Major finding: ZEB1 may block oncogene-induced DNA damage in mammary stem cells to prevent chromosomal instability.

Mechanism: ZEB1 upregulates MSRB3 to block ROS production in response to oncogene activation.

Impact: The differentiation state of tumor cells of origin may determine the extent of chromosomal instability.

ZEB1 UPREGULATES MSRB3 TO SUPPRESS ONCOGENE-INDUCED DNA DAMAGE

Chromosomal instability (CIN) drives tumorigenesis in many adult neoplasms. However, some tumor types, including a subset of triple-negative breast cancers (TNBC), harbor few genomic alterations, suggesting that in these tumors oncogenic transformation occurs independently of CIN. Claudin-low TNBCs exhibit low CIN and may originate from early epithelial precursor cells with stem cell features, prompting Morel and colleagues to hypothesize that traits of the cell of origin might influence genomic instability. A hierarchy of normal human mammary epithelial cells was established and their differentiation potential was evaluated. Three mammary stem cell–enriched populations were identified. These cells were resistant to oncogene-induced DNA damage, whereas RAS activation or Cyclin E overexpression induced massive DNA damage in more differentiated cell types. Gene expression analysis showed that mammary stem cells and TNBCs with low CIN had increased expression of epithelial–mesenchymal transition–inducing transcription factors including ZEB1. ZEB1 suppressed oncogene-induced DNA damage by reducing reactive oxygen species (ROS). Mechanistically, ZEB1 bound to the promoter of the antioxidant methionine sulfoxide reductase gene MSRB3, promoting MSRB3 expression to suppress ROS production after oncogene activation. Accordingly, MSRB3 was highly expressed in mammary stem cells compared with more differentiated cells, and MSRB3 expression was inversely correlated with CIN in breast cancer cell lines and primary TNBCs.

Analysis of data from The Cancer Genome Atlas showed that low expression of ZEB1 predicts CIN and TP53 mutations across various tumor types. Further, ZEB1-mediated suppression of CIN may prevent induction of the p53-dependent DNA-damage response to promote transformation. Altogether, these findings suggest that ZEB1 expression prevents oncogene-induced DNA damage and CIN in stem cells, and indicate that the cellular differentiation state may determine the genetic route to oncogenic transformation.


Clinical Trials

Major finding: Adoptive T-cell therapy achieved responses in 35% of patients with metastatic uveal melanoma.

Clinical relevance: A subset of patients who were refractory to immune checkpoint blockade responded to T-cell therapy.

Impact: Autologous T-cell therapies warrant further investigation in patients with uveal melanoma.

ADOP TIVE T-CELL THERAPY HAS ANTITUMOR ACTIVITY IN UVEAL MELANOMA

There are no established treatments for metastatic uveal melanoma, and, to date, immunotherapies have had disappointing results despite their success in metastatic cutaneous melanoma. It has been suggested that uveal melanoma is resistant to immunotherapy, but adoptive T-cell therapies have not been investigated. Chandran and colleagues performed a single-arm phase II trial to evaluate the safety and efficacy of adoptive transfer of autologous tumor-infiltrating lymphocytes (TIL) in 21 patients with metastatic ocular melanoma. The patients underwent metastasectomies to obtain tissue for the generation of autologous TILs and were treated with chemotherapy to deplete lymphoid cells prior to autologous TIL infusion with high-dose IL2. The primary endpoint was objective tumor response. Secondary endpoints included toxicity and immunologic correlates of clinical response. Of the 20 evaluable patients, 7 (35%) achieved partial responses, 2 of which are ongoing, and one patient achieved a complete response of hepatic metastases. Three of the responding patients were refractory to previous therapy with immune checkpoint inhibitors, and 4 of the 7 responders harbored mutations in the BAP1 tumor suppressor gene. Grade 4 lymphopenia and neutropenia occurred in all 21 patients, and grade 3–4 thrombocytopenia occurred in all patients due to the lymphodepleting chemotherapy. There was one treatment-related death due to sepsis-induced multiorgan failure. Significant autoimmune adverse events were not observed. The results of this phase II trial suggest that metastatic uveal melanoma may not be resistant to immunotherapy, and support further refinement and investigation of T-cell therapy for the treatment of patients with uveal melanoma.


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