Study uncovers mechanism by which melanoma drug accelerates secondary skin cancers

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Patients with metastatic melanoma taking the recently approved drug vemurafenib (Zelboraf) responded well to the twice daily pill, but some of them developed a different, secondary skin cancer. Now, researchers at UCLA's Jonsson Comprehensive Cancer Center, working with investigators from the Institute of Cancer Research in London, Roche and Plexxikon, have elucidated the mechanism by which vemurafenib excels at fighting melanoma but also allows for the development of skin squamous cell carcinomas.

The very action by which the pill works, blocking the mutated BRAF protein in melanoma cells, sets off a cellular cascade in other skin cells if they have another pre-disposing cancer mutation and ultimately accelerates the secondary skin cancers, said Dr. Antoni Ribas, co-senior author of the paper and a professor of hematology/oncology.

About 50 percent of patients who get melanoma have the BRAF mutation and can be treated with vemurafenib, Ribas said. Of those, a fourth of the patients develop skin squamous cell carcinomas. The squamous cell carcinomas were removed surgically, and vemurafenib was not discontinued for this side effect.

"We wondered why it was that we were treating and getting the melanoma to shrink, but another skin cancer was developing," said Ribas, who studies melanoma at the Jonsson Cancer Center. "We looked at what was likely making them grow and we discovered that the drug was making pre-existing cells with a RAS mutation grow into skin squamous cell cancers."

The 18-month study appears in the Jan. 19, 2012 edition of the New England Journal of Medicine.

The combined research team performed a molecular analysis to identify the oncogenic mutations in the squamous cell lesions of patients treated with the BRAF inhibitor. Among 21 tumor samples studied, 13 had RAS mutations. In a different set of 14 samples, eight had RAS mutations, Ribas said.

"Our data indicate that RAS mutations are present in about 60 percent of cases in patients who develop skin squamous cell cancers while treated with vemurafenib," Ribas said. "This RAS mutation is likely caused by prior skin damage from sun exposure, and what vemurafenib does is accelerate the appearance of these skin squamous cell cancers, as opposed to being the cause of the mutation that starts these cancers."

Ribas' group found that blocking the non-mutated BRAF in cells with mutated RAS caused them to send signals around BRAF that induced the growth of the squamous cell cancers.

The discovery of the squamous cell cancer mechanism has led to strategies to inhibit both the BRAF mutation with vemurafenib and block the cellular cascade with a different drug, a MEK inhibitor, before it initiates the secondary skin cancers, said co-senior author Professor Richard Marais from the Institute of Cancer Research in London, who developed the animal model for the study.

"By understanding the mechanism by which these squamous cell cancers develop, we have been able to devise a strategy to prevent the second tumors without blocking the beneficial effects of the BRAF drugs," Marais said. "This may allow many more patients to benefit from these important drugs."

Ribas said that this is one of the very few times that oncologists understand molecularly why a side

effect to cancer treatment is happening.

"The side effect in this case is caused by how the drug works in a different cellular setting," he said. "In one case it inhibits cancer growth, and in another it makes the malignant cells grow faster."

Studies currently are under way testing BRAF and MEK inhibitors in combination in patients with metastatic melanoma, Ribas said.

"Our data provide a molecular mechanism for the clinical toxicity of a targeted oncogene inhibitor that apparently contradicts the intended effects," the study states.

Provided by University of California - Los Angeles