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Review

VMP1 in Pancreatic Cancer: A Rationale for Targeted Protein Degradation

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Abstract: Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal malignancies, with a five-year survival rate below 12%. The intrinsic chemoresistance of PDAC underscores the urgent need for novel therapeutic targets. Vacuole Membrane Protein 1 (VMP1) is a transmembrane protein that functions as a master regulator of autophagy, phospholipid scrambling, and membrane contact site dynamics. VMP1 is markedly overexpressed in PDAC downstream of oncogenic KRAS. Recent work from our group demonstrated that VMP1 is regulated by non-degradative polyubiquitination. Here, we review VMP1 biology and its regulation by the ubiquitin system, proposing it as an attractive candidate for Targeted Protein Degradation (TPD). We discuss how emerging TPD platforms could be leveraged to selectively eliminate VMP1, thereby establishing a conceptual framework for next-generation therapeutic approaches in pancreatic cancer.

Keywords: pancreatic ductal adenocarcinoma (PDAC); VMP1; targeted protein degradation (TPD); autophagy; ubiquitination; KRAS

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the predominant form of pancreatic cancer and is projected to become the second leading cause of cancer-related mortality in the United States by 2030 [1]. The scarcity of durable targeted therapies and the intrinsic resistance of PDAC cells to conventional and novel treatments underscore the urgent need for innovative therapeutic strategies [1,2]. This dismal outcome reflects the combined effects of late diagnosis, early metastatic dissemination, and profound resistance to both conventional chemotherapy and targeted therapies. The molecular landscape of PDAC is dominated by activating mutations in KRAS, which occur in more than 90% of cases, together with inactivating alterations in CDKN2A, TP53, and SMAD4 [3]. PDAC develops through a multistep process involving pancreatic intraepithelial neoplasms (PanINs), whose initiation and progression are driven by oncogenic KRAS and inflammatory stimuli, including those associated with chronic pancreatitis [3]. Among the numerous downstream effectors of oncogenic KRAS, autophagy has emerged as a critical metabolic adaptation that supports tumor initiation, progression, and therapeutic resistance.

One of the defining metabolic features of PDAC is its remarkable dependence on autophagy—the lysosome-mediated intracellular degradation pathway—for energy production, metabolic homeostasis, and adaptation to cellular stress [4,5]. Unlike most normal tissues, PDAC cells rely on constitutively elevated autophagic activity to sustain rapid proliferation, maintain redox balance, and survive under nutrient-deprived and therapeutic stress conditions. This dependency has been extensively validated in genetically engineered mouse models and human PDAC cell lines [4]. Consequently, inhibition of autophagy has long been considered an attractive therapeutic

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strategy. However, pharmacological inhibition of core autophagy components has shown limited clinical success owing to systemic toxicity and the indispensable role of basal autophagy in normal tissues. These limitations underscore the need to identify tumor-selective regulators of autophagy that can be therapeutically targeted while preserving physiological autophagic function [6].

Vacuole Membrane Protein 1 (VMP1) has emerged as one such regulator. Originally identified as a gene induced during acute pancreatitis in the rat pancreas, VMP1 encodes a multi-pass membrane protein that localizes to the endoplasmic reticulum (ER) [7] and autophagosomal membranes, and whose expression alone is sufficient to initiate autophagy in mammalian cells [8]. In PDAC, VMP1 is markedly overexpressed relative to normal pancreatic tissue and is transcriptionally upregulated by oncogenic KRAS through the AKT1–GLI3–p300 signaling axis [9]. Beyond its central role in autophagy, this tumor-selective expression pattern makes VMP1 an attractive therapeutic candidate. More recently, we demonstrated that VMP1 undergoes non-degradative polyubiquitination mediated by the CRL4/Cdt2 E3 ubiquitin ligase complex, revealing an unexpected regulatory connection between VMP1 and the ubiquitin system [10]. This discovery raises the intriguing possibility that the endogenous ubiquitination of VMP1 could be therapeutically reprogrammed using Targeted Protein Degradation (TPD) technologies, converting a regulatory ubiquitin signal into a degradative one.

In this review, we integrate current knowledge of VMP1 biology, its role in pancreatic tumorigenesis, and its regulation by the ubiquitin system to provide a molecular rationale for considering VMP1 a novel candidate for Targeted Protein Degradation (TPD). We further discuss how current and emerging TPD platforms could be leveraged to selectively eliminate VMP1 in pancreatic cancer, thereby establishing a conceptual framework for tumor-selective autophagy inhibition and opening new therapeutic opportunities for PDAC.

2. VMP1: Structure, Localization, and Multifunctional Roles

Vacuole Membrane Protein 1 (VMP1) is a mammalian-specific protein composed of 406 amino acids and containing multiple predicted transmembrane domains. It localizes predominantly to the endoplasmic reticulum (ER) [7] and the autophagosomal membranes [8,11]. VMP1 contains a highly conserved C-terminal hydrophilic peptide, which we termed the VMP1-ATG domain, that mediates its interaction with BECN1, a core component of the class III phosphatidylinositol 3-kinase (PI3KC3) complex required for autophagosome initiation [8]. The main cellular functions described for VMP1 are summarized in Figure 1.

