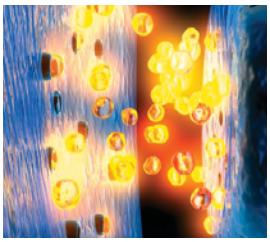
Drug Resistance

Major finding: Platinum-activated MSCs release distinct fatty acids that mediate resistance to chemotherapy.

Impact: COX-1 or TXAS inhibitors may prevent MSC-induced chemoresistance.

Clinical relevance: Fish oil and algae extracts rich in these fatty acids neutralize the effect of cisplatin.

STEM CELL–SECRETED FATTY ACIDS CONFER CHEMORESISTANCE



Platinum-based chemotherapy is the major treatment for many types of cancer, but development of resistance is a major obstacle to effective treatment. Roodhart and colleagues show that mouse tumors recruit mesenchymal stem cells (MSC) that are specifically activated by platinum chemotherapy and induce resistance to a broad range of chemotherapeutic agents by activating a cytoprotective response in the host tissue. A systematic metabolomic analysis of medium harvested from platinum-treated MSCs identified two distinct platinum-induced fatty acids (PIFA), KHT and 16:4(n-3), that could individually induce complete resistance to cisplatin at picomolar concentrations. Increased MSC levels were identified in patients with metastatic disease and a specific increase in PIFAs was identified in patients treated with platinum-based chemotherapy, validating these findings in human cancers. Because KHT is a by-product of thromboxane A2 synthesis, which requires both thromboxane-A synthase (TXAS) and upstream processing by cyclooxygenase (COX) of fatty acids released from cell membranes, the authors preincubated MSCs with inhibitors targeting individual steps of this metabolic pathway. They observed that administration of indomethacin (a COX-1 inhibitor) or ozagrel (a TXAS inhibitor) prior to platinum treatment abrogated MSC-induced resistance and enhanced the antitumor efficacy of platinum compounds in mouse tumor models, suggesting potentially druggable targets to prevent chemoresistance. Importantly, 16:4(n-3) is abundant in frequently used supplements such as fish oil and algae extract, indicating that rather than having beneficial effects on health in cancer patients, these natural supplements may promote resistance to chemotherapy. Indeed, a single oral dose of either fish oil or algae extract in mice neutralized the effect of cisplatin on tumors, further demonstrating the clinical relevance of fatty acids in chemoresistance. ■

Roodhart JM, Daenen LG, Stigter EC, Prins HJ, Gerrits J, Houthuijzen JM, et al. Mesenchymal stem cells induce resistance to chemotherapy through the release of platinum-induced fatty acids. Cancer Cell 2011;20:370–83.

Breast Cancer

Major finding: BRCA1 is required for DNA condensation and satellite repression.

Impact: This work establishes a key mechanism of tumor suppression by BRCA1.

Concept: Decreased Ub-H2A underlies the cellular consequences of *BRCA1* mutation.

BRCA1 MAINTAINS HETEROCHROMATIN STRUCTURE

The increased risk of breast and ovarian cancer caused by mutation of *BRCA1* has been attributed to increased genomic instability, presumably due to impaired homologous recombination. However, cancer-predisposing mutations in BRCA1 frequently compromise its E3 ubiquitin ligase activity, which is not required for homologous recombination. Zhu and colleagues demonstrate that increased genomic instability caused by BRCA1 loss is due to loss of constitutive heterochromatin and abnormal expression of highly repetitive DNA elements. The authors initially noted that targeted deletion of *Brca1* in murine neural stem cells led to altered heterochromatin structure corresponding with diminished levels of histone H2A ubiquitination (Ub-H2A) and elevated expression of normally silenced major and minor satellite repeats. BRCA1 was enriched at satellite DNA regions in both mouse and human cells, and BRCA1 ubiquitin ligase activity was specifically required for satellite repression and accumulation of Ub-H2A at these loci. Further, ectopic expression of Ub-H2A restored proliferation and satellite DNA repression in BRCA1-deficient cells, suggesting that H2A is likely the principal substrate of BRCA1 involved in establishment of heterochromatic foci and normal cell growth. Importantly, aberrant satellite DNA derepression was observed in both *Brca1*-deficient murine mammary tumors and breast tumors of women carrying *BRCA1* mutations. Forced expression of satellite DNA induced the same mitotic and DNA repair defects observed following BRCA1 loss, indicating that derepression of these transcripts underlies the genomic instability caused by *BRCA1* mutation. These findings clarify the mechanism of tumor suppression by BRCA1 and suggest that satellite DNA expression may have diagnostic applications in breast cancer. ■

Zhu Q, Pao GM, Huynh AM, Suh H, Tonnu M, Nederlof PM, et al. BRCA1 tumour suppression occurs via heterochromatin-mediated silencing. Nature 2011;477:179–84.