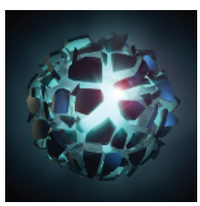
Targeted Therapy

Major finding: Phthalimide conjugates induce destabilization of target proteins such as BRD4 *in vitro* and *in vivo*.

Concept: Phthalimide conjugation triggers cereblon-mediated proteasomal degradation of target proteins.

Impact: This chemical strategy may represent a broad approach to develop new cancer therapeutics.

PHTHALIMIDE-CONJUGATED LIGANDS PROMOTE SELECTIVE PROTEIN DESTABILIZATION



Despite the clinical efficacy of compounds such as fulvestrant that induce ligand-dependent destabilization of target proteins, the development of additional target-degrading compounds has remained limited due to ligand requirements, lack of specificity, and low cellular potency. Recent work has shown that phthalimide-based drugs target cereblon (CRBN), a member of the cullin–RING ubiquitin ligase complex, to promote proteasomal degradation of specific transcription factors. To test the broader applicability of this concept, Winter, Buckley, and colleagues generated a bifunctional phthalimide-conjugated version of JQ1, a BET bromodomain inhibitor that displaces the transcriptional coactivator bromodomain-containing 4 (BRD4) from chromatin, resulting in transcriptional downregulation of *MYC* and induction of antiproliferative responses in leukemia cells. Chemical substitutions at the carboxyl group of JQ1 and the aryl ring of thalidomide yielded dBET1, which retained specific BRD4 binding, bridged BRD4 and CRBN, and rapidly destabilized BRD4 protein in a dose-dependent manner in acute myeloid leukemia (AML) cells. Mechanistically, dBET1-mediated BRD4 protein destabilization was dependent on the proteasome and BRD4–CRBN engagement. Functionally, dBET1 resulted in selective proteomic changes in AML cells, including downregulation of MYC and PIM1, similar to the effects of JQ1 treatment, as well as a marked reduction in the levels of other BET family members, reinforcing compound specificity. Treatment with dBET1 induced a superior apoptotic response compared with JQ1 in leukemia cells and primary human leukemic blasts *in vitro*, and attenuated proliferation and leukemic progression *in vivo* without toxicity, underscoring the potential clinical utility of this approach. In addition, this strategy was applied to design phthalimide-conjugated ligands that stimulated CRBN-dependent degradation of a second target, the cytosolic protein FK506-binding protein 1A (also known as FKBP12). Together, this work highlights a chemical approach for inducing selective protein degradation that has the potential for broader application in the development of new anticancer therapies. ■

Winter GE, Buckley DL, Paulk J, Roberts JM, Souza A, Dhe-Paganon S, et al. Phthalimide conjugation as a strategy for in vivo target protein degradation. Science 2015 May 21 [Epub ahead of print].

Prostate Cancer

Major finding: Extensive intratumoral genetic heterogeneity exists among prostate tumors with similar pathology.

Approach: A low-input library protocol allowed whole-genome sequencing of routine biopsies.

Impact: Intratumoral heterogeneity should be considered in the clinical management of localized prostate cancer.

LOCALIZED PROSTATE CANCER IS SPATIALLY AND GENOMICALLY HETEROGENEOUS

Most patients with prostate cancer are diagnosed with localized disease, but significant clinical heterogeneity exists among patients who are assigned the same prognostic risk category and whose tumors share similar pathologic features. Boutros and colleagues performed genomic profiling of 74 prostate cancer samples from untreated patients with localized, intermediate-risk, Gleason score 7 disease. Significant intrapatient heterogeneity was observed, with genomic instability and copy-number abnormalities varying widely between patients. In addition to several genomic abnormalities previously associated with aggressive disease, several recurrent alterations not previously linked to prostate cancer were identified, such as focal amplification of *MYCL*. *MYCL*-amplified tumors were genomically distinct from *MYC*-amplified tumors and were associated with younger age at treatment, suggesting that *MYCL*-amplified tumors may represent a separate disease subtype. *MYCL* amplification was heterogeneous among glands within an individual prostate; consistent with these findings, whole-genome sequencing of 23 spatially distinct tumor regions within formalin-fixed, paraffin-embedded routine biopsy specimens from 5 patients revealed extensive intraprostatic heterogeneity at the level of copy-number abnormalities, genomic rearrangements, and single-nucleotide variants. Evidence of clonal evolution could be observed in each tumor, and one tumor appeared to be multiclonal in nature. Nonsynonymous mutations, including those deemed to be potentially actionable or have prognostic value, were rarely observed in every sampled region of an individual tumor. The high degree of intraprostatic heterogeneity observed even in localized disease suggests a potential reason for the heterogeneous clinical outcomes observed among patients with similar disease pathology and should be considered in stratification and treatment of patients with potentially curable prostate cancer. ■

Boutros PC, Fraser M, Harding NJ, de Borja R, Trudel D, Lalonde E, et al. Spatial genomic heterogeneity within localized, multifocal prostate cancer. Nat Genet 2015 May 25 [Epub ahead of print].