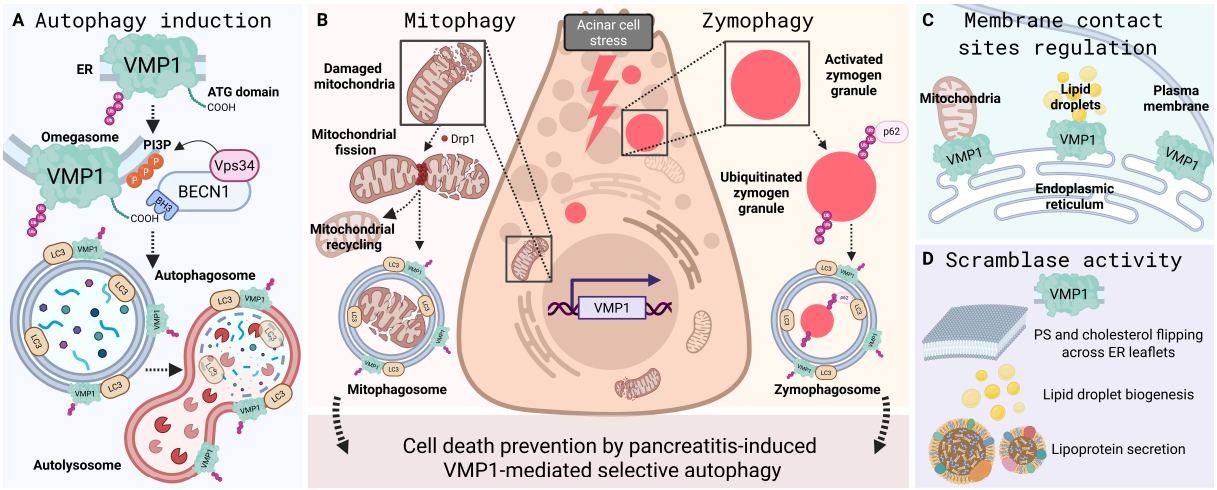


Figure 1. Schematic representation of the main cellular functions of VMP1. (**A**). Autophagy induction: At the endoplasmic reticulum (ER), the C-terminal ATG domain of VMP1 interacts with the BH3 domain of BECN1. This interaction promotes PI3KC3 (Vps34) complex assembly and PI3P production at the omegasome, driving autophagosome formation. Notably, VMP1 remains ubiquitinated and embedded in the membrane throughout the entire autophagic flux, from the omegasome to the autolysosome. (**B**). Cell death prevention via selective autophagy: Pancreatitis-inducing stress triggers the transcriptional induction of VMP1 in acinar cells, activating protective mechanisms. Through mitophagy, damaged mitochondria undergo Drp1-mediated fission and are targeted for recycling. Concurrently, zymophagy selectively targets ubiquitinated, activated zymogen granules for degradation via the p62 receptor, thereby preventing acute pancreatitis. (**C**). Membrane dynamics: VMP1 regulates membrane contact sites between the ER and mitochondria, lipid droplets, and the plasma membrane. (**D**). Lipid homeostasis: VMP1 scramblase activity facilitates the flipping of phosphatidylserine (PS) and cholesterol across

ER leaflets, which is essential for normal lipid droplet biogenesis and lipoprotein secretion. Created with BioRender.com (accessed on 20 October 2026).

2.1. VMP1 as a Master Regulator of Autophagy

VMP1 was first identified as an essential regulator of autophagy when we demonstrated that its ectopic expression alone is sufficient to induce autophagosome biogenesis in mammalian cells. Mechanistically, VMP1 interacts with the BH3 domain of BECN1 through its C-terminal ATG domain, disrupting the inhibitory BCL-2–BECN1 interaction and thereby promoting assembly of the PI3KC3 complex [8]. This event stimulates the localized production of phosphatidylinositol 3-phosphate (PI3P) at ER-associated omegasomes, leading to the recruitment of downstream autophagy proteins, including ATG16L1 and LC3 [8,12]. In addition to autophagosome initiation, VMP1 functions throughout the entire autophagic process, from phagophore nucleation and autophagosome closure to autolysosome formation and resolution [10,13].

2.2. Phospholipid Scramblase Activity and ER Membrane Homeostasis

Beyond autophagy, VMP1 functions as a phospholipid scramblase at the ER membrane, acting in concert with its paralog TMEM41B. This scramblase activity is essential for the redistribution of phosphatidylserine (PS) and cholesterol across leaflets of the ER bilayer, and is required for normal lipid droplet biogenesis and lipoprotein secretion [14–16]. VMP1 also regulates membrane contact sites (MCS) between the ER and other organelles—including mitochondria, lipid droplets, and the plasma membrane—by controlling the size, stability, and lipid flux at these intracellular junctions [13,17].

