PROTAC degraders with ligands recruiting MDM2 E3 ubiquitin ligase: an updated perspective

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ABSTRACT

Mouse double minute 2 (MDM2) is an oncogenic E3 ligase that effectively degrades the tumor suppressor p53. In the past two decades, many MDM2 inhibitors that disrupt MDM2-p53 binding have been discovered and developed. Given that MDM2 and p53 form an auto-regulatory loop, in which p53 undergoes targeted degradation as a substrate of MDM2, and p53 targets MDM2 for transcriptional upregulation, these MDM2 inhibitors have limited efficacy. After rapid in vivo clearance of the MDM2 inhibitors, p53 is degraded by accumulated MDM2. Fortunately, proteolysis targeting chimeras (PROTACs), a novel therapeutic strategy, overcome the limitations of MDM2 inhibitors. Several MDM2 inhibitors developed in the past two decades have been used in PROTAC technology in two applications: 1) binding and targeting endogenous MDM2 for PROTAC-based degradation and 2) binding endogenous MDM2 as a PROTAC E3 ligand for PROTAC-based degradation of other oncogenic proteins. In this review, we summarize current progress in the discovery and development of MDM2-based PROTAC drugs, and discuss future perspectives and challenges in their application as effective treatments for human cancer.

Keywords: MDM2, E3 ligase ligand, PROTAC, degradation, human cancer, drug discovery

1. INTRODUCTION

The p53 tumor suppressor is a potent transcription factor with key roles in cancer prevention [1, 2]. After activation by a variety of internal or external stresses, p53 induces either growth arrest if the damage is repairable or apoptosis to eliminate cells incapable of repair [3, 4]. The loss of p53 tumor-suppressor activity through point mutations or gene deletions, as frequently seen in many human cancers, prevents p53 from acting as a genome guardian and enables the abnormal proliferation of cells carrying damaged genomes [5]. Such uncontrolled proliferation leads to cancer development. Thus, restoring p53 activity or function in cancer cells has been a longstanding goal in the field of cancer drug discovery [6].

MDM2 has been well characterized as a negative regulator targeting p53 direct binding to promote subsequent p53 ubiquitination [7]. A variety of stress signals disrupt the MDM2-p53 interaction, thus leading to p53 activation, and cellular responses such as growth arrest and apoptosis induction [8, 9]. MDM2 effectively inactivates p53 through three general mechanisms [10-12]: 1) MDM2 directly binds the transcriptional activation domain of p53 and inhibits p53-mediated transcriptional activation; 2) MDM2’s nuclear export signal sequence induces p53 nuclear export after binding, thereby preventing p53 from binding target DNA; and, in the most effective mechanism, 3) MDM2 acts an E3 ubiquitin ligase promoting the ubiquitylation and degradation of p53. Thus, in the past two decades, disruption of the MDM2-p53 interaction has become an effective strategy for the discovery and development of potent MDM2 inhibitors that disrupt MDM2-p53 binding, and stabilize and restore p53 function, for the treatment of human cancers with wild-type p53 [13-16].
Table 1 | Summary of MDM2 inhibitors and degraders

| No. | Name          | Structure | Category | E3 ligase ligand | Target protein |
|-----|---------------|-----------|----------|------------------|----------------|
| 1   | Nutlin-3      | ![Nutlin-3](image1) | Inhibitor | --   | --             |
| 2   | RG7388        | ![RG7388](image2) | Inhibitor | --   | --             |
| 3   | RG7112        | ![RG7112](image3) | Inhibitor | --   | --             |
| 4   | MI-77301/     | ![MI-77301](image4) | Inhibitor | --   | --             |
|     | SAR405838     |           |          |                  |                |
| 5   | HDM201        | ![HDM201](image5) | Inhibitor | --   | --             |
| 6   | DS-3032b      | ![DS-3032b](image6) | Inhibitor | --   | --             |
| 7   | APG-115       | ![APG-115](image7) | Inhibitor | --   | --             |
| 8   | MK-8242       | ![MK-8242](image8) | Inhibitor | --   | --             |
| No. | Name   | Structure | Category | E3 ligase ligand | Target protein |
|-----|--------|-----------|----------|------------------|----------------|
| 9   | NVP-CGM097 | ![NVP-CGM097](image) | Inhibitor | --               | --             |
| 10  | AMG-232 | ![AMG-232](image) | Inhibitor | --               | --             |
| 11  | WB214  | ![WB214](image) | Degrader  | CRBN             | MDM2           |
| 12  | TW-32  | ![TW-32](image) | Degrader  | CRBN             | MDM2           |
| 13  | MD-224 | ![MD-224](image) | Degrader  | CRBN             | MDM2           |
| 14  | MG-277 | ![MG-277](image) | Degrader  | CRBN             | MDM2           |
| 15  | –      | ![–](image) | Degrader  | Nutlin-3         | AR             |
| 16  | A1874  | ![A1874](image) | Degrader  | RG-7388          | BRD4           |
In the past two decades, PROTAC strategies have gained momentum and shown promise in the discovery and development of new types of small-molecule therapeutics by inducing targeted protein degradation [17-22]. A PROTAC molecule consists of three components [23-27]: 1) a small molecule that specifically binds targeted proteins; 2) another small molecule or peptide that binds an E3 ligase as an E3 ligand; and 3) a chemical linker that connects the first two components. To date, PROTAC technology has been used to target various proteins, including transcription factors, skeleton proteins, nuclear receptors, enzymes, and regulatory proteins [28-37]. In cancer therapy, many studies have shown that degrading a protein is more effective than inhibiting it [38-41].

