Acta Pharmaceutica Sinica B 2025;15(9):4964−4966

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

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HIGHLIGHT

Chemical and genetic molecular glues to degrade CoREST corepressors

KEY WORDS

UM171;
Molecular glue;
KBTBD4;
CUL3-RING E3 ubiquitin ligase;
HDAC1/2;
CoREST corepressors

Targeted protein degradation (TPD) technology mainly utilizes the natural degradation systems within cells to specific and efficient degradation of disease-related proteins[1]. The ubiquitin−proteasome system (UPS) is the most important way of protein degradation in eukaryotic cells, which is involved in more than 80% of degradation processes[2]. Molecular glues are mostly small molecules to stabilize existing interactions between two proteins or induce new protein−protein interactions[3]. In the case of molecular glues between the target protein and an E3 ligase, the formation of a ternary complex facilitates the transfer of ubiquitin from the E2 conjugating enzyme to the target protein, which is subsequently recognized and degraded by the proteasome[4].

Recently, chemical and genetic molecular glues, UM171 and KBTBD4 cancer mutations, were discovered by the research groups of Ning Zheng and Brian B. Liau and published in *Nature*[5,6]. These glues were found to facilitate the degradation of CoREST corepressors (Fig. 1). UM171 functions as a chemical glue that enhances the interaction between KBTBD4 and HDAC1/2, promoting degradation of corepressors. Meanwhile, the endogenous cofactor inositol hexakisphosphate (InsP6) acts as a second molecular glue, and the overall CoREST−HDAC1/2−KBTBD4 complex is further buttressed. Additionally, the authors reveal a striking mechanistic mimicry between UM171 and the KBTBD4 cancer mutations. KBTBD4 is frequently mutated in medulloblastoma (MB), the most prevalent embryonal brain tumor in children, and the mutations impart gain-of-function to KBTBD4, which was identified as a genetic glue. Genetic glue refers to a type of molecule obtained through gene mutations that enhances the interaction between E3 ubiquitin ligases and substrates, induces the formation of stable complexes between target proteins and E3 ubiquitin ligases, and promotes the degradation of target proteins. KBTBD4 induces aberrant degradation of the transcriptional corepressor CoREST, suggesting that insertional mutagenesis in cancer is similar to the mechanism of action of chemical molecular glues. These findings indicate that UM171 and the KBTBD4 cancer mutations possess the same molecular glue degradation function, proposing a new concept of genetic glue.

Cullin−RING E3 ubiquitin ligases (CRL3) are comprised of the Cullin scaffold, an adapter, a substrate receptor, as well as an E2-recruiting subunit RBX1/2[7]. As the largest family of E3 ubiquitin ligases, CRL3 plays a crucial role in various cellular processes, including cell cycle progression, DNA damage repair, and maintenance of chromatin integrity[8]. KBTBD4, a CRL3 substrate receptor subunit, is recurrently mutated in medulloblastoma (the most common embryonal brain tumor in children)[9]. Interestingly, these mutations impart gain-of-function to KBTBD4 to induce aberrant degradation of the transcriptional corepressor CoREST, which functions as a scaffold to recruit LSD1 and either the histone deacetylase HDAC1 or the paralogue HDAC2 at its two ends, forming the core LSD1−HDAC1/2−CoREST (LHC) corepressor complex.

Meanwhile, they identified the direct binding target of UM171 by global proteomic analysis in UM171-sensitive cell lines treated with vehicle (DMSO) or UM171. The results showed that several proteins exhibited significant depletion in levels after treatment with UM171, including LSD1, two CoREST paralogues, as well as components of the broader LHC complex (RREB1, GSE1, and HMG20B). Additionally, they assessed which downregulated proteins were direct versus collateral targets of UM171−KBTBD4, and found that many depleted proteins were

Peer review under the responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

https://doi.org/10.1016/j.apsb.2025.07.006

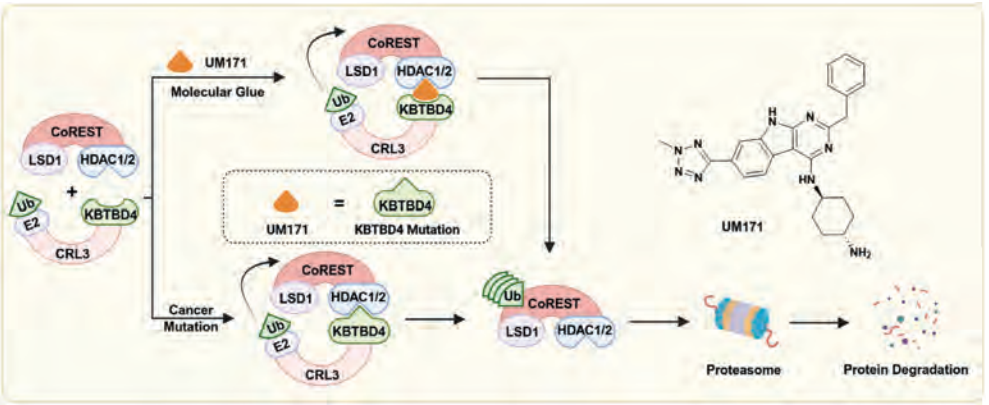

Figure 1 UM171 and KBTBD4 cancer mutations structurally and functionally mimic each other, prompting the degradation of CoREST corepressors.

