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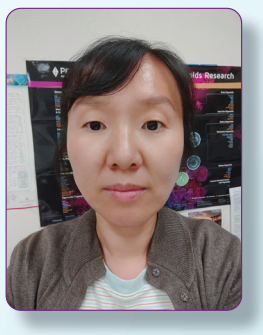

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Cell Reports

A NRF2 inhibitor selectively sensitizes KEAP1 mutant tumor cells to cisplatin and gefitinib by restoring NRF2-inhibitory function of KEAP1 mutants

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Even effective anticancer therapies are often limited by the development of therapeutic resistance, which is the most common ultimate cause of death. The mechanisms are often multiple, and inhibiting such mechanisms may sensitize the tumor to treatment but may also result in prohibitive healthy tissue toxicity. The transcription factor nuclear factor erythroid 2-related factor 2 (NRF2) is a master regulator of protective responses in healthy tissues. However, when it is active in tumor cells, it can result in drug resistance.

KEAP1, the endogenous NRF2 inhibitor, binds NRF2 and redirects it to proteasomal degradation, so the KEAP1/NRF2 interaction is critical for maintaining NRF2 at a basal level. A number of clinically relevant KEAP1 mutations were shown to disrupt this critical KEAP1/NRF2 interaction, leading to elevated NRF2 levels and drug resistance.

Here, we describe a small-molecule NRF2 inhibitor, R16, that selectively binds KEAP1 mutants and restores their NRF2-inhibitory function by repairing the disrupted KEAP1/NRF2 interactions. R16 substantially sensitizes KEAP1-mutated tumor cells to cisplatin and gefitinib but does not do so for wild-type KEAP1 cells and sensitizes KEAP1 G333C-mutated xenograft to cisplatin.

We developed a BRET2-based biosensor system to detect the KEAP1/NRF2 interaction and classify KEAP1 mutations. This strategy would identify drug-resistant KEAP1 somatic mutations in clinical molecular profiling of tumors.

As NRF2 has been demonstrated to play a role in the efficacy of a variety of anticancer therapies, the potential utility of our approach could be enormous. Indeed, it is possible that all forms of treatment could be enhanced by co-administration of the genotype-specific KEAP1 mutant correctors, such as R16 or its analogs. However, it remains very challenging to fully address how R16 might achieve the selectivity toward multiple KEAP1 mutants while remaining not active against WT-KEAP1.

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