In this review, we describe a battery of MDM2 inhibitors, and discuss how some of these inhibitors are used to accumulate several MDM2-recruiting PROTAC degraders (Table 1) that 1) disrupt MDM2-p53 binding and stabilize p53, and 2) act as E3 ligand components of PROTACs for the degradation of other targeted oncogenic proteins (Figure 1).

### 2. MDM2 INHIBITORS

The MDM2 E3 ubiquitin ligase is overexpressed in several human cancers, particularly soft-tissue sarcomas [42-45]. MDM2’s main function is ubiquitylating the tumor suppressor p53, thus targeting it for proteasomal degradation; therefore, MDM2 acts as an oncogenic protein promoting tumorigenesis [46]. Targeting MDM2 via disrupting MDM2-p53 binding has therefore been found to be an effective approach for p53 activation and targeted anti-cancer therapy [47]. Many small-molecule inhibitors targeting the p53-MDM2 protein-protein interaction have been discovered in past two decades, starting with nutlin-3 [2]. Several inhibitors are currently in clinical development, and may be effective in the treatment of cancer and other related diseases; these include RG7388 (NCT02407080) [48], RG7112 (NCT01605526, NCT01143740, and NCT01677780) [49, 50], SAR405838 (NCT01636479 and NCT01985191) [5, 51, 52], HDM201 (NCT02143635 and NCT02343172) [53-55], DS-3032b (NCT01877382, NCT02579824, NCT02319369, and NCT03634228) [56, 57], APG-115 (NCT03781986 and NCT02935907) [58, 59], MK-8242 (NCT01451437 and NCT01463696) [60-62], NVP-CGM097 (NCT01760525) [63-65], and AMG-232 (NCT03217266, NCT03107780, NCT03041688, and NCT03031730) [66-68] (Figure 2 and Table 1).

Although MDM2 targets p53 as a substrate for targeted degradation, MDM2 itself is a p53 target affected by p53 upregulation [69]. This auto-regulatory feedback loop compromises the therapeutic effects of
MDM2 inhibitors: disruption of MDM2-p53 binding results in the accumulation of free p53, which trans-activates MDM2 and causes MDM2 accumulation; subsequently, p53 is degraded after MDM2 inhibitors are rapidly cleared in vivo. In fact, studies have shown that p53 protein accumulates in xenograft tumor tissue for only several hours after a single dose of MDM2 inhibitor is administered. Furthermore, the accumulation of MDM2 protein in normal tissues may have deleterious effects, because MDM2 is itself oncogenic [5]. To overcome these potential drawbacks of MDM2 inhibitors, new strategies are needed to target MDM2 more effectively.

3. PROTACS AND MDM2-ASSOCIATED DEGRADERS

Targeted protein degradation (TPD) via the ubiquitin-proteasome system has received substantial interest among medicinal chemists and biologists, and is an emerging direction in the field of drug development [70-73]. Bi-functional molecules called proteolysis-targeting chimeras (PROTACs) have been developed, which hijack the cellular ubiquitin-proteasome system and consequently degrade disease-related target proteins [74-77]. Structurally, PROTACs are new chimeric molecules consisting of three components: one end binds the target protein, also known as the protein of interest (POI), and is connected by a linker to the other end, which acts as a ligand for E3 ubiquitin ligase recruitment (Figure 3) [78, 79].

After multiple rounds of recruitment of ubiquitin to a target protein and polyubiquitination of the target, the PROTAC-target molecule is recognized by the 26S proteasome, which catalyzes target degradation [80]. The PROTAC molecule is then recycled for the next round of POI targeting. Thus, PROTACs act as small-molecule drugs that target POIs through an “event-driven” mode rather than an “occupation-driven” mode [81, 82]. The advantages of PROTAC molecules include their...
ability to overcome drug resistance and target undruggable targets with low toxicity, and high efficiency and selectivity [83, 84]. Notably, drug resistance eventually develops to varying degrees after the clinical use of almost all traditional small-molecule drugs. PROTACs effectively overcome this problem via degrading the target proteins. Furthermore, whereas most traditional small-molecule drugs work by binding the active site of an enzyme or receptor, PROTACs work efficiently as long as effective binding to POIs occurs at essentially any site (Figure 3).

