p53-dependent functions of CTSF may explain why its expression was downregulated in certain cancers and upregulated in others. For example, unlike other cancer cells lines, *HeLa* cells, which lack *p53*, display an increased expression of *CTSF*. Over 90% of patients with cervical cancer lack a functional p53 protein due to infection by the human papilloma virus (Hietanen et al., 2000). Accordingly, strong positive staining of CTSF was observed in the epithelium of cancer tissue samples across different stages of cervical carcinogenesis (Vazquez-Ortiz et al., 2005). Coupled with the degradative properties of CTSF on proteoglycan-bound LDL particles in the ECM, these results suggest a possible invasive role for CTSF in cervical cancer progression (Oörni et al., 2004). Therefore, CTSF functioning as an oncoprotein in cervical cancer appears to rely on the loss of *p53*.

THE NCL PATHWAY PLAYS A ROLE IN IMMUNE SYSTEM FUNCTION

The function of microglia in the CNS immune system

Microglia play a vital role in the CNS (Colonna and Butovsky, 2017). In response to neuronal damage or the pathological accumulation of indigestible material, microglia become activated and release pro-inflammatory mediators (Colonna and Butovsky, 2017). Once toxic aggregated proteins and cellular debris are removed, the response is then shifted to an anti-inflammatory state dominated by M2 microglia, where tissue damage is repaired, and homeostasis is restored (Colonna and Butovsky, 2017). When the pro-inflammatory response is prolonged, it causes neuronal degeneration, which defines the hallmarks of neurodegenerative diseases, including the NCLs (Houck et al., 2018).

In CNS tumors, specifically GBM, glioma cells actively recruit glioma-associated microglia/macrophages (GAMs) and induce the pro-tumorigenic M2 microglia phenotype (Roesch et al., 2018). GAMs, in turn, secrete soluble factors such as interleukin-6 and MMPs that promote glioma growth, migration, and invasion (Roesch et al., 2018). GAMs also foster neoangiogenesis and contribute to shaping an immunosuppressive TME, thereby potentiating cancer progression (Roesch et al., 2018). Thus, this positive feedback loop between glioma malignant cells and GAMs drives oncogenesis.

NCL genes regulate central and peripheral immune responses

In several NCL subtypes, microglia participate in the inflammatory response and their activation precedes neuronal death (Cárcel-Trullols et al., 2015). Some NCL genes have been associated with microglial function. In mice, *Cln5* mRNA is expressed higher in activated microglia than in unstimulated microglia, while PGRN functions to suppress the activation of microglia (Schmiedt et al., 2012). Since these genes have been associated with cancer, they may also play an important role in cancer immunology via microglial function.

In addition, NCL proteins are also involved in the adaptive immune response. CTSF plays a critical role in peptide loading of MHC class II molecules, while CTSD is involved in processing epitopes and presenting antigens to helper T cells (Shi et al., 2000; Tulone et al., 2011) (Table 1). Additionally, pro-CTSD and AP stimulate the secretion of cytokines, which have mitogenic and immunomodulating effects that can enhance cancer development (Fusek et al., 2007; Hanahan and Weinberg, 2017) (Table 1). Together,

these studies point to the possible roles of CTSD and CTSF in modulating the immune response, which has implications for their functions in tumor progression.

The link between PPT1 and PGRN in cancer immunology

PPT1 and PGRN have been associated with the immunoevasion of cancer cells. Sharma et al., 2020 demonstrated that *PPT1* inhibition alters the polarization of macrophages (i.e., from an M2 to an M1 polarization state) and promotes the secretion of interferon-β in macrophages, which enhances T-cell anti-tumor cytotoxicity in mouse melanoma (Table 1). Similarly, PGRN inhibition enhances the sensitivity of HCC cell lines to anti-tumor natural killer cytotoxicity (Cheung et al., 2014) (Table 1). Hence, future efforts in PPT1- and PGRN-based therapies should aim toward blocking their actions in preventing immune evasion by cancer cells.

In summary, NCL genes appear to modulate the immune system in a contrasting manner in cancer and the NCLs, which could partially explain the disparity observed between the two diseases. Strikingly, Lisi et al. (2014) were able to manipulate the activation state of microglia, inducing the M1 profile to eradicate tumors. Hence, understanding the dynamic balance between the M1/M2 switch in microglia/macrophages, in the context of NCL, and the mechanism that leads to their activation, may provide therapeutic benefit.

CONCLUSION

This review highlights the shared nature of genes and pathways associated with cancer and the NCLs. In the scientific literature, there is evidence of genetic alterations in NCL genes in cancer for *CLN1* to *CLN5* and *CLN10* to *CLN13* (summarized in Table 1). Cell cycle regulation, Ras and PI3K signaling pathways, apoptosis, and lysosome-associated functions such as autophagy and lysosomal pH regulation appear to be common links between both diseases.

Despite our analyses in Figures 1, 2, and 3 showing genetic perturbations in *CLN6, MFSD8, CLN8,* and *KCTD7* across various tumors and their influence on patient prognosis with respect to brain cancer, the specific roles of these genes in cancer-related processes has yet to be explored in detail. However, the pathways regulated by these genes also encompass pathways that are shared between cancer and the NCLs (e.g., ceramide pathway and protein homeostasis) (Cárcel-Trullols et al., 2015; Huber, 2020; Persaud-Sawin et al., 2007). These findings indicate their possible involvement in oncogenesis and should be investigated further.

In conclusion, more in-depth investigations on the distinct and shared molecular mechanisms between the NCLs and cancer can provide a better understanding of both diseases. Such research will improve our understanding of NCL protein function and regulation, as well as the pathways they participate in. It will also be of clinical interest to further examine the potential of NCL genes to serve as biomarkers and therapeutic targets in cancer.

AUTHOR CONTRIBUTIONS

Conceptualization, R.J.H.; writing – original draft preparation, S.Q.Y. and S.M.; writing – review & editing, S.Q.Y., S.M., and R.J.H.; supervision, R.J.H.; funding acquisition, R.J.H.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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