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HIGHLIGHT

Unlocking the potential of targeted protein degradation *via* nanoparticle-based universal strategy

KEY WORDS

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Proteins of interest;
PROTAC;
Lysosomes

In the cutting-edge realm of contemporary biomedical research, targeted protein degradation (TPD) technology has garnered significant attention due to its rapid advancement[1,2]. This approach modulates protein levels by harnessing the cell's intrinsic degradation machinery, and shows therapeutic potential for diverse diseases, such as cancer and neurodegenerative disorders. However, TPD tools require laborious case-by-case design tailored to different diseases and cell types when targeting new proteins, particularly for extracellular protein targets. A recent paper titled "Targeted protein degradation *via* cellular trafficking of nanoparticles" published in *Nature Nanotechnology*, presents a groundbreaking strategy for TPD utilizing the cellular trafficking of nanoparticles, which provided a fresh perspective for treating various diseases associated with protein abnormalities[3].

1. The significance of TPD

Proteins play a central role in cellular functions, and their dysregulation is often associated with disease states. TPD is a strategy that employs small molecules or biomacromolecules to specifically tag target proteins and direct their elimination *via* the cell's intrinsic degradation systems, such as the ubiquitin−proteasome system or lysosomal system (Figs. 1 and 2). Its core mechanism involves "degraders" to recruit E3 ubiquitin ligases or lysosome-targeting receptors to the target protein, triggering ubiquitination and subsequent degradation[4,5]. TPD offers great hope for targets that have been undruggable by traditional drugs. For instance, over a dozen drugs based on proteolysis-targeting chimeras (PROTAC) have entered clinical trials for the treatment of diseases such as cancer[6]. To fully appreciate the significance of this work, it is helpful to use two vivid metaphors to describe the importance of TPD:

As "sanitation workers" within the cell: if we liken the human body to a city, proteins within cells function like essential urban infrastructure. When proteins become damaged, misfolded, or excessively accumulated—such as β-amyloid plaques in Alzheimer's disease—they act as "cellular waste", disrupting normal functions and triggering diseases. TPD serves as "sanitation workers" within cells, precisely identifying and clearing these harmful proteins to maintain a clean cellular environment. For instance, TPD technology can specifically degrade pathological β-amyloid proteins, offering a novel therapeutic strategy for neurodegenerative disorders[7,8].

As a "weapons control system": in cellular physiological processes, many proteins act as "weapons" functioning under specific conditions to defend against pathogen invasion or regulate growth and division. However, if their quantity or activity becomes uncontrolled—such as the overactivation of oncoproteins in cancer—they disrupt cellular homeostasis. TPD operates like a precise "weapon control system" selectively eliminating aberrant proteins. For example, when tyrosine kinases encoded by oncogenes become hyperactive, they drive malignant cell proliferation. TPD technology can specifically degrade these rogue "weapons" restoring normal regulation and thereby suppressing tumor progression[9].

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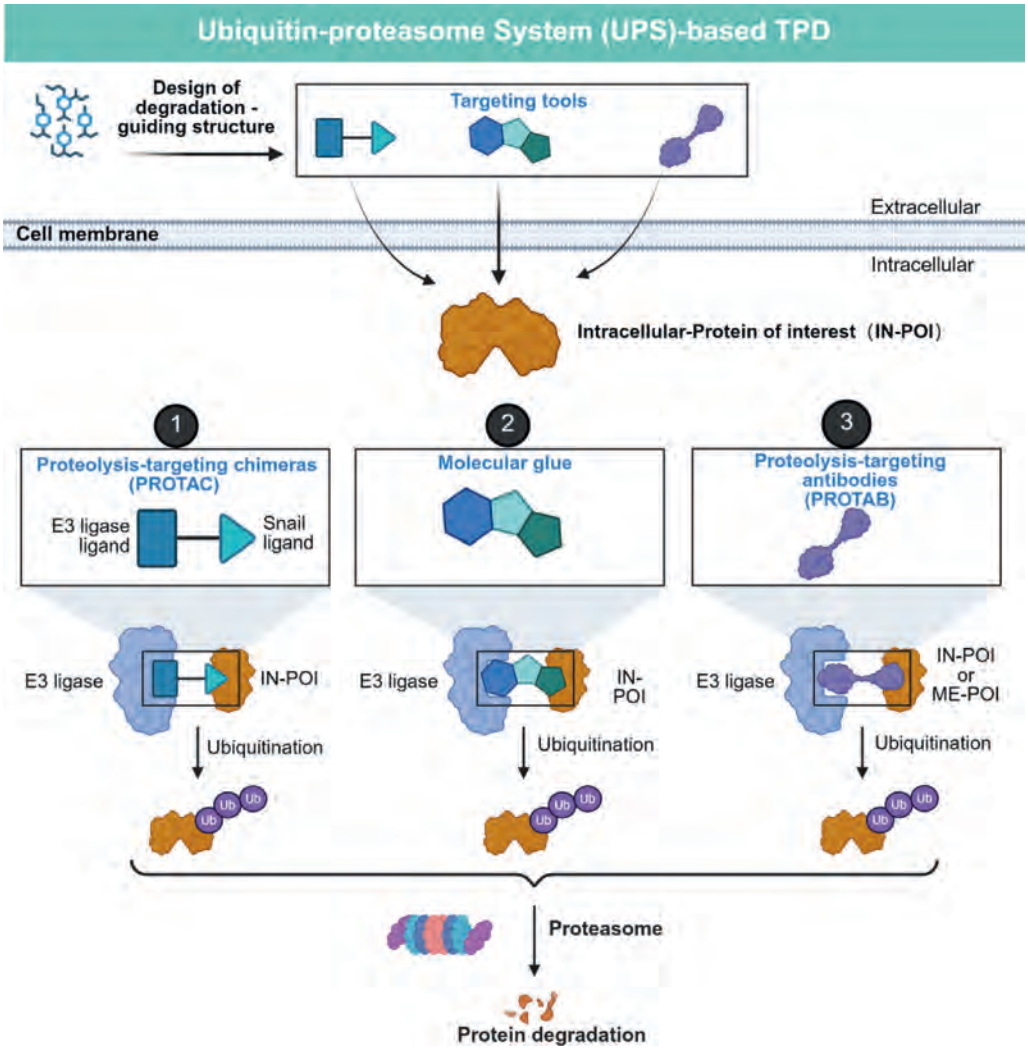