The human genome encodes more than 600 E3 ligases, but only a small fraction have been used in designing PROTACs to date, including Cereblon (CRBN), von Hippel-Lindau (VHL), MDM2, and cellular IAP1 (cIAP1) [85-87]. Two types of MDM2-associated PROTAC degraders have been developed. One type recruits an MDM2 inhibitor as an MDM2-binding partner, thus resulting in MDM2 degradation. The second type recruits MDM2 as an E3 ligand to target other POIs for degradation, although these degraders are less effective than those recruiting CRBN and VHL.

4. PROTAC DEGRADERS TARGETING MDM2

The first type of PROTACs, based on nutlin or idasanutlin (RG7388), was developed with the representative CRBN-based MDM2 degraders shown in Figure 4. However, the number of these MDM2 degraders remains limited, owing to their challenging physicochemical profiles and limited degradation activity (e.g., WB214 and TW-32) [88]. Recently, the Wang group has reported a series of potent PROTAC MDM2 degraders, including MD-224 as a lead compound targeting the MDM2 protein to CRBN for degradation (Figure 4) [33]. MD-224 effectively and rapidly degrades MDM2 in leukemia cells. Intravenous
administration of MD-224 has achieved complete and durable tumor regression in an RS4-11 xenograft model. Moreover, MD-224 inhibits the growth of only leukemia cells carrying wild-type p53, not p53 mutants. The Wang group has reported additional analogues based on the previously reported PROTAC MDM2 degrader MD-224. Interestingly, MG-277, an analogue of MD-224, unexpectedly has shown conversion of the PROTAC into a
5. PROTAC DEGRADERS RECRUITING MDM2 TO TARGET OTHER POIs

5.1 MDM2-based PROTAC AR degrader

Nutlin-3 is a potent MDM2 inhibitor that binds the p53-binding pocket of MDM2 [90]. Interestingly, nutlin-3 has also been used for the design of the second type of PROTACs recruiting endogenous MDM2 for targeting androgen receptor (AR), by the Crews group in 2008 [91]. This was the first report of an all-small-molecule PROTAC degrader, consisting of an AR antagonist and the nutlin motif, which disrupts the interaction between MDM2 and p53 without affecting the E3 ligase activity of MDM2. Specifically, this first synthetic all-small-molecule PROTAC AR degrader is a heterobifunctional compound consisting of a bicalutamide analogue (non-steroidal androgen receptor ligand) and MDM2 inhibitor joined by a PEG-based linker (Figure 5, compound 15). This cell-permeable PROTAC successfully recruits AR to MDM2 for ubiquitination and proteasomal degradation, but has relatively weak potency [91].

RG7388, another typical MDM2-p53 inhibitor, has also been found to bind MDM2 and has been used in PROTAC design [92]. However, the poor physiochemical properties of nutlin-3 have been exacerbated after incorporation into PROTACs. Recent efforts have identified that MDM2-p53 PPI inhibitors with better solubility and activity may broaden the applications of MDM2 in PROTACs (Figure 6) [92-94].

5.2 MDM2-based PROTAC BRD4 degrader

Recently, numerous BET PROTAC degraders have been generated and tested in vitro and in vivo [95, 96]. Various E3 ligases, including VHL, CRBN, IAP, MDM2, aryl hydrocarbon receptor (AHR), DDB1-cullin 4 associated factor 16 (DCAF16), RING finger protein 114 (RNF114), and RNF4, have been used as E3 ligands to degrade BET proteins [81, 96-102]. In 2019, the Crews group reported an MDM2/nutlin-based BRD4 PROTAC (compound 15,
A1874 [92], which not only degrades BRD4 protein but also stabilizes the p53 gene, thus eliciting strong anti-proliferative effects in several tumor cell lines, such as myeloid leukemia cells (Figure 7). Moreover, this compound increases p53 levels in HCT116 colon cancer cells with wild-type p53, owing to the activity of RG7338 against MDM2. A1874 potently inhibits the proliferation of p53-wild-type cancer cells, presumably through dual inhibition of BRD4 and MDM2.

