New molecular targets identified in some hard-to-treat melanomas

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Two novel BRAF fusions were identified in melanomas previously considered to be negative for molecular targets, and melanomas with these fusions were found to be potentially sensitive to anticancer drugs called MEK inhibitors, according to a study published in *Clinical Cancer Research*, a journal of the American Association for Cancer Research.

"About 35 percent of melanomas are, as of today, considered 'pan-negative,' which means they are devoid of any previously known driver mutations in the genes BRAF, NRAS, KIT, GNAQ, and GNA11," said Jeffrey A. Sosman, M.D., professor of medicine at Vanderbilt-Ingram Cancer Center in Nashville, Tenn., and a Stand Up To Cancer Melanoma Dream Team investigator. "Here at Vanderbilt, we have been interested in looking at patients whose tumors have none of these driver mutations, to see what their tumors do have that can be targeted therapeutically.

"We used the FoundationOne platform to perform a sophisticated analysis called targeted next-generation sequencing. Based on our findings, it appears that about 8 percent of pan-negative melanomas have BRAF fusions," said Sosman. "Our results are important because they obviously suggest that there probably are other, as yet unidentified, molecular changes that make these melanomas susceptible to drugs that are available right now."

In some cancers, two or more genes fuse erroneously to produce abnormal proteins, which can function as the "drivers" of those cancers.

In a pan-negative melanoma sample from one of their patients, Sosman; William Pao, M.D., Ph.D., a co-author on this study and a 2009 Stand Up To Cancer Innovative Research Grant recipient; and their colleagues identified a fusion between two genes, PAPSS1 and BRAF, which they called PAPSS1-BRAF. They then evaluated melanomas from an additional 51 patients, 24 of which were pan-negative. In one of these 24 pan-negative samples, they identified a second novel BRAF fusion, called TRIM24-BRAF.

The investigators conducted further studies in the laboratory and found that both BRAF fusions activated a pathway in the cancer cells called the MAPK signaling pathway. They then treated these fusion-bearing cells either with the BRAF inhibitor vemurafenib or with trametinib, a drug that inhibits a protein in the MAPK signaling pathway called MEK. They found that signaling induced by the BRAF fusions was not responsive to vemurafenib but could be inhibited by trametinib, which led them to suggest that the novel fusions they identified could make melanoma cells harboring them sensitive to MEK inhibitors.

"Currently, there is immense value in identifying novel mutations in untreatable cancers because many of them are clinically relevant, which means they may be sensitive to drugs that are either being developed or are already FDA approved," said Sosman. "Our data support the idea that 'pan-negative' cancers are not truly pan-negative."

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