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PROTACs and Molecular Glues: An overview

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Abstract
PROTACs (Proteolysis-Targeting Chimeras) and Molecular Glues are thoroughgoing small molecules that confiscate the cell's ubiquitin-proteasome system (UPS) to demean disease-causing "undruggable" proteins, opening new approach for cancer and other treatments. PROTACs are bifunctional degraders (ligand-linker-E3 ligase binder) with reasonable design, molecular glues (monovalent) persuade new PPIs, frequently discovered fortunately but progressively reasonably, with superior drug-like properties like oral bioavailability, both working by generating a ternary complex for protein demolition, with proceeding research focusing on linker optimization, AI-driven design, and get the better of restraints like the "hook effect" for superior clinical success.

Molecular Glues are small molecules with low molecular weight that proceed as a molecular bridge, ease interaction between a target protein and an E3 ubiquitin ligase to permit degradation without necessary classical binding pockets. PROTACs are heterobifunctional small molecules that concurrently captivate a target protein and an E3 ligase to persuade particular degradation through a catalytic mechanism. Both approach have extremely expanded the druggable proteome and carry considerable assurance for therapeutic interventions.

In cellular protein-degrading systems, K11, K48, and K63 included in ubiquitin linkages can act as degradative labels, namely K11 and K48 for proteasomal pathway and K63 for lysosomal pathway. The ubiquitination process, a step-wise enzymatic cascade involving ubiquitin activation, ubiquitin conjugation and ubiquitin ligation, includes all types of ubiquitinating enzymes.

This review furnishes a relative outline of Molecular Glues and PROTACs, involving their mechanisms, advantages and design principles.

Keywords: PROTACs, Molecular Glue, E3 ubiquitin ligase, lysosomal pathway, mechanism of action, advantages

Introduction

The term **PROTACs (proteolysis-targeting chimeras)** was invented by Sakamoto and coworkers in 2001 [1]. The original development of PROTAC degraders is constructed on the permanently founded knowledge that protein levels in the cell are organized through the action of the ubiquitin-proteasome system. This system degrades targeted proteins through substrate-specific ubiquitination and identification [2]. Ubiquitination includes three-step procedure that includes the proximity of three different enzymes: ubiquitin-activating enzymes (E1), followed by ubiquitin-conjugating enzymes (E2), and, finally, substrate-specific ligases (E3). Ubiquitination mechanism can be recycled to construct a poly-ubiquitin chain connected to the target protein, aligned the marked protein to the 26S proteasome [3].

This intracellular protein demolition process has been commandeered by PROTACs, which at the same time enlist the E3 ligase and the protein of interest, thus generating a favorable juxtaposition between this protein of interest and the E3 ligase [4]. PROTACs are thus bifunctional tiny molecules that can hold together both a given targeted protein to be degraded and a component of the ubiquitin-proteasome system. A single PROTAC molecule can degrade collective copies of its target protein, consequently making commensurate low concentrations of PROTACs required to attain an anticipated biological effect [5].

Advantages of PROTACs

1. The catalytic nature of PROTACs qualify efficacious action at low concentrations, contrasting with conventional small-molecule drugs that needs high stoichiometrically doses, possibly leading to unexpected side effects. [6]

2. PROTACs attain POI inhibition through degradation, needed new protein synthesis for improvement, providing longer-term efficacy contrast to conventional small-molecule drugs whose results decline with reducing plasma concentration. [7]
3. PROTACs only require a suitable surface-exposing lysine residue for ubiquitination and a warhead binding pocket, while conventional small-molecule drugs depend on high-affinity active binding sites. [8]
4. PROTACs can target conventionally undruggable proteins, such as scaffold protein and transcriptional factors, providing their ligands have been recognized. At the same time, conventionally druggable proteins are also manageable to PROTACs using corresponding small-molecule drugs as warheads. [9]

