Researchers find cause of chemotherapy resistance in melanoma

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Researchers with UC Irvine's Chao Family Comprehensive Cancer Center have identified a major reason why melanoma is largely resistant to chemotherapy.

UCI dermatologist Dr. Anand Ganesan and colleagues found a genetic pathway in melanoma cells that inhibits the cellular mechanism for detecting DNA damage wrought by chemotherapy, thereby building up tolerance to cancer-killing drugs.

Targeting this pathway, comprising the genes RhoJ and Pak1, heralds a new approach to treating the deadly skin cancer, which claims nearly 10,000 U.S. lives each year. Study results appear online in *Cancer Research*, a journal of the American Association for Cancer Research.

"If we can find a way to turn off the pathway responsible for this resistance, melanoma tumors would suddenly become sensitive to therapies we've been using for the last 20 years," said Ganesan, assistant professor of dermatology and biological chemistry at UCI.

In pursuit of a cause for the chemo tolerance, he and his colleagues performed a genome-wide scan for genes controlling drug resistance in melanoma cells. Their search identified RhoJ, a gene normally involved in blood vessel growth. They saw that in response to drug-induced DNA damage in a melanoma cell, RhoJ activated another gene, Pak1, which initiated a molecular cascade suppressing the cell's ability to sense this damage – and blocking the apoptosis process.

"Normally, such drug-induced DNA damage would result in cell death," Ganesan said. "But this blunting of DNA damage response allows melanoma cells to mutate and proliferate. Being capable of rapid adaptation and change is a hallmark feature of this challenging form of cancer and makes it very difficult to treat."

On the heels of this discovery, he and colleagues have begun exploring methods to inhibit the genes responsible for this DNA damage tolerance. What they come up with could one day supplement chemotherapy treatments for melanoma, Ganesan added.

More information: cancerres.aacrjournals.org/con … CAN-12-0775.abstract

Provided by University of California, Irvine

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