Overcoming taxane resistance in cancer

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Taxanes, a group of cancer drugs that includes paclitaxel (Taxol®) and docetaxel (Taxotere®), have become front-line therapy for a variety of metastatic cancers. But as with many chemotherapy agents, resistance can develop, a frequent problem in breast, ovarian, prostate and other cancers. Now, cancer researchers at Children's Hospital Boston report a protein previously unknown to be involved in taxane resistance and that could potentially be targeted with drugs, making a cancer more susceptible to chemotherapy.

The researchers believe that this protein, prohibitin1, could also serve as a biomarker, allowing doctors to predict a patient's response to chemotherapy with a simple blood test. The study was published online by the Proceedings of the National Academy of Sciences in its online early edition during the week of January 25.

The study, led by Bruce Zetter, PhD, of Children's Vascular Biology Program, used proteomics techniques to compare the proteins present in Taxol-susceptible versus Taxol-resistant human tumor cell lines. The researchers found that the resistant cell lines, but not the susceptible cell lines, had prohibitin1 on their surface. When they suppressed prohibitin1 with RNA interference techniques, the tumor cells became more susceptible to Taxol, both in cell culture and in live mice with implanted Taxol-resistant tumors.

Zetter's lab is still investigating why having prohibitin1 on the cell surface makes a tumor cell resistant to taxanes. But in the meantime, he believes that not only could prohibitin1 be suppressed to overcome

taxane resistance, but that it could also be exploited as a means of targeting chemotherapy selectively to resistant cancer cells.

"We are working to target various cancer drugs to taxane-resistant cells by attaching them to compounds that bind to prohibitin," Zetter explains. One such compound is already known, and works well in animals to target other prohibitin-rich cells, but has yet to be tested in humans.

Suppressing prohibitin1 alone probably isn't enough to make a cancer fully Taxol-susceptible, but could be combined with other strategies aimed at increasing taxane susceptibility, such as targeting another protein called GST Pi, the researchers say. Other mechanisms of resistance are known, but they so far haven't been shown to present effective targets for therapy.

Zetter's lab is also trying to develop prohibitin1 as a biomarker for taxane resistance that physicians could use in the clinic. Since it's on the surface of the cell, Zetter believes prohibitin1 may circulate in the blood where it could easily be detected. His lab is in talks with several cancer centers to obtain serum samples from patients who did and didn't respond to Taxol, so that prohibitin1 levels could be measured and compared.

Zetter notes that prohibitin1 could easily have been overlooked, and was found only because the team happened to look specifically at proteins in the cell membrane, rather than simply doing a whole-cell proteomic analysis.

"The interesting finding was that prohibitin was not just another over-expressed protein," Zetter says. "It was up-regulated primarily on the cell surface. When we looked at the whole cell, the absolute amount of prohibitin wasn't changed. Instead, prohibitin was moving from the inside of the cell to the cell surface. It had shifted from one location to

another, and when it did, the tumor cells became resistant to taxanes. The fact that it moves to the cell surface also makes it easier to direct drugs to it."

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