Molecular Glues

Molecular Glues are tiny, monovalent molecules that persuade or fix novel protein-protein interactions (PPI) between an E3 ubiquitin ligase and a protein of interest (POI). This imposed accessibility facilitates ubiquitination and proteasomal degradation of the POI, even in the non-appearance of classical ligand-binding pockets [9]. Most Molecular Glues were discovered opportunely, with thalidomide and its analogs helping as prototypical examples. [9]

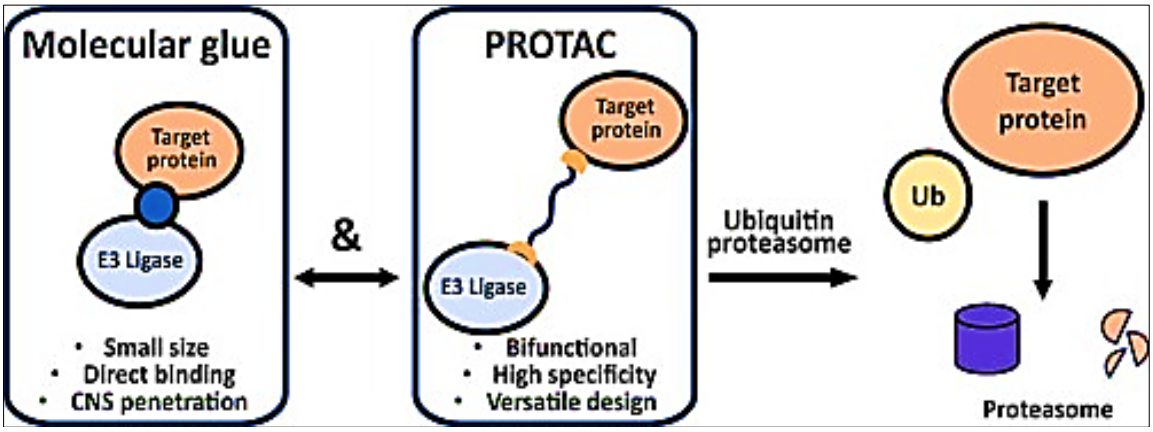

Fig 1: Structure of PROTACs and Molecular Glues (5)

Molecular glues embrace two vital categories: PPI stabilizers and chemical inducers of proximity (CIPs). (10) PPI stabilizers, a subcategory of PPI modulators, modulate PPI networks by increasing the thermodynamic stability of native PPIs. Particularly, paclitaxel embellishes this mechanism by stabilizing the microtubule interaction between α-tubulin and β-tubulin, hindering microtubule depolymerization and inducing mitotic arrest. [11] Phenothiazine drugs, trifluoperazine and prochlorperazine, disrupt S100 calcium binding protein A4 (S100A4)-myosin-IIA interaction by stabilizing S100A4 oligomers, inhibiting S100A4 activity, and hindering analogous diseases. [12]