2.3. VMP1 in Pancreatitis and Pre-Neoplastic Pancreatic Disease

We originally identified VMP1 as a stress-inducible gene in pancreatic acinar cells during experimental acute pancreatitis in the rat. Under physiological conditions, VMP1 expression is virtually undetectable in the exocrine pancreas, whereas it is rapidly and robustly induced during acute pancreatitis. In this context, VMP1 mediates a specialized form of selective autophagy—termed zymophagy—that selectively targets and degrades activated zymogen granules, thereby preventing intracellular digestive enzyme activation, a key initiating event in acute pancreatitis [11]. Additionally, VMP1 mediates mitophagy in response to acute pancreatitis-inducing stimuli [18]. Together, VMP1-mediated selective autophagy exerts a protective role, damping both local pancreatic and systemic histopathological damage during severe acute pancreatitis [19]. Conversely, loss of VMP1 in acinar cells leads to spontaneous pancreatitis, acinar-to-ductal metaplasia, and fibrosis in mouse models, recapitulating features of human chronic pancreatitis [20]. These observations position VMP1 at the crossroads of pancreatic homeostasis, inflammation, and tumorigenesis, suggesting that dysregulation of its physiological functions may drive the transition from adaptive autophagy to malignant transformation [1].

3. VMP1 in Pancreatic Ductal Adenocarcinoma

The different pathways regulating VMP1 expression and their primary effects in pancreatic cancer are summarized in Figure 2.

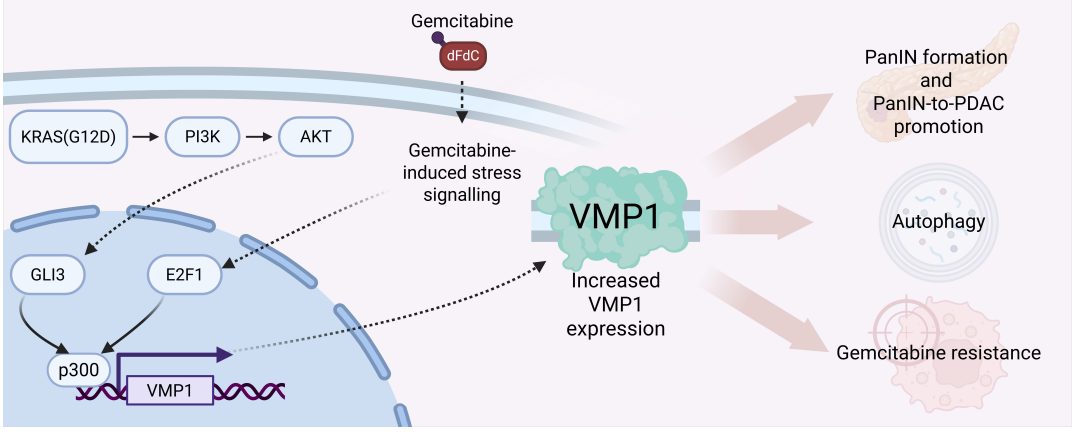


Figure 2. Transcriptional regulation and pro-tumorigenic roles of VMP1 in pancreatic ductal adenocarcinoma (PDAC). Schematic representation of the signaling pathways controlling VMP1 expression and its functional consequences in PDAC. (**Left**): Oncogenic KRAS(G12D) signaling through the PI3K–AKT axis promotes GLI3

nuclear translocation and p300 co-activator recruitment to the VMP1 promoter, driving VMP1 transcription during tumor initiation. Under cellular stress induced by gemcitabine (dFdC) treatment, an independent E2F1–EP300 transcriptional axis is activated to further upregulate VMP1 expression. (**Center**): Upregulated VMP1 protein. (**Right**): Elevated VMP1 levels promote PanIN formation and PanIN-to-PDAC promotion, sustain high autophagic flux required for tumor cell survival, and mediate resistance to gemcitabine-based chemotherapy. Created with BioRender.com (accessed on 24 July 2026).

3.1. Oncogenic KRAS Drives VMP1 Overexpression

The link between VMP1 and pancreatic ductal adenocarcinoma (PDAC) is mechanistically rooted in oncogenic KRAS signaling. In 2012, we demonstrated that oncogenic KRAS activates VMP1 transcription through the AKT1–GLI3 signaling axis by recruiting the transcriptional co-activator p300 to the VMP1 promoter [9]. This pathway induces VMP1 expression in pre-neoplastic pancreatic cells, enabling KRAS-driven pancreatic intraepithelial neoplasias (PanINs) to maintain the autophagic flux required to support their increased metabolic demands. Consistent with these findings, both VMP1 mRNA and protein are markedly upregulated in human PDAC specimens compared with adjacent non-neoplastic pancreatic tissue [9,21].

