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Protein Degraders and Cancer Treatment

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Abstract

Targeted Protein Degradation (TPD) represents a promising approach in cancer therapeutics. It offers a precise mechanism for eliminating disease-driving proteins. Unlike traditional inhibitors, TPD utilizes small-molecule degraders, such as PROTACs (Proteolysis Targeting Chimeras) and molecular glue degraders, to hijack the ubiquitin-proteasome system (UPS) for protein disposal. This strategy has shown particular promise in hematologic malignancies like multiple myeloma, where degradation of key transcription factors such as IKZF1/3 enhances tumor regression and immune modulation. Novel Cereblon E3 Ligase Modulators (CELMoDs), including Mezigdomide (CC-92480), Iberdomide (CC-220), and CFT-7455, demonstrate improved potency and selectivity, overcoming resistance to existing immunomodulatory drugs.

Abbreviation: TPD:Targeted protein degrader; IMiDs: immunomodulatory drugs; SERDs: selective estrogen receptor degraders; PROTACs: proteolysis-targeting chimeras; UPS: the ubiquitin–proteasome system; CELMoDs: Cereblon E3 Ligase Modulatory Drugs

Keywords: Protein degrader; Cereblon; Immunomodulatory drugs; Mezigdomide

Introduction

Targeted protein degraders (TPD) are an emerging promising therapeutic approach in cancer treatment. They selectively degrade disease-causing proteins. Historically, they can modulate 'undruggable' non-enzyme proteins for cancer treatment [1]. Targeted protein degraders have potential advantage over anticancer-targeted therapies which have mostly occupancy-driven catalytic activity. Anticancer-targeted therapies inhibit several kinases implicated in cancer. However, the inhibition of many cancer-related targets is difficult because they are non-enzyme proteins without active sites for small molecules. The number of targeted proteins used in cancer treatment exceeds the number of currently developed drugs for cancer therapy. There is a need for discovery of new drugs that target non-enzyme proteins [1].

TPD categories

based on the location of the degraded target proteins in the cells, TPD are categorized into either intracellular (iTPD) or extracellular (eTPD) protein degraders [2].

Intracellular protein degraders (iTPD)

iTPD degrades intracellular proteins utilizing the ubiquitin-proteasome system (UPS) primarily. Another distinct class is the autophagy-lysosome system [2].

Ubiquitin–proteasome-based system (UPS)

Its ability to induce protein ubiquitination is vastly different. However, they degrade target proteins in a similar manner. This enables distinct clinical applications. The iTPD therapies consists of three main classes based on their molecular structure and their mechanisms of action [1]. These three classes are

i. Immunomodulatory drugs (IMiDs). They acts as 'molecular glue'. They bind to cereblon (CRBN), reshape its surface to recruit unpredictable proteins and induce their degradation via the UPS.

ii. Selective estrogen receptor degraders (SERDs)

iii. PROteolysis-TArgeting Chimera (PROTACs). A synthetic

degrader molecule comprising two ligands. One binds to a protein of interest (POI) while the other recruits an E3 ubiquitin ligase. The POI– PROTAC–E3 ligase ternary complex transfer ubiquitin from E2 to the target protein. The proteasome then degrades the polyubiquitin-labeled POI. The PROTAC is recycled to degrade continuously the POI through this catalytic mechanism [1]. Many PROTAC degraders are available for a wide range of targets, particularly proteins involved in the pathogenesis of severe diseases, especially cancers [2].

The autophagy-based degraders

the protein of interest (POI) is degraded mainly by the autophagy-lysosome system degrade instead of the UPS system. AuTophagosome-TEthering Compounds (ATTECs), AUtophagy-TArgeting Chimeras (AUTACs), and AUTOphagy-TArgeting Chimeras (AUTOTACs) are examples of this group. The autophagosome-lysosome pathway degrades pathogenic protein aggregates, of large size which are inapplicable for proteasome-dependent iTPD [2].

Extracellular TPD (eTPD)

In this technique, lysosome selectively degrade the extracellular proteins [2]. LYsosomal TArgeting Chimeras (LYTACs) is the prototypic of this technology. It links the secreted or membrane-associated extracellular target proteins to lysosome-targeting receptors (LTRs) on the cell surface. The resulting complex is then internalized by endocytosis and trafficked to lysosomes. The target protein is degraded in the lysosomes. LYTACs can eliminate various extracellular proteins including important targets that drive tumor growth and dissemination [2].

