Physician-scientist David Solit

Summary

Research led by investigators at Memorial Sloan Kettering has identified a previously unknown mechanism of resistance to the newly approved melanoma drug vemurafenib.

Memorial Sloan Kettering researchers have uncovered a previously unknown mechanism by which tumors can become resistant to vemurafenib — a newly approved drug used to treat patients with advanced melanoma.

“We hope our findings will lead to the development of more-effective treatments for patients with this aggressive disease,” notes laboratory researcher

and medical oncologist David B. Solit, of Memorial Hospital's Human Oncology and Pathogenesis Program (HOPP). He led the study, published in the December 15 issue of *Nature*, together with clinician-scientist Neal Rosen, of the Sloan Kettering Institute's Molecular Pharmacology and Chemistry Program, and melanoma clinicians at Memorial Sloan Kettering and other institutions.

As with antibiotics, drug resistance limits the effectiveness of many cancer therapies. To improve upon currently available therapies, scientists need to understand the basic mechanisms by which tumor cells develop resistance, Dr. Solit explains.

Vemurafenib — also known as Zelboraf® or PLX4032 — has been heralded as one of the biggest advances in the treatment of advanced melanoma in the past two decades. Memorial Sloan Kettering investigators led preclinical and clinical studies of this targeted therapy, which is taken in pill form.

Earlier this year, the positive results of an international phase III trial led by medical oncologist Paul Chapman, of Memorial Sloan Kettering's Melanoma and Sarcoma Service, prompted the US Food and Drug Administration to approve vemurafenib for the treatment of some types of melanoma.

In approximately 50 percent of people with the disease, the tumors have mutations in a gene called *BRAF*. Vemurafenib is effective only in patients who carry such mutations. The drug works by binding to the protein produced from the abnormal *BRAF* gene and interfering with its activity, restricting the ability of tumor cells to grow and survive.

The treatment produces remarkable results in some patients, whose tumors rapidly shrink or even disappear. But these effects rarely last.

"Tumors invariably develop resistance to vemurafenib," Dr. Solit explains. "In most patients, the drug stops working within a year."

Working with melanoma cells that are grown in the laboratory, he and his coworkers identified a novel mechanism that allows tumor cells to evade the therapy in some patients. The investigators observed that cells that have developed the ability to survive and divide in the presence of vemurafenib often produce a truncated, or shortened, form of *BRAF* — the protein the drug binds to and acts upon. This short form of the protein is generated by a mechanism called alternative splicing.

Alternative splicing can lead to the production of altered versions of a protein, called splice variants, which derive from the same DNA sequence though their function might differ. The study indicates that by producing a truncated variant of BRAF that lacks the middle section of the protein tumor cells are able to sidestep the therapeutic activity of vemurafenib.

By studying tumors removed from patients who had initially responded to vemurafenib and then developed resistance to the drug, the researchers were able to identify BRAF splice variants in six of 19 tumor samples. "These results suggest that this resistance mechanism might be quite common," Dr. Solit says.

"Our study provides clues as to how vemurafenib may be administered in combination with other new drugs to prolong its effectiveness," he adds. "In addition, we hope our findings will inform the design of next-generation drugs that are not as susceptible to this form of drug resistance."

He offers the example of imatinib (Gleevec®), a targeted therapy used to treat some types of leukemia as well as gastrointestinal stromal tumors. Like vemurafenib, imatinib often controls cancer successfully for months or years, but then loses its effectiveness.

Research led by HOPP Chair Charles L. Sawyers, who helped develop imatinib, has revealed that resistance to this therapy can arise when tumors develop new gene mutations that prevent the drug from binding to its target. Based on this discovery — which Dr. Sawyers made while working at the University of California, Los Angeles — he and other scientists developed an alternative therapy, dasatinib (Sprycel®), which today is being used in some leukemia patients who no longer benefit from imatinib or are not able to tolerate its side effects.

However, Dr. Solit explains, "our findings show that melanoma tumors become resistant to vemurafenib in a manner different from imatinib." Rather than arising from secondary mutations in the BRAF gene, vemurafenib resistance results from a change in the processing of the gene's mRNA, or messenger RNA. (A molecule that resembles DNA, mRNA is used by the cell as a recipe to make proteins.)

"This resistance mechanism is conceptually new," Dr. Solit says. "In fact, changes that occur during mRNA processing may be a common yet largely unexplored feature of disease and drug resistance."

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