5.3 MDM2-based PROTAC PARP1 degrader

PARP1 poly(ADP-ribose) polymerase is a ubiquitously expressed DNA-dependent nuclear poly(ADP-ribosyl) transferase that regulates multiple nuclear events, such as transcription, rRNA biogenesis, and DNA repair [103, 104]. Because of its essential role in the DNA-damage response, PARP1 is considered a potent cancer therapeutic target. Several PARP1 inhibitors, such as niraparib, iniparib, and olaparib, are in various stages of clinical development; however, cytotoxicity and drug resistance are the primary problems restricting their clinical use [105, 106]. Thus, additional therapeutic methods to overcome these obstacles are required.

In 2018, the Rao group reported the first PARP1-targeting PROTAC by linking the PARP1 inhibitor niraparib and the MDM2 inhibitor nutlin-3. Compound
was obtained after detailed degradation screening in several triple-negative breast cancer cell lines (Figure 8) [94]. Impressively, compound 17 selectively induces substantial PARP1 degradation and cell apoptosis in MDA-MB-231 cells and has fivefold more potent anti-proliferative activity than the PARP1 inhibitors niraparib, olaparib, and veliparib, without showing cytotoxicity in normal cells.

### 5.4 MDM2-based PROTAC homo-MDM2 degrader

Inspired by previous efforts to design small molecules targeting the MDM2-p53 interaction, the first homo-PROTAC, targeting MDM2 by inducing its self-degradation has recently been reported by the Sheng group (Figure 9) [93]. Compound 18 efficiently induces MDM2 dimerization with highly competitive binding activity, and induces proteasome-dependent self-degradation of MDM2 in A549 non-small cell lung cancer cells. Impressively, compound 18 has been found to effectively inhibit tumor growth in a xenograft mouse model derived from A549 cells, thus providing the first demonstration of the in vivo efficacy of homo-PROTAC, which may serve as an alternative therapeutic tool for effective targeting of human cancers with overexpressed MDM2.

### 5.5 MDM2-based PROTAC EGFR degrader and TrkC degrader

In 2020, the Ding group reported a series of PROTAC EGFR degraders based on different E3 ligase ligands, one of which was the MDM2 inhibitor RG7388 [107]. Compound 19 elicits moderate degradation of an EGFR(L858R/T790M) mutant (Table 1). In 2019, the Burgess group reported a class of TrkC-targeted kinase PROTACs formed through linking the TrkC-targeted kinase inhibitor IY–IY and the MDM2 ligand nutlin-3 [108]. However, compound 20 has very weak potency in degrading TrkC protein (Table 1).

All 20 compounds described herein are summarized in Table 1.

### 6. SUMMARY AND OUTLOOK

As the third decade of research on TPD strategies begins, following the first report in 2001 [109], PROTACs are expected to remain at the forefront of research on targeted degradation of POIs, and have begun to transition from vertical to horizontal development. A variety of TPD technologies have been discovered and developed, including photo-controlled PROTACs, homo-PROTACs,
Figure 8 | Schematic design of an MDM2 (nutlin-3a)-based PROTAC PARP1 degrader. A) Structure of PARP1 inhibitors and the crystal structure of niraparib bound to the PARP1 catalytic domain (PDB code: 4R6E). A click-chemistry strategy was used to construct the PROTAC candidates targeting PARP1. B) Structure of the MDM2 inhibitor nutlin-3a and its crystal structure with MDM2.

Figure 9 | Homo-PROTAC design strategy. A) Chemical structures of nutlin-3. B) Binding model of nutlin-3 with MDM2 (PDB: 4IPF).
covalent PROTACs, dual-PROTACs, antibody-PROTACs, lysosome-targeting chimeras (LYTACs), autophagy-targeting chimeras (AUTACs), and peptide-based PROTACs [110–115]. MDM2-based PROTACs selectively bind the p53 site on the surface of MDM2, thereby stabilizing p53 and degrading target proteins with favorable anti-cancer activity. However, the major bottleneck in the development of effective PROTAC drugs lies in achieving good oral bioavailability, given that PROTAC molecules are beyond the “Lipinski’s rule of 5” for small-molecule inhibitors, owing to their relatively high molecular weight, poor solubility (logP), high topological polar surface area and other poor physicochemical properties. Compounds with favorable physicochemical properties, such as lower molecular weight (<800 Da), good water solubility, ideal topological polar surface area, and fewer aromatic groups, must be discovered to increase oral bioavailability. The application of molecular glue may serve as an effective approach [116, 117]. The second challenge is to develop more effective E3 ligases to act as ligands for PROTACs, given that the human genome encodes more than 600 E3 ligases. Currently, several orally administered PROTAC drugs are in clinical trials for cancer treatment [19, 21, 22, 118, 119]. The knowledge gained from basic research and clinical trials in combination with technological development is expected to further advance the field of cancer therapies based on PROTAC strategies.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest in this work.

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