Figure 1 The targeted protein degradation based on ubiquitin−proteasome system.

From this, we understand that TPD can not only act like a "sanitation worker" within the cell, pulling disease-related proteins into the cellular "recycling station" for degradation and clearance, but also function like a "weapons control system" to regulate the quantity or activity of out-of-control proteins to within normal ranges. Traditional therapeutic approaches, such as small-molecule inhibitors or antibodies, primarily target the activity of proteins rather than their abundance. TPD aims to reduce the levels of specific proteins, offering a more direct and potentially more effective intervention. This method holds promise to address the limitations of current therapies, especially in cases where protein overexpression or accumulation is a key driver of pathology[10].

2. Nanoparticle-based TPD technology

Over the past few decades, various TPD platforms have garnered substantial research interest, with these pioneering studies highlighting the potential for targeting undruggable proteins. However, most of these TPD platforms have been designed to target proteins located in the cytoplasm. To achieve TPD of extracellular proteins, the following components are required: specific binders to hijack the target protein, cell-penetrating ligands for the internalization of the target protein, and motifs that can direct the target protein complex to protein recycling mechanisms for degradation. Nevertheless, applying the aforementioned TPD strategies to target any new protein necessitates cumbersome case-by-case designs for different diseases and cell types (Table 1). Therefore, there is a need for a universal and simplified TPD tool design strategy to circumvent the complex design requirements mentioned above.

Biocompatible nanoparticles (NP) have been utilized in clinical practice for drug delivery, ranging from pioneering cases such as Doxil (liposomal delivery) and Abraxane (albumin-bound paclitaxel) to the more recent lipid nanoparticles (LNP) delivering mRNA COVID-19 vaccines. The structural flexibility and ease of surface modification of these nanoparticles make them an attractive property for developing multifunctional TPD tools. More importantly, engineered nanoparticles can be taken up into cells through multiple endocytic processes after administration, without the need for cell type-specific receptors to facilitate their transport (Table 1). Following endocytosis, nanoparticles are transported through the endosomal maturation process and are either recycled or, ultimately,

