Cisplatin-resistant cancer cells sensitive to experimental anticancer drugs, PARP inhibitors

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Poly (ADP-ribose) polymerase inhibitors may be a novel treatment strategy for patients with cancer that has become resistant to the commonly used chemotherapy drug cisplatin, according to data from a preclinical study published in *Cancer Research*, a journal of the American Association for Cancer Research.

"Cisplatin is one of the most widely used conventional, anticancer chemotherapy drugs," said Guido Kroemer, M.D., Ph.D., professor at University Paris Descartes in Paris, France. "Unfortunately, most patients respond only transiently to cisplatin therapy because their cancer cells develop ways to resist the effects of the drug."

Kroemer and colleagues set out to identify the biochemical changes that arise as cancer cells become resistant to cisplatin in the hope that the information could provide clues to potential new therapies. They focused their study on non-small cell lung cancer (NSCLC) cells because NSCLC is the leading cause of cancer-related morbidity and mortality worldwide and patients with NSCLC are frequently treated with cisplatin, according to Kroemer.

The researchers found that most NSCLC cell lines resistant to cisplatin had high levels of the protein poly (ADP-ribose) polymerase 1 (PARP1) and elevated amounts of poly (ADP-ribosyl) (PAR). In addition, they found that the PARP1 was hyperactivated. They observed similar results

for cisplatin-resistant mesothelioma, ovarian cancer and cervical cancer cell lines.

When cisplatin-resistant NSCLC cell lines with high levels of hyperactivated PARP1 and PAR were exposed to each of two distinct PARP inhibitors, the cell lines initiated a cellular process that resulted in their death. Levels of PAR were more predictive of response to PARP inhibitors than were levels of PARP1 itself, suggesting that PAR may be an effective biomarker of response to cisplatin, according to Kroemer.

He and his colleagues then examined whether treatment with a PARP inhibitor affected the growth of tumors in mice xenografted with human NSCLC cell lines. They found that treatment significantly slowed tumor growth.

"Our data show that in most cases, cisplatin resistance is linked to stereotyped biochemical changes in cancer cells that render them vulnerable to PARP inhibitors," said Kroemer. "This has clear implications for new treatment regimens and for developing biomarkers of response to cisplatin. We are following up these exciting clinical possibilities in our laboratory."

Provided by American Association for Cancer Research

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