# Studies identify cell-signaling pathway alterations responsible for melanoma drug resistance

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Genomic profiling of treatment-resistant, BRAF-mutated melanomas revealed multiple gene alterations, mostly involving a cell-signaling pathway called the MAPK pathway, and more potent forms of existing drugs and drugs targeting the protein ERK may provide durable control of the disease, according to two studies published in *Cancer Discovery*, a journal of the American Association for Cancer Research.

"Currently there is not enough known about the genetic and molecular changes that may cause drug resistance in melanomas harboring BRAF mutations," said Levi A. Garraway, M.D., Ph.D., associate professor in the Department of Medicine at the Dana-Farber Cancer Institute at Harvard Medical School in Boston, Mass. "We applied whole-exome and, in some cases, transcriptome sequencing to study drug-resistant melanoma samples from patients treated either with BRAF inhibitor monotherapy, or with combined BRAF and MEK inhibitors.

"Drug resistance is solvable, but it is more complicated than we had initially assumed," added Garraway. "We are hopeful that utilizing systematic approaches in partnership with large, multi-institutional clinical collaborations, like we have done here, will help us design new therapeutic combinations. The ultimate goal is to find new and long-lasting solutions to drug-resistant melanomas and other cancers."

BRAF and MEK are proteins involved in a cell-signaling pathway called the MAPK pathway. Melanomas that harbor mutations in BRAF respond to BRAF and MEK inhibitors; however, almost all of them develop resistance to these drugs within months.

"Analyses of melanomas that were treated with monotherapy showed there are some genes that are commonly mutated, but there may be many other relevant genes that are less commonly mutated, a phenomenon we call a 'long-tail distribution,'" said Garraway. "Of the resistance genes that we could characterize, the majority seemed to affect the MAPK pathway.

"What is also intriguing is that, in a second study, we analyzed samples from melanomas that became resistant to both BRAF and MEK inhibitors, and found exactly the same kinds of alterations [in the MAPK pathway] that we saw in melanomas treated with BRAF inhibitors alone," added Garraway. "This tells us that we still may not be hitting the MAPK pathway adequately enough, possibly because of drug side effects that may occur at higher doses. It would be of great interest to test more potent BRAF and MEK inhibitors, or possibly ERK inhibitors, in future clinical trials."

In the first study, Garraway and colleagues analyzed samples of metastatic melanomas harboring the BRAF V600E mutation, collected and archived from 45 patients who received BRAF-inhibitor monotherapy, either vemurafenib or dabrafenib. In 51 percent of the samples, they detected multiple alterations in genes involved in the MAPK pathway, including the genes MEK1, MEK2, and a gene regulated by the MAPK pathway called MITF.

The researchers also found that multiple known resistance-causing mutations were sometimes observed within the same tumor, indicating BRAF-mutant melanomas may use multiple resistance mechanisms simultaneously.

In the second study, Garraway and colleagues evaluated samples from five patients whose melanomas had become resistant to combined

BRAF and MEK inhibition. In three drug-resistant tumor samples, they found alterations in the MAPK pathway not seen in the pretreatment tumors, including a novel mutation in the gene MEK2. However, the alterations found in these samples were mostly similar to those found in melanomas that developed resistance to treatment with BRAF-inhibitor monotherapy.

Follow-up experimental studies using melanoma cells rendered drug-resistant in the laboratory showed that melanomas with resistance mutations in MEK1 or MEK2 were still sensitive to an inhibitor that acts on another component of the MAPK pathway, called ERK. This led the researchers to suggest that targeting ERK, in addition to BRAF and MEK, might be an effective strategy to tackle drug-resistant melanomas with BRAF mutations.

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