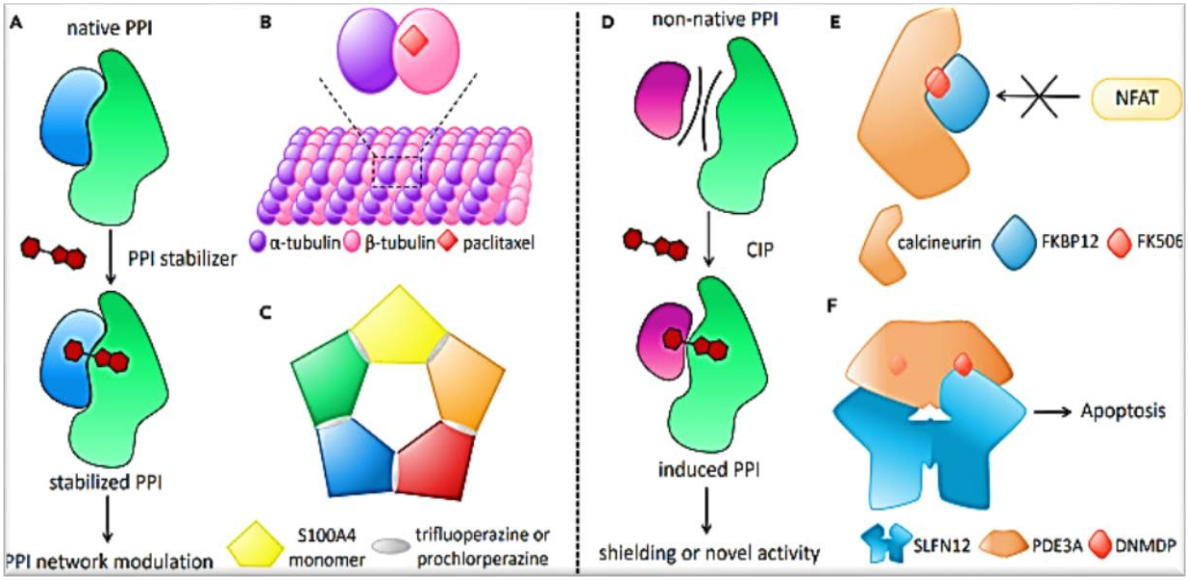

Fig 2: Schematic representation of molecular glues [10]

Molecular glues are suitable to increase pre-existing surface alignment between an E3 ligase and a target protein to induce its degradation following ubiquitination. This mechanized discernment into thalidomide activity corroborates the discovery that this drug and its congeners are efficient of evolving antitumoral activity in multiple myeloma as molecular glues, prompting the degradation of transcription factors IKZF1 and IKZF3 [13]. Lenalidomide, a derivative of thalidomide, constructs the backbone of treatments for multiple myeloma and myelodysplastic

syndrome [8]. Structural biology research has disclosed that the site of fixation for thalidomide and its derivatives on the transcription factors at first recognized as their chief targets is also present in other proteins, thus enlarging the area of prospective targets for this category of molecular glues [14].

Mechanism of action of PROTACs

In eukaryotic cells, protein elimination happens through either the proteasomal or lysosomal pathway. The previous essentially degrades intracellular proteins, enclosing defaced, misfolded, and nonfunctional proteins. This is responsible for detaching long-lived, extracellular, membrane-located proteins, additionally insoluble protein aggregates. Lysosomal pathways govern the ejection of other biomacromolecules and defaced organelles [15]. UPS orchestrates protein ejection, containing of ubiquitin, ubiquitin-activating enzymes (E1s), ubiquitin-conjugating enzymes (E2s), ubiquitin ligases (E3s), and the proteasome. Ubiquitin is a 76-amino acid protein with seven lysine residues. Particularly, in cellular protein-degrading systems, K11, K48, and K63 included in ubiquitin linkages can act as degradative labels, namely K11 and K48 for proteasomal pathway and K63 for lysosomal pathway [16].