We subsequently identified a complementary transcriptional mechanism involving E2F1 and EP300 in the context of gemcitabine treatment. Under chemotherapy-induced cellular stress, activation of the E2F1–EP300 axis further enhances VMP1 transcription, leading to increased autophagic activity and promoting resistance to gemcitabine [9]. These findings establish VMP1 as a downstream effector of both oncogenic KRAS signaling and chemotherapy-induced stress, highlighting its central role in PDAC promotion and therapeutic resistance.

3.2. VMP1 Facilitates PDAC Initiation and Promotion

Functional evidence for VMP1's pro-tumorigenic role in PDAC comes from the study by Loncle and colleagues (2016), who generated a genetically engineered mouse model expressing VMP1 in the context of oncogenic Kras(G12D). VMP1 overexpression markedly increased the number and grade of PanIN lesions, accompanied by enhanced cell proliferation (Ki67 positivity) and reduced apoptosis (caspase-3 activity) [22]. Crucially, co-administration of chloroquine, an autophagy inhibitor, abrogated the promoting effect of VMP1 on PanIN formation, confirming that its oncogenic function depends on autophagy induction [22]. These *in vivo* data establish VMP1 as a bona fide co-driver of KRAS-mediated PDAC initiation, operating through its autophagy-inducing function.

3.3. VMP1 Mediates Chemotherapy Resistance

Beyond tumor initiation, VMP1 confers resistance to first-line chemotherapy in PDAC. VMP1 expression modulates the response of pancreatic cancer cells to gemcitabine, with VMP1-high cells showing greater autophagic flux and reduced drug sensitivity [9]. This chemoresistance mechanism is consistent with the broader role of autophagy in PDAC: by recycling damaged organelles and maintaining redox balance [23]. These studies highlight VMP1 not merely as a marker of aggressive PDAC, but as an active mediator of therapy resistance.

4. Ubiquitination of VMP1: A Non-Degradative Regulatory Modification

Ubiquitination is a reversible post-translational modification in which the small protein ubiquitin is covalently attached to lysine residues on a substrate [24]. It proceeds through a sequential enzymatic cascade involving three classes of enzymes: an E1 ubiquitin-activating enzyme, which activates ubiquitin in an ATP-dependent manner; an E2 ubiquitin-conjugating enzyme, which receives the activated ubiquitin; and an E3 ubiquitin ligase, which recognizes the substrate and facilitates ubiquitin transfer [25]. Ubiquitin can be attached as a single moiety (monoubiquitination) or as chains (polyubiquitination), in which ubiquitin molecules are linked through any of their seven lysine residues (K6, K11, K27, K29, K33, K48, K63) or the N-terminal methionine (M1). The type of linkage determines the fate of the modified protein: K48-linked chains typically target substrates for proteasomal degradation, whereas other linkages, such as K63, regulate non-proteasomal processes including protein trafficking, complex assembly, and signaling, and can also mark cargo for selective autophagy [26]. Deubiquitinating enzymes (DUBs) reverse this modification, making the system highly dynamic [27–29].

The ubiquitin system regulates autophagy at multiple levels, from receptor-mediated cargo selection to the control of ATG protein activity, localization, and stability [26,30]. Our first evidence linking VMP1 to the ubiquitin system emerged from studies on zymophagy during experimental acute pancreatitis, in which we identified an interaction between VMP1 and the deubiquitinase USP9X [11]. Subsequently, Karanasios and

colleagues [31] reported the co-localization of VMP1 with ubiquitin-positive structures by immunofluorescence, further supporting a functional association between VMP1 and the ubiquitin machinery.

More recently, we demonstrated that VMP1 itself undergoes ubiquitination, representing a major advance in understanding the regulation of autophagy initiation at the level of this essential transmembrane protein [10]. Using biochemical and cell biological approaches, we showed that VMP1 undergoes polyubiquitination from the earliest stages of autophagosome biogenesis and remains ubiquitinated throughout the autophagic process until autolysosome formation [10]. Importantly, this ubiquitination is non-degradative. Neither proteasome inhibition with MG132 nor pharmacological blockade of autophagy altered VMP1 protein levels, indicating that ubiquitination does not target VMP1 for either proteasomal or lysosomal degradation [10]. Instead, ubiquitination is required for VMP1 recruitment to autophagic membranes and for its function during autophagosome biogenesis.

We identified Cdt2, the substrate recognition component of the CRL4/Cdt2 cullin-RING E3 ubiquitin ligase complex, as the factor responsible for VMP1 ubiquitination [10]. CRL4/Cdt2 is a well-characterized oncogenic E3 ligase involved in DNA replication, cell-cycle progression, and genome stability, and is frequently overexpressed in several human malignancies, including PDAC [32,33]. Consistent with its role in VMP1 regulation, pharmacological inhibition of cullin-RING ligases with the neddylation inhibitor MLN4924 markedly reduced VMP1 ubiquitination, impaired VMP1 recruitment to autophagic membranes, and inhibited autophagosome biogenesis. Conversely, Cdt2 overexpression enhanced VMP1 ubiquitination [10]. Together, these findings identify a CRL4/Cdt2–VMP1 regulatory axis that couples ubiquitination to autophagy initiation and provides a molecular basis for exploring therapeutic strategies.

