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New study could enhance treatments for drug-resistant melanoma

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Melanoma is the deadliest form of skin cancer, killing more than 8,000 in the U.S. each year. Approximately 40 percent of advanced melanoma tumors are driven to grow by the presence of mutations in a gene known as the BRAF gene. And although new drugs called BRAF inhibitors have shown an ability to rapidly shrink melanoma tumors, BRAF-mutated tumors often resist early treatment and only partially respond to BRAF inhibitors, which leaves behind cancer cells that can eventually grow into new tumors.

Today, two studies by researchers from UCLA's Jonsson Comprehensive Cancer Center were published online in the journal *Cancer Discovery* that provide critical insights into two important ways that tumors resist BRAF inhibitors. The researchers found the key cell-signaling pathways used by BRAF-mutant melanoma to learn how to become resistant to inhibitor drugs, and how the limited focus of BRAF inhibitors allows melanoma cells to evolve and become drug-resistant. The studies will appear later in the journal's print edition.

Led by Dr. Roger Lo, a member of the Jonsson Cancer Center and associate professor and director of the melanoma clinic in dermatology, the studies utilized patients' biopsy samples to give researchers powerful information that can be translated directly into the clinic. Specifically, the findings should help oncologists make better use of BRAF inhibitor drugs in combination with other drugs for melanoma patients.

In the first study, Lo and colleagues discovered how tumor cells escaped

the effects of BRAF inhibitors by tracking the outgrowth of melanoma cells that had learned from different cell-signaling pathways how to become BRAF inhibitor–resistant. This work, based on an analysis of 100 biopsies from patients who had been treated with BRAF inhibitors, revealed that BRAF inhibitor–resistant tumors use a variety of different signaling routes to learn resistance and that people can have more than one resistance route. Clinical trials have rarely studied these phenomena at the molecular level, which Lo said provides a much more robust view of the scale and scope of the problem.

Understanding the mechanisms of tumor resistance could help doctors identify the optimal combination of inhibitor drugs to block multiple resistance routes, which eventually could shrink tumors for a much longer period, or eradicate them completely.

"By helping us understand the core resistance pathways and tumor heterogeneity, fitness and mutational patterns that emerge under drug selection, this study lays a foundation for clinical trials to investigate the mechanisms of tumor progression in BRAF-mutant melanoma patients," Lo said.

The second study, also led by Lo, found that as soon as melanomas face BRAF inhibitors they are able to quickly turn on drug resistance pathways—a process called early adaptive resistance. Over time, these early adaptive resistance pathways are further fortified, allowing the tumor cells to break free of the BRAF inhibitor and resume growth. Therefore, early and late resistance processes are linked, and can lead to cancer recurrence and death, although the means or mechanisms may be different. Discovering the core melanoma escape pathways is an important conceptual advance when fighting BRAF inhibitor resistance, because treatments can then be designed to block these pathways all at once when treatment is initiated.

"We now have a landscape view of how melanoma first adapts and then finds ways to overcome what is initially a very effective treatment," said Dr. Antoni Ribas, a Jonsson Cancer Center member, professor of medicine and co-investigator on both studies. "We have already incorporated this knowledge into testing new combination treatments that we hope will get us back ahead of melanoma and not allow it to escape the initial treatment effectiveness and return."

Both studies were international collaborations, involving scientists from Vanderbilt University in Nashville, Tenn.; the Melanoma Institute of Australia in Sydney; and the Ludwig Institute for Cancer Research in Brussels.

The studies highlight the excellence of the translational oncology being conducted by UCLA physician-scientists, who are working to ensure that laboratory discoveries reach cancer patients as quickly as possible.

Provided by University of California, Los Angeles