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UC San Diego
University Archives. RSS 6020

Variation of Normal Protein Could Be Key to Resistance to Common Cancer Drug

August 27, 2008

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Researchers at the Moores Cancer Center at the University of California, San Diego (UC SD) in La Jolla have found evidence explaining why a common chemotherapy drug, cisplatin, may not always work for every cancer patient. They have shown that when a variant version of a key protein that normally causes cell death is active, patients may be resistant to the cancer-killing drug.

The scientists say that such findings, reported online this week in the journal *Proceedings of the National Academy of Sciences*, are important to understanding how personalized therapies may be developed for patients.

In a series of experiments, Jean Wang, Ph.D., distinguished professor of medicine and Associate Director of Basic Research at the Moores UCSD Cancer Center, Richard Kolodner, Ph.D., professor of medicine at UC San Diego and Executive Director, Laboratory Science and Technology at the Ludwig Institute for Cancer Research and their co-workers found evidence that when a specific variant form of a so-called "mismatch repair" protein, PMS2, is active, cisplatin doesn't kill cancer cells the way it normally does. The cancer is, in effect, resistant to the drug.

As a repair protein, PMS2 is crucial to fixing mistakes in DNA that may occur during replication. It also has a darker side, playing a role in instructing cells to kill themselves. For example, Wang, Kolodner and their colleagues had previously shown that PMS2 is needed for cisplatin to kill cancer cells, activating another protein, p73, which in turn begins a cascade of steps leading to cell suicide. Since most cancer cell-killing therapies such as chemotherapy and radiation take advantage of this process, the team wanted to better understand how cancer cells might evade such suicide instructions, rendering the therapy ineffective.

Defects in such mismatch repair genes and proteins can increase cancer risk, particularly for hereditary colon cancer. The researchers knew that the PMS2 gene had at least 12 different forms in humans. In studies on mouse cells lacking PMS2, they tested several different variations of the human PMS2 protein, for the most part showing that PMS2 indeed sensitized cells to cisplatin, causing cell suicide. They finally found that one variant, PMS2 (R20Q), failed to activate p73 and bring about cell death in response to cisplatin. The drug's toxic effects were compromised in cells with the PMS2 (R20Q).

Wang sees many possibilities for future research. "We don't know how many people have this PMS2 variant," she explained, noting that cisplatin is the first-line therapy for testicular and ovarian cancers. "We would like to take these findings to human tumor samples. If we could find out which individuals carry this variant, it might change our decisions about treating them with cisplatin."

If researchers could track how fast ovarian cancer patients' tumors develop resistance to cisplatin, she said, correlation studies might be performed to find risk factors, such as gene variants.

Ideally, scientists will ultimately design new drugs that can push cancer cells into cell suicide, rather than repairing themselves, she noted.

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The work received funding support from the National Institute for Environmental Health Sciences, the National Cancer Institute and the Japan Society for the Promotion of Science Research Fellowships for Young Scientists.

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