The non-degradative nature of VMP1 ubiquitination is particularly intriguing from a therapeutic perspective. Rather than serving as a degradation signal, ubiquitination regulates VMP1 activity during autophagy. These findings raise the possibility of reprogramming VMP1 ubiquitination by exploiting targeted protein degradation (TPD) technologies. In principle, bifunctional degraders could redirect VMP1 from its endogenous CRL4/Cdt2 complex to alternative E3 ligases that catalyze K48-linked polyubiquitination, thereby promoting selective proteasomal degradation of VMP1 in tumor cells.

5. Targeted Protein Degradation: Principles and Platforms

Targeted Protein Degradation (TPD) has emerged as a transformative modality in drug discovery, shifting the therapeutic paradigm from occupancy-based inhibition to the catalytic, event-driven elimination of disease-causing proteins [34,35]. This approach exploits endogenous cellular degradation machinery to permanently remove a target protein, offering several advantages over classical inhibitors: activity against proteins lacking druggable binding pockets, catalytic mechanism of action (sub-stoichiometric drug), and potential to overcome resistance mutations that alter target activity without affecting its abundance.

5.1. PROTACs

Proteolysis-Targeting Chimeras (PROTACs) are heterobifunctional molecules consisting of a ligand for the protein of interest (POI), a chemical linker, and a ligand for an E3 ubiquitin ligase [34,36]. Upon formation of a ternary complex between the POI, the PROTAC, and the E3 ligase, the POI is polyubiquitinated and delivered to the 26S proteasome for degradation. PROTACs have demonstrated efficacy against a broad range of targets, including transcription factors and signaling proteins previously considered “undruggable”. Several PROTAC candidates targeting the androgen receptor, estrogen receptor, and BTK have advanced into clinical trials, demonstrating the feasibility of event-driven pharmacology in oncology and other diseases [34,36]. Despite their broad applicability, PROTACs are generally best suited for intracellular proteins with accessible ligand-binding sites and cytosolic exposure to E3 ligases.

5.2. LYTACs

Lysosome-Targeting Chimeras (LYTACs) were developed to address targets inaccessible to the proteasome, including extracellular-facing membrane proteins and extracellular proteins [37]. LYTACs are bifunctional molecules that engage a cell-surface lysosome-targeting receptor (LTR) on one end and the POI on the other, inducing receptor-mediated endocytosis and lysosomal delivery of the target. Early LYTACs utilized the cation-independent mannose-6-phosphate receptor (CI-M6PR), whereas GalNAc-LYTACs exploit the asialoglycoprotein receptor (ASGPR) for liver-selective degradation [38]. LYTACs exclusively target extracellular and cell-surface proteins, making intracellular targets inaccessible.

5.3. AUTACs

Autophagy-Targeting Chimeras (AUTACs) were introduced to harness the macroautophagy pathway, expanding the scope of TPD beyond intracellular proteins to include accumulated aggregates and entire dysfunctional organelles. AUTACs are heterobifunctional molecules comprising a POI-specific ligand linked to a degradation tag, typically a guanine derivative (e.g., p-fluorobenzylguanine) [35]. Mechanistically, the guanine tag mimics S-guanylated cellular cargo, a physiological danger signal that triggers K63-linked polyubiquitination of the target. This specific ubiquitin topology recruits endogenous autophagy receptors, such as p62/SQSTM1, which escort the cargo into the nascent autophagosome for subsequent lysosomal degradation [39]. AUTACs have demonstrated efficacy in degrading protein aggregates, damaged mitochondria, and other intracellular structures, highlighting their potential for diseases characterized by defective protein or organelle homeostasis [40].

5.4. ATTECs

Autophagosome-Tethering Chimeras (ATTECs) represent an alternative autophagy-mediated platform designed to bypass the multi-step ubiquitin machinery entirely [41]. These molecules—frequently operating as molecular glues or bifunctional entities—simultaneously bind the POI and LC3, a ubiquitin-like protein that becomes lipidated and densely embedded in the phagophore and autophagosome membranes [12]. By directly tethering the POI to LC3, ATTECs drive the physical engulfment of the target into the autophagosome without relying on intermediate E3 ligases or receptor-mediated K63 ubiquitination. This platform has proven effective in degrading non-proteinaceous targets such as lipid droplets, as well as disease-associated proteins [41]. ATTECs therefore represent an attractive alternative for degrading intracellular proteins and macromolecular assemblies independently of the canonical ubiquitin-E3 ligase cascade [35].

Figure 3 shows a comparison of major targeted protein degradation platforms and their mechanisms of action.