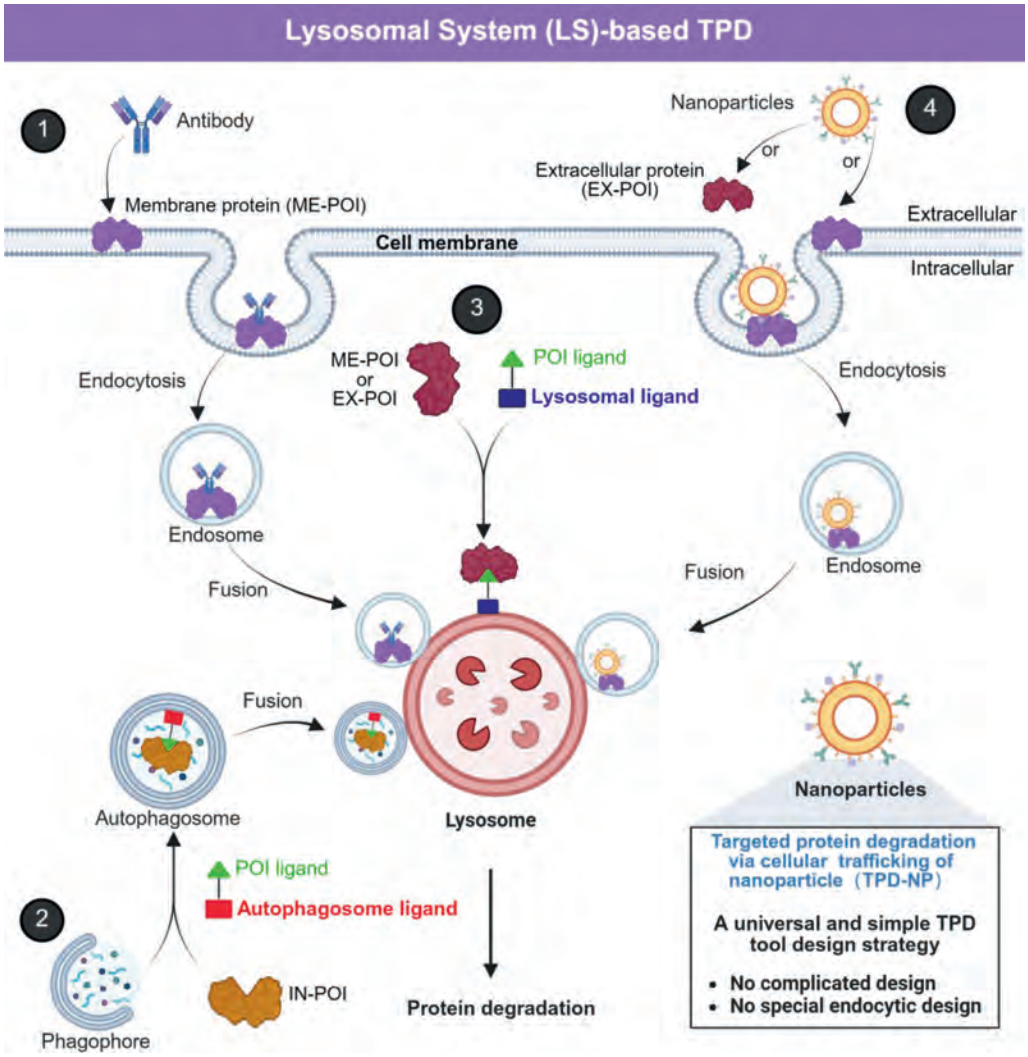

Figure 2 The targeted protein degradation based on lysosomal system.

the endosomes containing the nanoparticles fuse with lysosomes, without the need for specific receptors to promote their entry into cells and targeting to lysosomes. Moreover, nanoparticles also possess high potential for surface modification. All these advantages indicate that engineered nanoparticles have the potential to bypass all the obstacles faced by current TPD tools.

3. Key findings and implications

Specifically, this study proposed a universal strategy that utilizes engineered nanoparticles to design and develop effective TPD tools for the degradation of extracellular proteins of interest (POI). TPD-NP are composed of three parts: POI-binding ligand anchored onto NP by conjugated with a DSPE-PEG linker. Initially, they constructed TPD-NP by conjugating Nimotuzumab (NTZ), a monoclonal antibody targeting the membrane protein EGFR as POI-binding ligand, to a DSPE-PEG linker, and subsequently anchoring it onto PLGA core (as NP) to form NTZ-NP. The results showed that NTZ-NP effectively promoted the degradation of the membrane protein EGFR.

Further exploration indicated that this occurrence is generalizable, applicable to diverse targets and nanoparticle types. Concerning the POI-binding ligands, researchers attained selective target protein degradation by substituting various ligands. For example, PD-L1 degradation was induced by PD-1−targeting antibodies like camrelizumab (CRLZ) and atezolizumab (ATZ). HER2 protein degradation was prompted by antibodies such as pertuzumab (PTZ) and inetetamab (INE). Besides NTZ, cetuximab (CTX) also facilitated EGFR degradation. Beyond antibodies, alternative binding methods like peptide-based targeting were utilized. ACE2-targeting peptides and CD13-targeting peptides served as POI-binding ligands to promote the degradation of ACE2 and CD13 respectively. Regarding NP selection, TPD-NP demonstrated significant versatility. Researchers successfully created diverse TPD-NP platforms based on liposomes, liposome-PLGA, exosomes, red blood cell membranes, and Au nanoparticles. All these platforms enabled targeted EGFR degradation *via* the NTZ antibody.

