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Drug Development

Major Finding: DT2216, a proteolysis-targeting chimera (PROTAC), effectively targets BCL-X_L for degradation.

Concept: Unlike other drugs targeting cancer-promoting BCL-X_L, DT2216 spares platelets.

Impact: DT2216 is promising for BCL-X_L–dependent cancers; other tissue-specific PROTACs may be of interest.

THE PROTAC DT2216 TARGETS CANCER BY PROMOTING BCL-X_L DEGRADATION

Overexpression of antiapoptotic proteins in the B-cell lymphoma (BCL) family is a common feature of many cancers. In particular, BCL extra large (BCL-X_L) is a target of interest due to its high expression in solid tumors and some leukemias, but development of drugs targeting BCL-X_L has been thwarted by thrombocytopenia. Building on ABT263, a small-molecule BCL2/BCL-X_L inhibitor that exhibits this dose-limiting toxicity, Khan, Zhang, Lv, and colleagues developed a cell-selective proteolysis-targeting chimera (PROTAC), dubbed DT2216, with not only reduced platelet toxicity, but also improved antitumor efficacy relative to ABT263. This PROTAC was designed with a BCL2/BCL-X_L–binding moiety derived from ABT263 joined via an empirically optimized linker to a ligand of the Von Hippel-Lindau (VHL) E3 ligase, which is not highly expressed in platelets. DT2216 was confirmed to cause BCL-X_L–specific ubiquitination and subsequent proteasome-mediated degradation while sparing other BCL family members despite the ABT263-derived moiety's affinity for BCL2; this may be due to an inability of DT2216 to form a stable ternary complex with BCL2 and VHL in cells. In mouse experiments using T-cell acute lymphoblastic leukemia (T-ALL) xenografts, therapeutically equivalent doses of ABT263 and the PROTAC DT2216 exhibited marked differences in their effects on platelets, with DT2216 producing far lower platelet toxicity. The antitumor efficacy of DT2216 was associated with its ability to induce degradation of BCL-X_L, consistent with the notion that DT2216 acts as a BCL-X_L–specific PROTAC *in vivo*. Additionally, DT2216 exhibited synergistic effects with BCL-family inhibitors and conventional chemotherapy in cell line–derived xenograft models dependent on multiple BCL-family proteins as well as in a T-ALL patient-derived xenograft model that was highly chemotherapy resistant. In summary, the authors have developed a novel drug targeting the elusive BCL-X_L with improved efficacy and reduced toxicity compared to its predecessor, although further work would be needed to optimize the dose. Further, this work demonstrates how PROTACs that bind tissue-specific E3 ligases can be used to target the drugs to the desired sites, limiting their toxicity in other tissues. ■

Khan S, Zhang X, Lv D, Zhang Q, He Y, Zhang P, et al. A selective BCL-X_L PROTAC degrader achieves safe and potent antitumor activity. Nat Med 2019;25:1938–47.

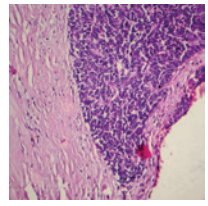
Epigenetics

Major Finding: Wilms tumor–linked ENL mutations cause dysfunctional nephrogenesis and target-gene hyperactivation.

Mechanism: Tumor-associated ENL mutations cause increased self-association of ENL at target genes.

Impact: This study suggests a causative role of ENL mutations in Wilms tumor and shows a possible mechanism.

WILMS TUMOR–ASSOCIATED ENL MUTANTS CAUSE TARGET-GENE OVEREXPRESSION



Recurrent hotspot mutations in the histone acetylation–reading YEATS domain of the eleven-nineteen leukemia protein (ENL) have been linked to Wilms tumor, a form of kidney cancer that almost exclusively affects children. However, whether the development of Wilms tumor is directly caused by these mutations, which consistently involve small in-frame insertions or deletions, is not known. In experiments using human kidney cell lines, Wan and colleagues found that these mutations in ENL's YEATS domain led to an apparent gain of function, increasing the transcription of ENL's target genes, some of which, such as *HOXA* genes, are involved in development. Experiments employing a three-dimensional model of nephrogenesis demonstrated that these mutations caused aberrant nephron development, increasing the abundance of undifferentiated structures that resemble the blastema components of Wilms tumors. Mechanistically, mutant ENL largely bound the same target genes as wild-type ENL, but mutant ENL's occupancy—as well as the occupancy of the larger protein complex ENL joins to activate transcription—was increased at some of those genes, including the *HOXA* cluster. Interestingly, like wild-type ENL, tumor-associated ENL mutants required the protein's reader function to drive localization to target genes, but the ENL mutants did not appear to have greater affinity for acetylated (or otherwise acylated) histone peptides, implying that increased binding strength did not explain the mutants' increased occupancy at these genes. Instead, tumor-associated ENL mutants exhibited greater self-association at target sequences, which may explain the increased expression of target genes caused by mutant ENL. This self-association–induced gene activation appeared to be driven not only by the mutant YEATS domain, but also by ENL's ANC1 homology domain and a predicted intrinsically disordered region. Collectively, these findings provide preliminary evidence for a causative role of tumor-associated ENL mutations and Wilms tumor, elucidate the mechanism by which these mutations may trigger dysfunctional development, and adds further evidence illustrating the importance of readers of histone modifications in disease. ■

Wan L, Chong S, Xuan F, Liang A, Cui X, Gates L, et al. Impaired cell fate through gain-of-function mutations in a chromatin reader. Nature 2020;577:121–6.

AACR American Association for Cancer Research

CANCER DISCOVERY

The PROTAC DT2216 Targets Cancer by Promoting BCL-X_L Degradation

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