

Extracellular protein sensitizes ovarian cancer cells to chemotherapy

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Scientists have uncovered critical new details about the mechanisms that modulate the response of ovarian cancer cells to chemotherapy. The research, published by Cell Press in the December issue of *Cancer Cell*, helps to explain why many patients develop resistance to the taxane class of drugs and may lead to improved treatment of ovarian cancer.

Cancer cells divide rapidly and undergo extensive microtubule-driven restructuring as they proliferate. Taxanes, such as paclitaxel (Taxol), interfere with the dynamic growth of microtubules by directly binding to them and making them more stable and, as a result, disrupt the normal process of cell division. Paclitaxel has been used extensively to treat lung, ovarian and breast cancers but drug resistance limits the clinical usefulness of this drug to only about half of breast or ovarian cancer patients.

Although it is clear that taxane resistance is associated with a loss of stable microtubules and that microtubule stability can be influenced by signals from the extracellular matrix (ECM), a role for ECM proteins in the modulation of paclitaxel sensitivity has not been established. To explore the connection between regulation of microtubules and taxane resistance, Dr. James D. Brenton from the Cancer Research UK Cambridge Research Institute in Cambridge, England and colleagues performed an extensive examination of ovarian cancer cell lines that were sensitive or resistant to paclitaxel.

The researchers found that the ECM protein, transforming growth factor beta induced (TGFBI), was significantly reduced in paclitaxel-resistant cells. Importantly, TGFBI mediated sensitization to paclitaxel and loss of TGFBI was sufficient to induce paclitaxel resistance. TGFBI induced microtubule stabilization that was dependent on integrin-mediated FAK and Rho signaling. Further, analysis of ovarian cancer samples taken after

treatment with paclitaxel revealed that paclitaxel-induced cell death was associated with high levels of TGFBI expression.

These results identify TGFBI as an ECM protein that induces microtubule stability and modulates sensitivity to paclitaxel in ovarian cell lines and in patients receiving paclitaxel therapy. "Our findings have potentially significant clinical applications as TGFBI protein expression is lost in one third of primary ovarian and lung cancers and FAK is low or absent in one-third of ovarian cancer patients," explains Dr. Brenton. "It is possible that TGFBI could be used as a biomarker for selecting patients likely to respond to taxane therapy. In addition, proteins that activate TGFBI or mimic its action may be an effective strategy for modulating the response to widely used drugs like paclitaxel or docetaxel."

Source: Cell Press

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