Challenge of drug resistance to protein-degrading drugs

Resistance to protein-degrading drugs may develop. An example of this challenge is the emergence of resistance to thalidomide analogues. Thalidomide analogues resistance is mediated through either CRBN or non-CRBN mechanisms. In CRBN-mediated mechanisms of resistance, malignant cells develop resistance by upregulating either competing unrelated substrates or by upregulating target substrates like IKZF1 and IKZF3, relying on increased CRBN availability. In non-CRBN-mediated mechanisms, resistance is mediated through immune and tumour microenvironmental interactions [3].

Major targets of action in TPD techniques

Hematologic malignancies are an example of diseases that have many targets still in need to be targeted by effective approaches. Targeting undruggable proteins without binding pockets or enzyme activity, target proteins with drug resistance mutations and others by TPD techniques can lead to potential improvement in the current therapeutic dilemma. These primaries include [4]:

- Ikaros (IKZF1) and Aiolos (IKZF3) transcription factors: representative drugs are CC-122C, C-99282, CC-92480, CC-220, CFT-7455 and ICP-490.
- G1 to S phase transition 1 (GSPT1): representative drugs are CC-885, CC-90009 and J6968
- c-Myc: representative drugs are GT19630 and GT19715
- Signal transducer and activator of transcription 3 (STAT3): representative drugs are SD-36 and KT-333
- Bruton's tyrosine kinase (BTK): representive drugs are NX-2127, NX-5948 and BGP-16673.
- BCR-ABL: representative drug is PMIBcr/Abl-R6 PROTAC.
- B-cell lymphoma-extra-large (BCL-XL): representative drug is DT-2216.
- Other targets are MDM2, FLT3, HPK1, MEK1/2, PDE6D and CK1α

TPD and multiple myeloma

TPD is an emerging new therapeutic option in the treatment of myeloma particularly relapsed or refractory MM patients. The US Food and Drug Administration (FDA) has approved thalidomide and its derivatives lenalidomide and pomalidomide for the treatment of multiple myeloma and other hematological disorders. These three degrader drugs belong to the molecular glues class. Their mechanism of action was degradation of Ikaros and Aiolos transcription factors by inducing their interaction with the cereblon (CRBN) component of the E3 ubiquitin ligase complex. Treatment of myeloma patients with IMiD for an extended period of time can lead to the development of drug resistance and tumor recurrence due to CRBN downregulation [4]. New TPD drugs degrade the pathogenic proteins associated with tumorigenesis and can inhibit myeloma growth and proliferation effectively. Examples of TPDs of notable value in myeloma are CC-92480, CC-220, CFT-7455, ICP-490. The most commonly observed side effects during treatment with CC-92480 and CC- 220 are grade 3/4 neutropenia, anemia and thrombocytopenia [4].

CC 92480 (Mezigdomide)

It is designed for treating relapsed/refractory multiple myeloma. It induces maximal degradation of IKZF1/3 [4]. It mediates its effects through tumor killing and immunostimulation which are higher than that of IMiD. Being CELMoDs, it activates and expands natural killer cells and T-cells as a possible contributing factor to overcome thalidomide analogue resistance [3]. It is evaluated with DEX alone or combination of bortezomib and dexamethasone in previous clinical trials. It also acts synergistically with DEX, bortezomib, daratumumab and elotuzumab [4].

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CC 220 (Iberdomide)

CC-220 affinity to CRBN is about 20 times higher than that of traditional IMiDs. It effectively degrades IKZF1/3. Its IKZF1/3 degradation effect is increased by increasing CC 220 concentrations. Its antimyeloma effect is exerted through cell killing effects. Other effects are anti-proliferative mediated by IKZF1/3 degradation, and stimulation of T and NK cells immunoreactivity. It mediates degradation of IKZF1/3 in B cell lymphoma (like DLBCL and FL). Previous research showed that treatment of patients with relapsed or refractory myeloma with CC-220 and DEX combination has ORR of 31.9% [4].

CFT 7455

The affinity of CFT-7455 for CRBN is 800–1600 times higher than pomalidomide. It mediates rapid and sustained degradation of IKZF1/3 in a preclinical model compared to CC-92480. It maintains its activity in models of IMiDs resistance or insensitivity [4].

ICP 490

ICP-490 selectively and potently degrades IKZF1/3 while spares IKZF2, IKZF4, GSPT1, PLZF1, and SALL4. Its therapeutic efficacy is superior to currently approved IMiDs in various models of MM and NHL. Its effectiveness and safety in relapsed or refractory MM are currently evaluated in clinical trials (NCT05719701). It is not cytotoxic to PBMC and other normal human cells [4].

Conclusion

Ongoing clinical trials explore the efficacy of TPD in combination therapies, offering a new hope for relapsed or refractory diseases patients. Future research aims to refine TPD's specificity, optimize drug design, and expand its applications beyond oncology especially in neurodegenerative and inflammatory conditions.

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