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Protacs: a novel approach to targeted protein degradation

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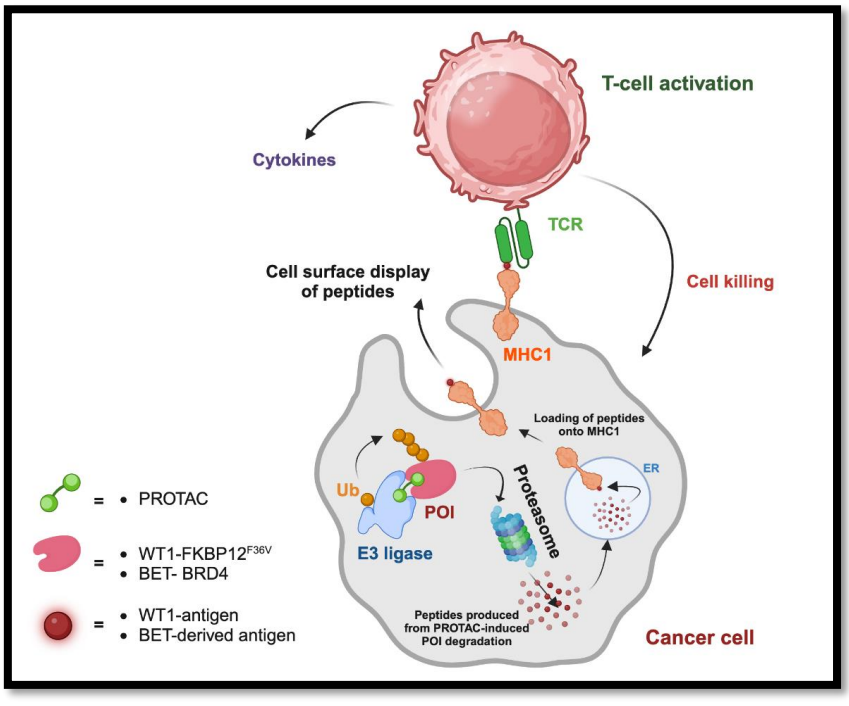
ABSTRACT:

Targeted protein degradation utilizing PROTACs technology is a possible therapeutic technique for treating disorders caused by abnormal synthesis of a disease-causing protein. Few currently used drugs are small, component-based and employ occupancy-driven MOA to impede protein activity for a short period of time to temporarily modify it. The proteolysis-targeting chimeras (PROTACs) technology is introducing a breakthrough technique by using an event-driven MOA. Heterobifunctional PROTACs based on small molecules hijack the ubiquitin–proteasome system to induce the destruction of the target protein. The key problem in the development of PROTACs presently is to discover powerful, tissue- and cell-specific PROTAC molecules with good drug-likeness and conventional safety procedures. This review focuses on approaches to enhance the effectiveness and selectivity of PROTACs. In the present review, we have emphasized the most relevant findings on the degradation of proteins by PROTACs, innovative targeted techniques to enhance the efficacy and development of proteolysis, and potential future avenues in medicine.

Keywords: PROTACs, proteolysis, developing medicine, degradation, druggable technologies

INTRODUCTION

PROTACs are heterobifunctional molecules consisting of a POI ligand and an E3 ligase ligand linked by a linker. Function is determined by proximity-induced deterioration. The PROTAC attaches an E3 ligase (part of the UPS cascade) to the POI, generating a ternary complex. This complex mediates the transfer of ubiquitin chains (particularly K48-linked polyubiquitin chains) onto the POI, targeting it for irreversible degradation by the 26S proteasome. Importantly, the PROTAC is then liberated and catalytically recycled. This event-driven mechanism allows PROTACs to exert their functional effect via the total degradation of the target protein, thereby removing all its related activities, including non-enzymatic ones efficiency is dictated by the stability and cooperativity of the ternary complex, generally mediated via neocontacts, and may provide extremely selective degradation even with a broad-binding warhead.



Mechanism of Action:

Hijacking the Ubiquitin-Proteasome System (UPS)

1. Molecule Structure and Components

A PROTAC is a hetero bifunctional molecule with three components:

a. POI Ligand (Warhead) Selective binding to the protein of interest (POI), conferring target specificity.

b. E3 Ligase Ligand (Reclutador): E3 ubiquitin ligase binder.

c. Linker: Connects the two ligands and provides the right spatial positioning of the POI and E3 ligase to allow ubiquitination

Due to their structural complexity PROTACs typically fall into the beyond Rule-of-Five (bRo5) chemical space

Degradation Cascade PROTACs cause targeted protein degradation by hijacking the ubiquitin proteasome system (UPS)

A. Ubiquitination Enzymatic Process:

• E1 uses ATP to activate ubiquitin.

