COMMENTARY

Epigenetic targeting of DNA repair in lung cancer

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Lung cancer is the most common cause of cancer death in both men and women worldwide. In North America alone, more than 257,000 new cases are expected in 2019 (1, 2). About 85% of these cases are nonsmall cell lung cancer (NSCLC), and despite recent treatment advances, long-term prognosis remains poor. For NSCLC patients with locally advanced disease involving mediastinal lymph nodes, concomitant radiotherapy and chemotherapy followed by immunotherapy represents a backbone of curative-intent treatment (3). Despite aggressive multimodality therapy, disease recurrence is common with ∼30% local and 45% distant failure rates reported at 2 y (4, 5). To date, efforts to improve these outcomes with additional combinations (e.g., cetuximab) or increased radiation dose have not been successful (4). Novel strategies that modulate DNA damage repair pathways in response to cytotoxic chemotherapy and radiation in lung cancer may provide a path forward.

In PNAS, Abbotts et al. (6) report the use of an epigenetic modifier to enhance antitumor response to these DNA-damaging therapeutics. The investigators find using cell lines and mouse models that DNA methyltransferase inhibitors (DNMTi) sensitize NSCLC to poly(ADP ribose) polymerase (PARP) inhibition and radiotherapy by down-regulating critical DNA damage repair pathways (6).

PARP Inhibitors Are Synthetic Lethal with Homologous Recombination Deficiency

PARP inhibition first gained real traction in cancer therapy in the context of BRCA-deficient tumors (7–9). PARP1 participates in a key pathway required for efficient repair of single-strand DNA breaks. PARP inhibition prevents resolution of single-strand breaks, leading to acquisition of double-strand breaks (DSBs) in replication that require homologous recombination (HR) for high-fidelity repair. *BRCA1* and *BRCA2* mutations disrupt the HR repair pathway, leaving these cancers exquisitely sensitive to the DNA lesions produced by PARP inhibitors (PARPi). This interaction between PARPi and HR-deficient tumors resembles a synthetically lethal relationship wherein alterations in 2 or more genes (or pathways) results in a lethal phenotype, while alteration of each alone is insufficient for cell death.

The success in targeting HR deficiencies in cancers is an attractive strategy. However, a major limitation is the modest number of cancers that are intrinsically HR deficient. Even expanding beyond *BRCA* to >100 HR core and related genes, only about 5% of human tumors (and a similar fraction of NSCLC) harbor biallelic alterations in a known HR target gene (10). Potentially addressing the supermajority of NSCLC that is HR proficient, Abbotts et al. (6) demonstrate a promising strategy whereby epigenetic targeting using DNMTi can pharmacologically induce a BRCA-like HR deficiency state in NSCLC, sensitizing these cells to PARPi. This strategy complements a broader array of recent efforts to expand the population that may benefit from induced HR deficiency, as reviewed in ref. 11.

Epigenetic Modifiers as Therapeutics

The epigenome comprises a diverse array of modifications to genomic DNA and DNA-associated proteins that together determine the gene expression patterns of a cell, ultimately dictating cell identity, behavior, and fate. Epigenetic dysregulation, including mutations disrupting key epigenetic control mechanisms, is increasingly recognized as a central hallmark of cancer, fundamental to oncogenesis, cancer progression, and acquired therapeutic resistance. Some recent efforts to target cancer-specific dysregulation of gene expression through targeted epigenetic therapies are reviewed in ref. 12 and, for lung cancer specifically, in ref. 13.

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The first epigenetic therapies, and still the class with the broadest and most clearly demonstrated anticancer efficacy, were inhibitors of DNMT. Agents in this class have regulatory approvals based on successful phase III studies in hematologic malignancies including myelodysplastic syndrome and acute myelogenous leukemia. Azacytidine (AZA) potently inhibits DNMT, resulting in DNA demethylation, reactivation of silenced genes, and in some instances cancer cell reprogramming to a terminally differentiated state. Finding a novel use for DNMT inhibitors, the Rassool laboratory had previously demonstrated that low doses of AZA can enhance the antitumor activity of PARPi in otherwise resistant breast and acute myeloid leukemia models by increasing association of both AZA and PARP1 at sites of DNA damage, resulting in increased DSB, synergistic cytotoxicity, and reduced clonogenicity (14).

Combination of DNMTi and PARPi or Radiotherapy in NSCLC

In the current report, the Rassool laboratory provides mechanistic insights into this combination effect, using ionizing radiation to initiate DNA damage in lung cancer models (6). The investigators find that DNMT inhibition abrogates both HR and nonhomologous end joining (NHEJ), 2 key complementary DSB repair pathways, in NSCLC cells. Notably with regard to HR, AZA reduced the protein expression and function of FANCD2, an important member of the Fanconi anemia family involved in DNA interstrand cross-link repair, resulting in an HR-deficient *BRCAness* phenotype that is synthetic lethal with PARPi.

We and others have reported that PARPi increases DSB formation and confers radiosensitization in lung cancer models through a PARP-trapping mechanism (15, 16). The work reported here suggests that DNMTi can augment PARPi radiosensitization and is a combination strategy with significant translational potential (6). The observation that AZA also down-regulates factors contributing to NHEJ, a nontemplate-dependent DSB repair pathway associated with imprecise repair, may further contribute to this effect. Both HR and NHEJ are important for radiotherapy-induced DNA DSB repair, with most radiotherapy-generated DSBs being repaired by NHEJ. The authors show AZA down-regulates Ku80, an important component of the Ku heterodimeric complex necessary for NHEJ (6).

Next Steps

Lung cancer incidence increases with age and in many patients is associated with substantial tobacco-related cardiopulmonary comorbidities. Many patients with locoregionally advanced NSCLC and these comorbidities are considered too frail for aggressive platinum-based chemoradiotherapy, and are offered sequential therapy or radiation alone, both associated with inferior survival. For patients that cannot tolerate platinum-based chemoradiotherapy, perhaps a PARPi and DNMTi combination with radiotherapy may be an alternative to the standard chemotherapy backbone. Phase I studies of this combination to explore the toxicity profile of this combinatorial strategy are warranted.

Expanded investigation of epigenetic modifiers for cancer therapy has the potential for further clinical impact. Additional work to identify epigenetic vulnerabilities and to define their appropriate therapeutic contexts is needed. Beyond DNMTi, a large universe of epigenetic modifiers may influence DNA repair and DNA replication stress. For example, complementary to the present study exploring DNMTi (6), histone deacetylase inhibitors (17) or EZH2 inhibitors (18) have been shown to activate a *SLFN11*-dependent replication stress response (19) and induce a *BRCAness* phenotype (20, 21) in cancer models, sensitizing tumors to PARPi and other DNA-damaging therapeutics.

Abbotts et al. demonstrate a promising strategy whereby epigenetic targeting using DNMTi can pharmacologically induce a BRCA-like HR deficiency state in NSCLC, sensitizing these cells to PARPi.

Rational application of these combination epigenetic approaches will also require a focus on predictive biomarker discovery, to identify molecular and histologic determinants of susceptibility. Devising and consistently applying methods to quantify epigenetic induction of *BRCAness* to optimally apply PARPi would advance precision oncology efforts. Overall, these efforts will require sustained collaborative teamwork between epigenetic and DNA repair researchers as well as clinical–translational investigators.

Lung cancer remains a lethal disease and patients depend on the entire biomedical community to explore, devise, and apply scientific, translational, and clinical expertise to improve outcomes. Understanding and harnessing epigenetic therapies is a relatively nascent but important and promising step in this endeavor.

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