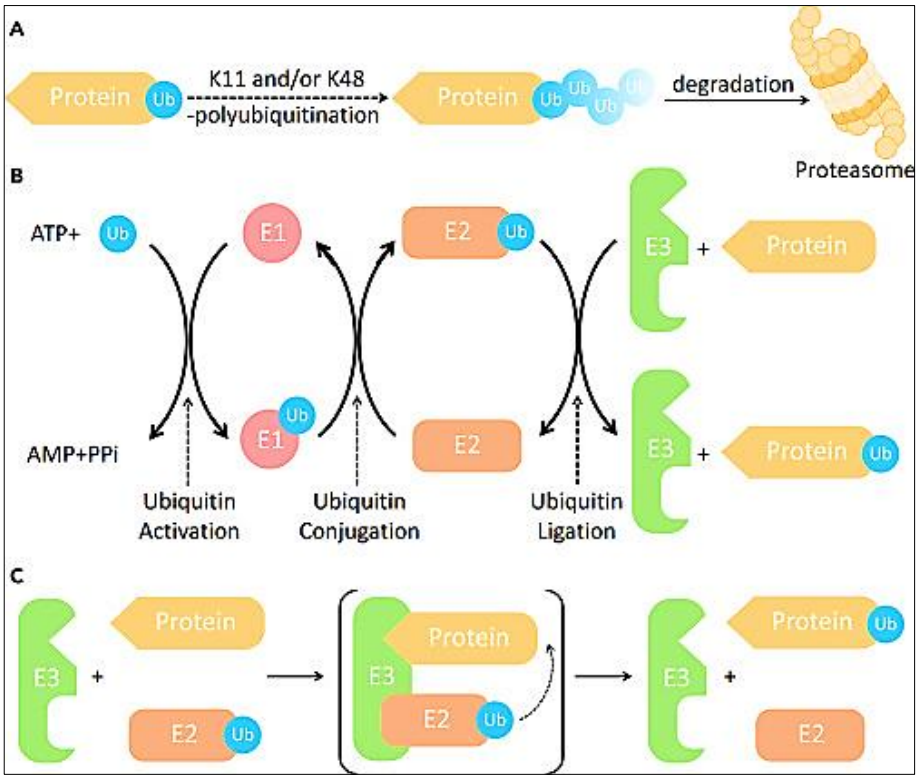

Fig 3: Schematic representation of ubiquitin-proteasome system [14]

The ubiquitination process, a step-wise enzymatic cascade involving ubiquitin activation, ubiquitin conjugation and ubiquitin ligation, includes all types of ubiquitinating enzymes as shown in Figure [17]. Ubiquitin is operated by E1 in an ATP-dependent manner, and then the operated ubiquitin is transferred from E1 to E2. In the concluding step, the E3 ligase binds concurrently to the ubiquitin-carrying E2 and its substrate protein and catalyzes the transfer of ubiquitin from E2 to the substrate proteins [16] The ubiquitin transfer process differs with the type of E3 ligases. [16] The E3 ligases can be classified into four types; specifically homologous to E6AP C-terminus (HECT) type, actually interesting new gene (RING) type, U-box type, and RING-between-RING (RBR) type; among which RING type E3 ligases are the vital type. For RING type and U-box type E3 ligases, the ubiquitin is transferred from E2 to the substrate protein directly and for HECT type and RBR type E3 ligases, the ubiquitin is first transferred to a catalytic cysteine on the E3 ligase and the RING2 domain individually, then to the substrate protein [18]. By utilizing molecular glues to alter the binding preferences of E3 ligases, a non-native PPI between E3 ligase and a neo-substrate can be persuaded, possibly reprogramming the E3 ligases for the ubiquitination of a pathology-analogous protein. [19]