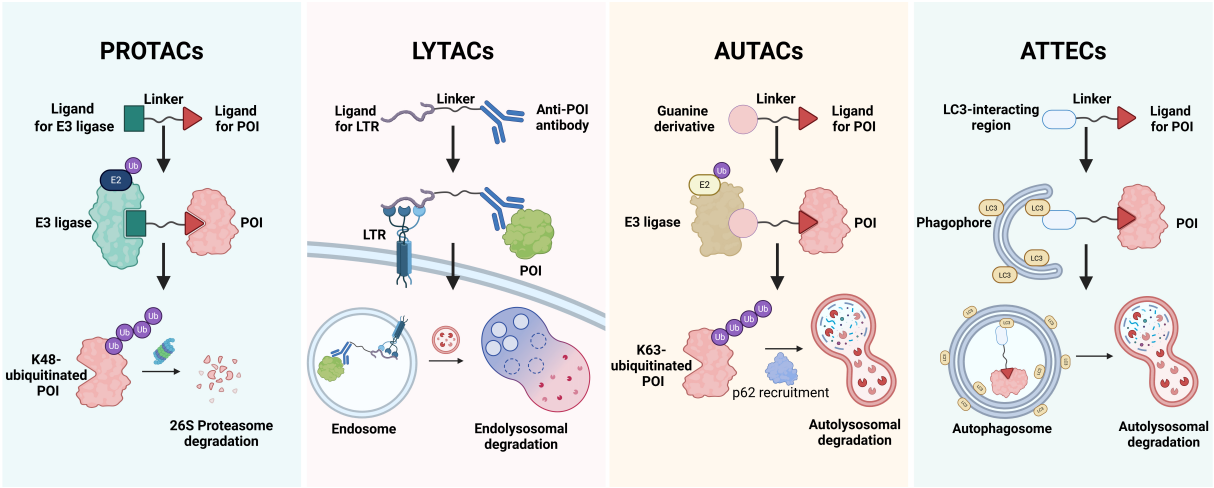


Figure 3. Comparison of major targeted protein degradation (TPD) platforms and their mechanisms of action. Overview of proteasomal and lysosomal targeted protein degradation strategies. PROTACs: Heterobifunctional molecules recruited via a ligand for an E3 ligase and a ligand for the protein of interest (POI) linked together. Ternary complex formation induces K48-linked polyubiquitination of the POI, directing it to the 26S proteasome for degradation. LYTACs: Chimeric degraders comprising an anti-POI antibody (or ligand) coupled to a ligand for a cell-surface lysosome-targeting receptor (LTR). Engagement of LTR triggers endocytosis and subsequent endolysosomal degradation of extracellular or cell-surface targets. AUTACs: Bifunctional molecules containing a guanine derivative tag linked to a POI ligand. This tag recruits the ubiquitination machinery to induce K63-linked polyubiquitination of the POI, promoting p62 recruitment, phagophore engulfment, and autolysosomal degradation. ATTECs: Degraders featuring an LC3-interacting region linked to a POI ligand. By tethering the target directly to LC3 embedded in the phagophore membrane, ATTECs drive target sequestration into the autophagosome for autolysosomal degradation independently of intermediate E3 ligases. Created with BioRender.com (accessed on 24 July 2026).

5.5. Tumor-Selective TPD Strategies

A critical challenge for TPD-based therapies is achieving tumor selectivity to minimize on-target toxicity in normal tissues. Multiple innovative approaches have been developed to address this need. Hypoxia-activated PROTACs incorporate bioreductive moieties that are selectively cleaved by tumor-overexpressed reductases

within the hypoxic microenvironment, releasing the active degrader exclusively at tumor sites [42,43]. Antibody-PROTAC conjugates (PROTAC-ADCs) use tumor antigen-targeting antibodies to deliver degrader payloads selectively to cancer cells [44,45]. Nanoparticle-encapsulated PROTACs achieve preferential tumor accumulation through a combination of passive mechanisms, driven by the enhanced permeability and retention (EPR) effect, and active targeting via surface ligand-receptor interactions [46]. These approaches represent an important advance toward improving the therapeutic index of TPD by restricting degrader activity to tumor tissue while minimizing toxicity in normal organs. Figure 4 schematically represents these three types of tumor-selective TPD strategies.