• E2 has the active ubiquitin.

• E3 ligase attaches ubiquitin to substrate; there are about 600 E3 ligases in humans.

B. Formation of Ternary Complex:

The PROTAC brings the POI and E3 ligase together to produce a stable POIPROTAC-E3 ternary complex.

C. Ubiquitylation:

The POI lysine residues are ubiquitinated by the E3 ligase. Further additions result in a K48-linked polyubiquitin chain, which marks the POI for destruction.

D. Proteasomal Degradation and Recycling:

The 26S proteasome then identifies the tagged POI and destroys it. The PROTAC is delivered intact and may frequently trigger fresh rounds of deterioration.

Structural Basis of Function:

Ternary Complex Dynamics and Neocontacts:

The stability and cooperativity of the ternary complex (TC) largely determine PROTAC efficiency, often outweighing the affinities of the individual ligands.

1. Structural Insights:

The first atomic-level PROTAC TC structure, MZ1, bound to VHL and the BRD4 bromo domain, showed that PROTACs induce new protein-protein and protein-ligand interactions at the interface.

• These interfaces exhibit strong surface complementarity (e.g., ~688 Aº) and are

Limitations of Traditional SMIs:

• SMIs depend on occupancy-driven pharmacology and require well-defined active pockets for high-affinity binding.

• Approximately 70-80% of human proteins lack such pockets, making them inaccessible to conventional small molecules

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How PROTACs Overcome These Barriers:

• PROTACs rely on proximity-induced degradation, not functional site inhibition.

• They require only any binding site on the POI, not a catalytic pocket.

• Even moderate or low-affinity ligands can be effective if they support ternary complex formation.

• Degradation results in the complete removal of the protein and all associated functions.

Examples of Previously Undruggable Targets Now Accessible:

• Transcription Factors: Proteins like MYC and STAT3 (e.g., SD-36 degrader) can now be selectively degraded.

Scaffolding/Regulatory Proteins: Nonenzymatic proteins such as FAK are now tractable targets.

Oncogenic Mutants: PROTACs have enabled new strategies against mutant oncoproteins, including KRAS

Mechanisms for Circumventing Resistance:

1. Complete Protein Removal: Degrading the entire POI prevents resistance caused by target upregulation or non-enzymatic (scaffolding/regulatory) functions.

.2. Mutation Tolerance: PROTACs only require transient binding to initiate degradation, making them less sensitive to point mutations that impair inhibitor occupancy.

.3. Use of Non-Inhibitory Ligands: Even loss of-function ligands or agonists can trigger Degradation.

4. Lower Drug Pressure: Catalytic activity and low dosing reduce evolutionary selection pressure for resistant mutations

CONCLUSION

The initial jump of PROTACs from the laboratory to the clinic in the last two decades has validated the theoretical potential of TPD as a therapeutic tool. But there are still many questions to be studied and answered.

An interesting direction for TPD development is the expansion of the POI spectrum. Conventional PROTACs have restricted POI to cytosolic proteins. However, many proteins that are important in cancer formation and metastasis are found on the cell membrane and serve as receptors. Researchers have tried to extend the POI scope to membrane-bound and circulating proteins, and even further, lipids and organelles by using autophagy and lysosomal processes.

Low bioavailability of most PROTAC compounds is another limitation for the deployment of PROTACs in clinical settings. The presence of three moieties in the structure means PROTACs are often associated with high molecular weights, making cell membrane penetration challenging.

To overcome this obstacle, researchers aim to use click chemistry, giving precursors of fully functioning PROTACs and self-assembling within cells.

Additionally, lysosome-based TPDs may cause the generation of endosomes and facilitate the degradation of POIs via the lysosomal route, and TPDs do not need to enter the cell to act on the destruction of membrane-bound or circulating POIs. Incidentally, these TPDs often have monoclonal antibody structures to bind target proteins, therefore an intravenous delivery must be taken into attention.

TPD may be used to non-oncology indications since it has the capacity to degrade any target of choice. An important feature of PROTACs, as mentioned earlier, is the capacity to breakdown “undruggable” proteins that lack active sites. This property is particularly interesting in targeting for numerous neurodegenerative disorders requiring toxic accumulation of proteins such as tau, mutant huntingtin, etc. Development of TPDs for inflammation, immunity-associated illnesses and viral infection are also underway.

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