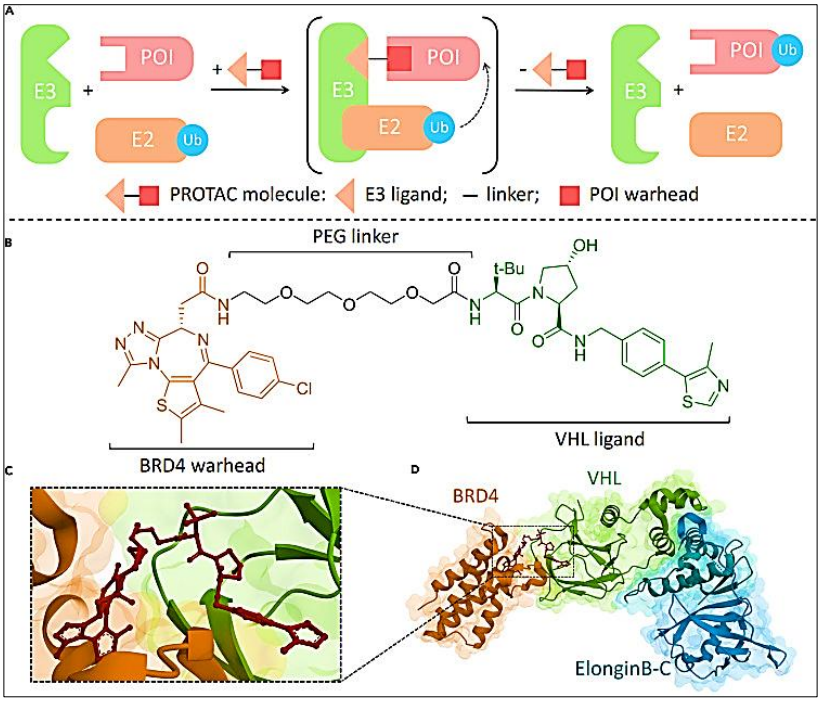

Fig 4: Illustration of the mechanism of action of PROTACs [19]

When a PROTAC molecule binds to the corresponding E3 ligase and the POI with the ligand and the warhead, an E3-PROTAC-POI ternary complex is formed. Subsequently, the POI undergoes ubiquitination by the E3 ligase, leading to its proteasomal degradation. The removal of POI induced by PROTAC results in the inhibition of its function. Notably, the formation of the E3-PROTAC-POI ternary complex in this process is reversible, making the ubiquitination of the POI catalytically induced by the PROTAC molecule [20].

Mechanism of action of Molecular Glues

Molecular glue degraders managed by persuading the interaction between E3 ligase and the protein of interest (POI). The generation of the E3-molecular glue degrader-POI ternary complex brings the E3 ligase and POI into juxtaposition, commencing POI ubiquitination and successive proteasomal degradation [21] Molecular glue degraders persuade PPI in a different manner. A standalone molecular glue degrader molecule may only have an empathy for either the E3 ligase or the POI. [22] The molecule first binds to the communicating protein with which it has high strength. Eventually, the enduring part of the molecule revealed outside the binding pocket generates a new interaction surface with the surrounding residues to enlist the other partner of the PPI. [23] Likely, lenalidomide, a compound presenting a phthalimide ring and a glutarimide ring persuades the interaction between CRBN and casein kinase 1α (CK1α) [24]. The glutarimide ring of lenalidomide binds to a hydrophobic pocket on CRBN's surface, while the revealed phthalimide ring of lenalidomide creates an interaction surface together with the surrounding residues of CRBN, which is harmonizing to a β-hairpin loop of CK1α and able to enlist CK1α to create CRBN-lenalidomide-CK1α ternary complex [25]

Conclusion

PROTACs, UPS-based technique, have initiated three generations of development. These challenges can be overcome by requiring further survey of rational design and optimization principles and the development of novel E3 ligase-based PROTACs. PROTAC molecules usually face the provocation of cell permeability and oral bioavailability due to their bigger size. Molecular glues are little and have some superiority over PROTAC molecules; though, they are additionally strenuous to logically design. Second, the supply of E3 ubiquitin ligase. Third, toxicity. PROTAC could consequence in extra toxicity than small molecular inhibitors because they debase whole targeted proteins, preferably than simply inhibit them. Molecular glue degraders, sharing way indistinguishable with conventional small-molecule drugs, have superiority in molecular weight. Notwithstanding the freshly evolved molecular glue degraders entering clinical trials for cancer treatment, the absence of reasonable design principles obstructs molecular glue degrader development, involving further investigation in this area. Molecular glues comprise a novel class of small-molecule drugs, giving a targeted degradation approach for inhibiting pathology-related proteins. This study allows molecular glue degraders to accomplish prolonged inhibition distinction to conventional occupancy-driven methods. Their catalytic mechanism be allowed inhibitory effects at less concentrations, decreasing side effects and acquired resistance during expanded administration. Molecular glues defeat the limitations of conventional small-molecule drugs, building many regularly undruggable proteins achievable. The molecular glue-mediated targeted protein degradation study clasps affirmation for treating diseases associated with uncontrollable proteins.

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Conflict of Interest

No

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