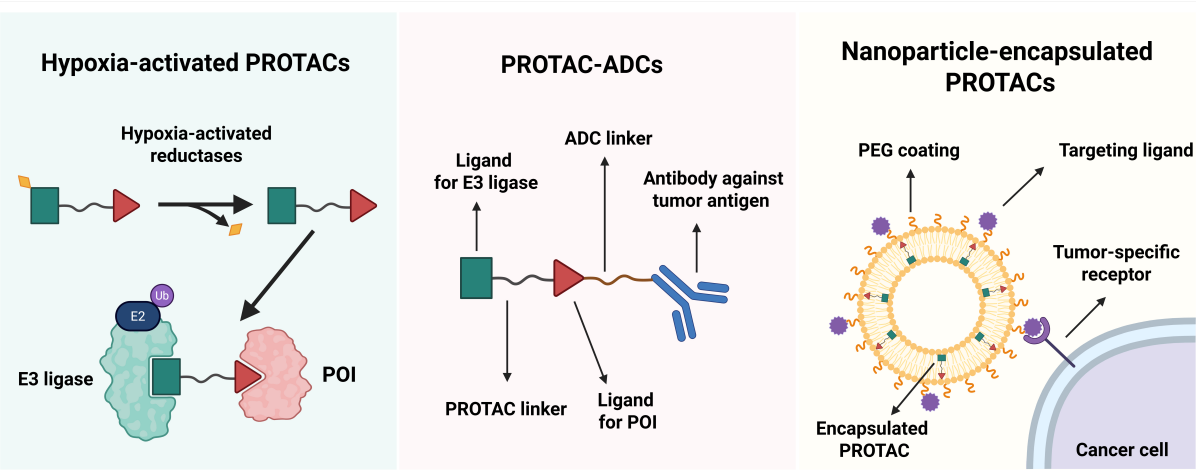


Figure 4. Tumor-selective targeted protein degradation strategies. Schematic representation of delivery and activation modalities designed to restrict PROTAC activity to the tumor microenvironment. Left (Hypoxia-activated PROTACs): Bioreductive moieties (caging groups) mask the degrader under normoxic conditions. In the hypoxic tumor microenvironment, hypoxia-activated reductases cleave the protecting group, releasing the active PROTAC to form a ternary complex between the E3 ligase and the POI. Middle (PROTAC-ADCs): Antibody-PROTAC conjugates utilize a tumor antigen-targeting antibody linked via an ADC cleavable linker to a PROTAC payload. Upon binding to specific cell-surface antigens and endocytosis, the PROTAC is released inside the cancer cell. Right (Nanoparticle-encapsulated PROTACs): PROTACs are encapsulated within nanoparticles coated with polyethylene glycol (PEG) for extended circulation and decorated with surface targeting ligands. These ligands engage tumor-specific receptors to promote receptor-mediated endocytosis and targeted intracellular delivery. Created with BioRender.com (accessed on 24 July 2026).

6. VMP1 as a Target for Targeted Protein Degradation in Pancreatic Cancer

The convergence of several lines of evidence makes VMP1 an attractive candidate for targeted protein degradation (TPD) in PDAC. First, VMP1 is markedly overexpressed in pancreatic tumor cells as a direct consequence of oncogenic KRAS signaling, whereas normal pancreatic tissue expresses only basal, physiologically regulated levels of the protein [9]. Second, VMP1 is functionally indispensable for PDAC initiation, promotion, and resistance to chemotherapy by sustaining the high autophagic flux required for tumor cell survival [9]. Third, VMP1 is naturally integrated into the ubiquitin system through CRL4/Cdt2-mediated ubiquitination, providing a molecular framework that could be exploited to redirect VMP1 toward selective degradation [10]. Together, these features identify VMP1 as a highly attractive therapeutic target for next-generation TPD approaches.

6.1. Redirecting VMP1 Toward Targeted Degradation

Under physiological conditions, CRL4/Cdt2-mediated ubiquitination regulates VMP1 activity during autophagy without promoting its degradation [10]. This endogenous ubiquitination machinery provides an attractive starting point for engineering degraders capable of redirecting VMP1 toward degradative pathways.

One potential strategy would involve PROTAC-like molecules that recruit an alternative E3 ubiquitin ligase, such as CRBN or VHL [47], thereby converting the native regulatory ubiquitination of VMP1 into K48-linked polyubiquitination and subsequent proteasomal degradation. However, because VMP1 is a multi-pass transmembrane protein, access of cytosolic E3 ligases to appropriate lysine residues may limit the efficiency of this approach.

Similarly, AUTAC-based strategies represent a promising alternative, particularly given the localization of VMP1 within autophagosomal membranes. However, although AUTACs are structurally suited to target intracellular, organelle-anchored proteins—much like PROTACs—their efficacy faces comparable limitations, as they also require accessible cytosolic lysine residues to serve as substrates for E3 ligases catalyzing K63-linked polyubiquitination.

Alternatively, LYTAC-based strategies could be considered, as a lysosomal degradation route appears mechanistically suitable for VMP1. However, LYTACs exclusively target extracellular and cell-surface proteins, rendering VMP1 inaccessible due to its intracellular localization.

Finally, based on VMP1 biology, a more tailored strategy could be envisioned. Our recent work demonstrated that VMP1 physically associates with LC3, as shown by co-immunoprecipitation of VMP1 together with LC3 and ubiquitinated proteins [10]. This interaction suggests that ATTEC-based degraders could exploit the native affinity of VMP1 for the autophagic machinery to promote its selective lysosomal degradation. Such an approach could bypass the structural constraints associated with PROTAC- and AUTAC-mediated ubiquitination while taking advantage of VMP1's intrinsic role within the autophagic pathway.

6.2. Tumor Selectivity Through KRAS-Dependent VMP1 Expression

One of the major advantages of targeting VMP1 is its tumor-selective expression profile. Oncogenic KRAS drives persistent VMP1 overexpression in PDAC cells, whereas normal pancreatic tissue maintains substantially lower physiological expression levels [9,21]. This differential expression creates a potentially favorable therapeutic window for selective protein degradation.