associated with LHC. These data indicated that CoREST was a direct neo-substrate of UM171−KBTBD4. Furthermore, ELM2 domains and the interactions between HDAC1 and/or HDAC2 with corepressors were demonstrated to be necessary for UM171-induced degradation of CoREST. In addition, the KBTBD4−UM171−LHC complex in the presence of InsP6 was assembled and determined its structure using cryo-electron microscopy (cryo-EM) to resolve the mechanism of action of UM171. The result showed that a single molecule of UM171 filled an exposed gap between the HDAC1 and KBTBD4-B with exquisite shape complementarity to act as a glue. Moreover, InsP6 served as a second glue, directly adjacent to the UM171 binding site and nestled at the three-protein junction between HDAC1, CoREST, and KBTBD4-B to stabilize the complex.

In this study, the authors also established that the *KBTBD4* mutations were required for the proliferation in MB. Compared with the *KBTBD4-WT*, the *KBTBD4* mutations possessed greater affinity with LHC, showing that the MB mutants were sufficient to drive E3 engagement with LHC. Similar to UM171, mutant KBTBD4-LHC binding required the addition of a second glue, InsP6, and HDAC1 was also the only subunit of LHC that made direct contact with the KBTBD4 mutations. Moreover, reconstituted $CRL3^{KBTBD4-PR}$ showed more CoREST ubiquitination than $CRL3^{KBTBD4-WT}$ *in vitro*. Collectively, these findings indicated that *KBTBD4* MB mutations were adequate to enhance CoREST ubiquitination and degradation of CoREST in an HDAC1/2-dependent fashion. By enhancing the shape complementarity and polar interactions, the KBTBD4 gain-of-function mutants facilitated the interaction between the E3 and the neosubstrate.

Notably, UM171 promoted the ubiquitination and degradation of CoREST by phenocopying and chemically mimicking the *KBTBD4* MB mutations. Meanwhile, by comparing the structures of the two LHC-bound *KBTBD4* MB mutations and the KBTBD4−UM171−LHC complex, a significant convergent mechanism that molecular glue and the cancer mutations complemented and optimized the suboptimal protein−protein interface between the E3 ligase and HDAC1 to drive their association was shown. The gain-of-function cancer mutations and the molecular glue structurally and functionally mimic each other, complementing the suboptimal protein−protein interface to promote the neomorphic interaction. The discovery of novel molecular glues could promote drug development in oncology and epigenetics by degrading 'undruggable' targets, overcoming drug resistance *via* dynamic protein degradation, and enhancing immunotherapy *via* immune checkpoint modulation, while enabling precise epigenetic control through chromatin regulator modulation. For clinical translation of molecular glues, advanced drug delivery systems are crucial to enhance tumor-targeting specificity, improve tissue penetration capabilities, and optimize blood−brain barrier permeability. Concurrently, engineering tissue-selective molecular glues could mitigate off-target interactions and prevent therapeutic resistance development. Finally, the combination of molecular glue with traditional targeted therapies, epigenetic treatments, or immunotherapy could potentially establish a novel treatment approach for cancer and complex diseases.

References

1. Zhao L, Zhao J, Zhong K, Tong A, Jia D. Targeted protein degradation: mechanisms, strategies and application. *Signal Transduct Targeted Ther* 2022;**7**:113.
2. Pohl C, Dikic I. Cellular quality control by the ubiquitin−proteasome system and autophagy. *Science* 2019;**366**:818−22.
3. Dong GQ, Ding Y, He SP, Sheng CQ. Molecular glues for targeted protein degradation: from serendipity to rational discovery. *J Med Chem* 2021;**64**:10606−20.
4. Domostegui A, Nieto Barrado L, Perez Lopez C, Mayor-Ruiz C. Chasing molecular glue degraders: screening approaches. *Chem Soc Rev* 2022;**51**:5498−517.
5. Yeo MJR, Zhang O, Xie X, Nam E, Payne NC, Gosavi PM, et al. UM171 glues asymmetric CRL3−HDAC1/2 assembly to degrade CoREST corepressors. *Nature* 2025;**639**:232−40.
6. Xie X, Zhang O, Yeo MJR, Lee C, Tao R, Harry SA, et al. Converging mechanism of UM171 and KBTBD4 neomorphic cancer mutations. *Nature* 2025;**639**:241−9.
7. Bulatov E, Ciulli A. Targeting cullin−RING E3 ubiquitin ligases for drug discovery: structure, assembly and small-molecule modulation. *Biochem J* 2015;**467**:365−86.
8. Hua Z, Vierstra RD. The cullin−RING ubiquitin−protein ligases. *Annu Rev Plant Biol* 2011;**62**:299−334.
9. Chagraoui J, Girard S, Spinella JF, Simon L, Bonneil E, Mayotte N, et al. UM171 preserves epigenetic marks that are reduced in *ex vivo* culture of human HSCs *via* potentiation of the CLR3−KBTBD4 complex. *Cell Stem Cell* 2021;**28**:48−62.e6.

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Received 27 April 2025
Received in revised form 27 May 2025
Accepted 2 July 2025