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GYNAECOLOGICAL CANCER

Chemoresistance — a little help from friends

Platinum-based treatments are a common first-line therapeutic option for patients with ovarian cancer, but resistance to these compounds can eventually arise over time. J. Rebecca Liu and Weiping Zou co-led a study in which they challenged the dogma that platinum resistance is caused by genetic alterations in tumour cells and, instead, investigated the contribution of the tumour micro-environment to platinum-resistant ovarian cancer.

In the initial experiments, cancer-associated fibroblasts (CAFs) and epithelial ovarian cancer cells isolated from patients with high-grade serous ovarian carcinoma (HGSOC) were co-injected into immunodeficient mice. The volume of tumours formed in untreated mice was not affected by injection of

CAFs; however, in cisplatin-treated mice, tumours that developed after injection of cancer cells and CAFs had larger volumes than tumours generated by the injection of cancer cells alone. This observation was consistent with the results of *in vitro* co-culture experiments, in which fibroblasts protected cancer cells from cisplatin-induced apoptosis.

The presence of tumour-infiltrating lymphocytes (TILs) has been described in many tumour types, including ovarian cancer. Interestingly, when supernatants derived from CD8⁺ T-cells were used in co-culture experiments, the researchers found that the protective effect of CAFs on cisplatin-induced apoptosis was abolished.

The results of the previously described *in vitro* experiments

suggest the existence of a link between TILs and chemoresistance. This potential link was examined in samples derived from patients with HGSOC whose clinical information was available. In these patients, an elevated presence of tumour stromal fibroblasts was associated with increased chemoresistance. The presence of CD8⁺ lymphocytes was also quantitated; higher levels of this cell population were found in patients with cisplatin-sensitive tumours than in those with chemoresistant tumours. Higher levels of CD8⁺ T cells were also correlated with improved overall survival. Thus, patients with tumours containing high numbers of CAFs and TILs are more likely to respond to platinum-based chemotherapy than patients with highly fibrotic tumours and lower levels of TILs.

“We have uncovered a novel mechanism of platinum resistance in ovarian cancer”, Liu and Zou explain, “and now we plan to examine whether the immune system has a role in modulating the effect of other types of chemotherapy.” These investigators expect the results of their research to enable the development of optimal combinations of chemotherapy with immune-checkpoint blockade and/or adoptive cell therapy in order to overcome the onset of resistance to chemotherapy in patients with ovarian cancer.

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ORIGINAL ARTICLE Wang, W. et al. Effector T cells abrogate stroma-mediated chemoresistance in ovarian cancer. *Cell* <http://dx.doi.org/10.1016/j.cell.2016.04.009> (2016)