

RESEARCH WATCH

DNA Damage

Major finding: DNA damage response alterations are linked to improved responses to anti-PD-1/PD-L1 in urothelial carcinoma.

Concept: Sequencing identified deleterious DNA damage response alterations in 80% of responding patients.

Impact: DNA damage response alterations may serve as biomarkers to predict responses to anti-PD-1/PD-L1.

DNA DAMAGE RESPONSE ALTERATIONS PREDICT RESPONSES TO ANTI-PD-1/PD-L1

Immune checkpoint inhibitors targeting PD-1 or PD-L1 provide clinical benefit in a subset of patients with metastatic urothelial carcinoma, but response rates are relatively low and biomarkers are needed to identify the patients most likely to benefit from immune checkpoint blockade (ICB). A high tumor mutation load has been linked to increased response rates, but does not sufficiently predict response. Urothelial carcinomas often have genomic alterations affecting genes involved in DNA damage response and repair (DDR), and these alterations are associated with an increased mutation load. Thus, Teo and colleagues hypothesized that DDR mutations might be associated with responses to immune checkpoint blockade. This hypothesis was tested in a study of 60 patients with metastatic urothelial carcinoma treated with anti-PD-1/PD-L1 antibodies on three separate prospective trials. All patients had targeted exon sequencing performed on preimmunotherapy tumor specimens. The primary objective was to determine the effect of DDR gene alterations on the overall response rate, and the secondary objective was to assess correlations between DDR alterations and both progression-



free and overall survival. Overall, 74 alterations in DDR genes were identified in 28 patients (46.7%), and 27 of these mutations, observed in 15 patients (25%), were considered deleterious. The presence of a DDR alteration was linked to a higher response to ICB, with 67.9% of patients responding compared with 18.8% of patients lacking DDR alterations. Further, an 80% response rate was observed in patients with DDR alterations known or likely to be deleterious, compared with a 54% response rate for DDR alterations of unknown significance. DDR alterations were also associated with an increased progression-free and overall survival. Collectively, these findings suggest that alterations in DDR genes may serve as biomarkers of response to anti-PD-1/PD-L1 therapy, and thus may guide treatment selection for patients with metastatic urothelial carcinoma. ■

Teo MY, Seier K, Ostrovnaya I, Regazzi AM, Kania BE, Moran MM, et al. Alterations in DNA damage response and repair genes as potential marker of clinical benefit from PD-1/PD-L1 blockade in advanced urothelial cancers. J Clin Oncol 2018 Feb 28 [Epub ahead of print].

Ewing Sarcoma

Major finding: Transcriptional dysregulation promotes R-loops and impairs homologous recombination in Ewing sarcoma.

Mechanism: EWS-FLI1 may suppress the function of EWSR1 in reducing transcription in response to DNA damage.

Impact: Impaired homologous recombination may confer sensitivity to chemotherapy in Ewing sarcoma.

EWING SARCOMAS PHENOCOPY BRCA1-DEFICIENT TUMORS

Ewing sarcomas are sensitive to genotoxic agents including etoposide, but the molecular mechanisms underlying sensitivity have not been elucidated. These tumors are characterized by a chromosomal translocation that generates the EWS-FLI1 fusion protein, and Gorthi and colleagues uncovered a role for EWS-FLI1 in DNA damage-induced transcription that may explain the chemosensitivity observed in Ewing sarcoma. EWS-FLI1 expression conferred sensitivity to etoposide, and in Ewing sarcoma cells EWS-FLI1 increased basal levels of transcription, promoting transcriptional dysregulation in response to DNA damage. This dysregulated transcription resulted in an increased accumulation of R-loops (DNA-RNA hybrids), especially at highly expressed genes. R-loop accumulation induced replication stress but surprisingly did not induce homologous recombination. This effect could be induced by EWS-FLI1 expression or loss of EWSR1 function, suggesting that this effect may be due to a dominant negative function of EWS-FLI1 in repressing EWSR1. The impairment of homologous recombination in Ewing sarcoma is similar

to the phenotype of BRCA1/2 mutant breast cancer; however, Ewing sarcoma cells exhibited robust BRCA1 expression and lacked *BRCA1* mutations. Unexpectedly, BRCA1 overexpression restored homologous recombination in Ewing sarcoma cells, although this effect was abrogated when EWSR1 was depleted. Mechanistically, BRCA1 associated with transcriptional complexes at R-loops and was unable to go to sites of DNA repair, indicating a redistribution of BRCA1 protein in Ewing sarcoma cells that results in homologous recombination defects. Thus, Ewing sarcomas may phenocopy BRCA1-deficient tumors despite robust BRCA1 expression. Collectively, these findings reveal a mechanism by which homologous recombination is impaired in Ewing sarcoma, which may underlie the exquisite sensitivity of Ewing sarcoma to PARP inhibitors and other genotoxic agents. ■

Gorthi A, Romero JC, Loranc E, Cao L, Lawrence LA, Goodale E, et al. EWS-FLI1 increases transcription to cause R-loops and block BRCA1 repair in Ewing sarcoma. Nature 2018;555:387–91.

CANCER DISCOVERY

Ewing Sarcomas Phenocopy BRCA1-Deficient Tumors

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