Additional selectivity could be achieved by combining VMP1 degraders with tumor-restricted activation strategies, including hypoxia-responsive or protease-activated prodrug designs that become active only within the PDAC microenvironment [45]. Such approaches could minimize interference with the physiological functions of VMP1 in normal tissues while maximizing antitumor activity.

6.3. Therapeutic Synergy with Current PDAC Treatments

Targeted degradation of VMP1 is expected to synergize with current therapeutic strategies for PDAC. Gemcitabine induces VMP1 expression through an E2F1–EP300-dependent mechanism, thereby enhancing protective autophagy and contributing to drug resistance [9]. Pharmacological elimination of VMP1 thus has the potential to restore chemosensitivity while simultaneously disrupting one of the principal adaptive mechanisms that sustain tumor survival. Consequently, VMP1-directed degraders could also enhance the efficacy of emerging targeted therapies in which autophagy represents an important mechanism of therapeutic escape, providing a broadly applicable strategy for overcoming autophagy-dependent treatment resistance in pancreatic cancer.

7. Conclusions and Future Perspectives

VMP1 occupies a unique position at the intersection of autophagy, oncogenic KRAS signaling, and the ubiquitin system in pancreatic cancer. Its tumor-selective overexpression, essential role in sustaining autophagy-dependent tumor growth and chemoresistance, and endogenous regulation by the CRL4/Cdt2 ubiquitin ligase together identify VMP1 as a particularly attractive candidate for targeted protein degradation (TPD). Importantly, the discovery that VMP1 undergoes non-degradative ubiquitination demonstrates that its function is already controlled by the ubiquitin machinery, providing a compelling molecular rationale for redirecting this regulatory modification toward selective protein degradation.

Several key challenges remain before this concept can be translated into therapeutic applications. These include the identification of high-affinity ligands for VMP1, structural characterization of the protein to enable rational degrader design, and the development of VMP1-directed degraders based on the most appropriate TPD platforms. Future studies should also establish which degradation modality—proteasomal or lysosomal—is best suited for VMP1 and determine how tumor-selective activation strategies can maximize therapeutic efficacy while minimizing toxicity in normal tissues.

Beyond pancreatic cancer, VMP1 contributes to autophagy-dependent processes in several other malignancies, including breast, colorectal, and hepatocellular carcinomas [9]. Consequently, successful targeting of VMP1 by TPD could establish a broader therapeutic paradigm for autophagy-addicted cancers. More generally, this concept illustrates how proteins that are not themselves oncogenic drivers, but are indispensable for maintaining tumor-specific adaptive pathways, may represent an emerging class of TPD substrates.

We propose that VMP1 represents a prototype of this new class of therapeutic targets. Its unique combination of tumor-selective overexpression, essential biological function, and regulation by the ubiquitin system provides

a strong rationale for developing next-generation targeted protein degradation strategies aimed at selectively dismantling the autophagic machinery that supports pancreatic cancer progression.

Author Contributions

F.J.R. and M.I.V. participated in the conception and design of this review, as well as in the acquisition, analysis, and interpretation of the relevant literature and data. Both authors drafted and revised the manuscript, ensuring its intellectual rigor. Each author approved the final version and is personally responsible for their work. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest

The authors declare no conflict of interest. The funders had no role in the design of the review; in the collection, analysis, or interpretation of the literature; in the writing of the manuscript; or in the decision to publish the article.

Use of AI and AI-Assisted Technologies

During the preparation of this work, the authors used AI-assisted tools for language editing and polishing of specific sentences. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Abbreviations

ASGPR, asialoglycoprotein receptor; ATG, autophagy-related; ATTEC, autophagosome-tethering chimera; AUTAC, autophagy-targeting chimera; BECN1, Beclin-1; Cdt2/DCAF2, CDC10-dependent transcript 2; CI-M6PR, cation-independent mannose-6-phosphate receptor; CRL4, Cullin-RING ligase 4; DDB1, DNA damage-binding protein 1; E2F1, E2F transcription factor 1; EP300/p300, E1A binding protein p300; EPR, enhanced permeability and retention; ER, endoplasmic reticulum; GalNAc, N-acetylgalactosamine; KRAS, Kirsten rat sarcoma virus oncogene homolog; LC3/MAP1LC3, microtubule-associated protein 1 light chain 3; LTR, lysosome-targeting receptor; LYTAC, lysosome-targeting chimera; MCS, membrane contact site; PanIN, pancreatic intraepithelial neoplasia; PDAC, pancreatic ductal adenocarcinoma; PI3K/PI3KC3, phosphatidylinositol 3-kinase class III; PI3P, phosphatidylinositol 3-phosphate; POI, protein of interest; PROTAC, proteolysis-targeting chimera; PS, phosphatidylserine; TMEM41B, transmembrane protein 41B; TPD, targeted protein degradation; USP9X, ubiquitin-specific peptidase 9 X-linked; VMP1, vacuole membrane protein 1.

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