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DRUG RESISTANCE

Destabilizing influence

Although the microtubule-stabilizing taxane paclitaxel is an effective chemotherapeutic agent, about 50% of ovarian and breast cancers are resistant to it. Many resistance mechanisms to taxanes have been identified, but the role of the extracellular matrix (ECM), which helps to regulate microtubule stability, is not known. James Brenton and colleagues now show that loss of the ECM protein TGFBI (transforming growth factor β-induced) in ovarian cancers modulates response to paclitaxel.

TGFBI was shown to be a candidate taxane resistance gene when the authors found that it is more than 1,000-fold underexpressed in a paclitaxel-resistant ovarian cancer cell line (SKOV-3TR) compared with the sensitive parent line (SKOV-3). They confirmed that knockdown of *TGFBI* made SKOV-3 cells resistant to paclitaxel.

Cells lacking TGFBI showed impaired paclitaxel-induced microtubule stabilization, so can TGFBI modulate paclitaxel sensitivity by microtubule-stabilizing effects, and, if so, how? TGFBI is known to mediate adhesion in an integrin-dependent manner, so the authors knocked down the downstream proteins focal adhesion kinase (FAK, also known as PTK2) and RHOA, which are required for fibronectin-induced stabilization of microtubules, and showed that both were required for microtubule stabilization in cells treated with recombinant TGFBI.

The authors also analysed tumour samples from 20 ovarian cancer patients participating in a prospective clinical trial that was designed to examine the molecular response to paclitaxel, and showed that morphological changes typical of paclitaxel-induced cytotoxicity were restricted to areas of high TGFBI expression within the tumours. They then analysed microarray expression sets from 233 ovarian and breast cancer samples and showed that *TGFBI* expression is tightly co-regulated with other ECM-related genes that induce paclitaxel sensitization, such as thrombospondin 1 (*THBS1*).

The authors have unpublished data to show that a third of primary ovarian cancers have lost TGFBI expression. In addition, FAK is known to be low or absent in one-third of patients with ovarian cancer. The authors therefore suggest that these proteins should be investigated as predictive biomarkers.

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ORIGINAL RESEARCH PAPER Ahmed, A. A. *et al.* The extracellular matrix protein TGFBI induces microtubule stabilization and sensitizes ovarian cancers to paclitaxel. *Cancer Cell* **12**, 514–527 (2007)