Subsequently, the study delved into what makes TPD-NP different from other TPD platforms by looking into how TPD-NP enable targeted protein degradation. Findings showed that TPD-NP

Table 1 The common strategies for targeted protein degradation.

No.	Strategy	Type	Degradation pathway	Advantage	Challenge
1	PROTAC	IN-POI	UPS	High selectivity; clear mechanisms	E3-dependency; potential off-target toxicity;
2	Molecular glue	IN-POI	UPS	Excellent cell permeability	Lack of effective design strategies
3	PROTAB	IN-POI/ME-POI	UPS	Wide target applicability	Limited distribution and permeability
4	LYTAC	EX-POI/ME-POI	LS	High selectivity	Poor tissue permeability and specificity
5	AbTAC	ME-POI	LS	Low immunogenicity	Unclear degradation mechanism
6	GlueTAC	ME-POI	LS	High-affinity	Low safety and uncertain half-life
7	AUTAC	IN-POI	LS	Wide degradation range	Complex degradation mechanism
8	ATTEC	IN-POI	LS	Wide degradation range	Concerns about safety and effectiveness
9	AUTOTAC	IN-POI	LS	Wide degradation range	Potential off-target toxicity and off-target effect
10	TPD-NP	EX-POI/ME-POI	LS	No complicated design and special endocytic design	The need for ligand modification

NOTE: IN-POI (intracellular protein of interest); EX-POI (extracellular protein of interest); ME-POI (membrane protein of interest); UPS (ubiquitin-proteasome system); LS (lysosomal system).

mainly enter cells through clathrin-mediated and caveolin-mediated endocytosis, not macropinocytosis. Once inside, they break down target proteins *via* the autophagy−lysosome pathway, not the proteasomal pathway. To confirm the therapeutic potential of TPD-NP, *in vivo* experiments were carried out on MDA-MB-231 human breast cancer-bearing mice and U87MG human glioma-bearing mice. Results showed that the optimized TPD-NP effectively broke down key tumor-associated proteins. This led to slower tumor growth and longer survival in treated mice. In summary, the TPD-NP strategy in this study has many advantages. It avoids complicated designs and is structurally flexible, easy to make and effective. This work is significant as it offers a novel TPD approach.

4. Challenges and prospectives

From an innovation perspective, this study breaks the reliance of traditional degradation tools on specific receptors or complex chemical modifications by proposing a "plug-and-play" universal platform that significantly simplifies design workflows. Leveraging the innate endocytic properties of nanoparticles, it not only lowers technical barriers but also enables flexible combinatorial solutions for personalized therapy. For example, mixing different antibodies or peptides allows rapid assembly of multi-target degradation systems, which holds critical value in addressing tumor heterogeneity. Furthermore, the use of US. Food and Drug Administration (FDA)-approved nanomaterials (*e.g.*, PLGA, liposomes) greatly enhances clinical translation feasibility.

Despite the encouraging results, several challenges remain to be addressed. First, although proteomic analyses detected no significant nonspecific degradation, long-term use may trigger immunogenicity or off-target effects, particularly in complex human microenvironments. Second, scalable manufacturing and quality control of nanoparticles require optimization, especially since multifunctional modifications (*e.g.*, dual targeting or drug loading) may introduce batch-to-batch variability, compromising clinical stability. Additionally, the precise regulatory mechanisms of the autophagy−lysosome pathway remain incompletely understood, such as differences in endocytic efficiency across cell types or molecular switches governing lysosomal fusion dynamics, limiting the ability to achieve fine-tuned control. Future studies could integrate single-cell sequencing or real-time imaging to dissect the intracellular trajectories of nanoparticles and heterogeneity in degradation efficiency, thereby refining design strategies. Expanding this platform to intracellular protein degradation, combined with cell-penetrating peptides or novel delivery systems, could broaden its scope to cover more "undruggable" targets. Integrating AI-assisted nanoparticle design may accelerate material screening and functional prediction, advancing precision medicine.

Overall, this study is a big step forward in targeted protein degradation tech. Its versatility, low toxicity, and multifunctionality mean it has great clinical potential. But to get from the lab to clinical use, we need to solve problems like scalable production, long-term safety checks, and better understanding of the mechanisms. If tech keeps improving and different fields work together, this method could become key for future targeted therapies.

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Author contributions

Ti-Qiang Zhou and Weilun Sun retrieved the related literatures and wrote the original manuscript. Zhen-Zhen Wei, Yuhua Weng, Dongxu Zhao and Mengjie Zhang revised the manuscript. Yuanyu Huang conceived the study and revised the manuscript. All authors have read and approved this version of manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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