A new paradigm in drug discovery

In-Vivo Target Protein Degradation

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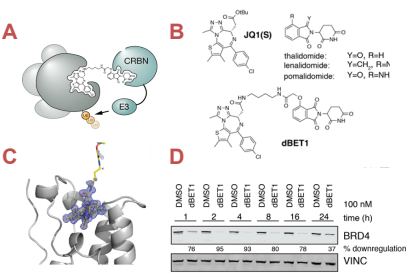
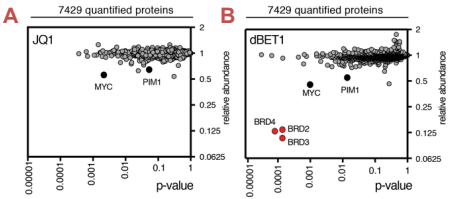
I

The development of effective pharmacological inhibitors of multidomain scaffold proteins, notably transcription factors, is a particularly challenging problem. In part, this is because many small-molecule antagonists disrupt the activity of only one domain in the target protein. We devised a chemical strategy that promotes ligand-dependent target protein degradation using as an example the transcriptional coactivator BRD4, a protein critical for cancer cell growth and survival. We appended a competitive antagonist of BET bromodomains to a phthalimide moiety to hijack the cereblon E3 ubiquitin ligase complex. The resultant compound, dBET1, induced highly selective cereblon-dependent BET protein degradation in vitro and in vivo and delayed leukemia progression in mice. A second series of probes resulted in selective degradation of the cytosolic protein FKBP12. This chemical strategy for controlling target protein stability may have implications for therapeutically targeting previously intractable proteins.

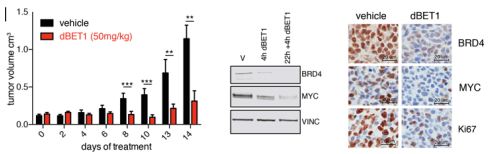
II



III



IV



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