Researchers discover mechanism leading to BRAF inhibitor resistance in melanoma

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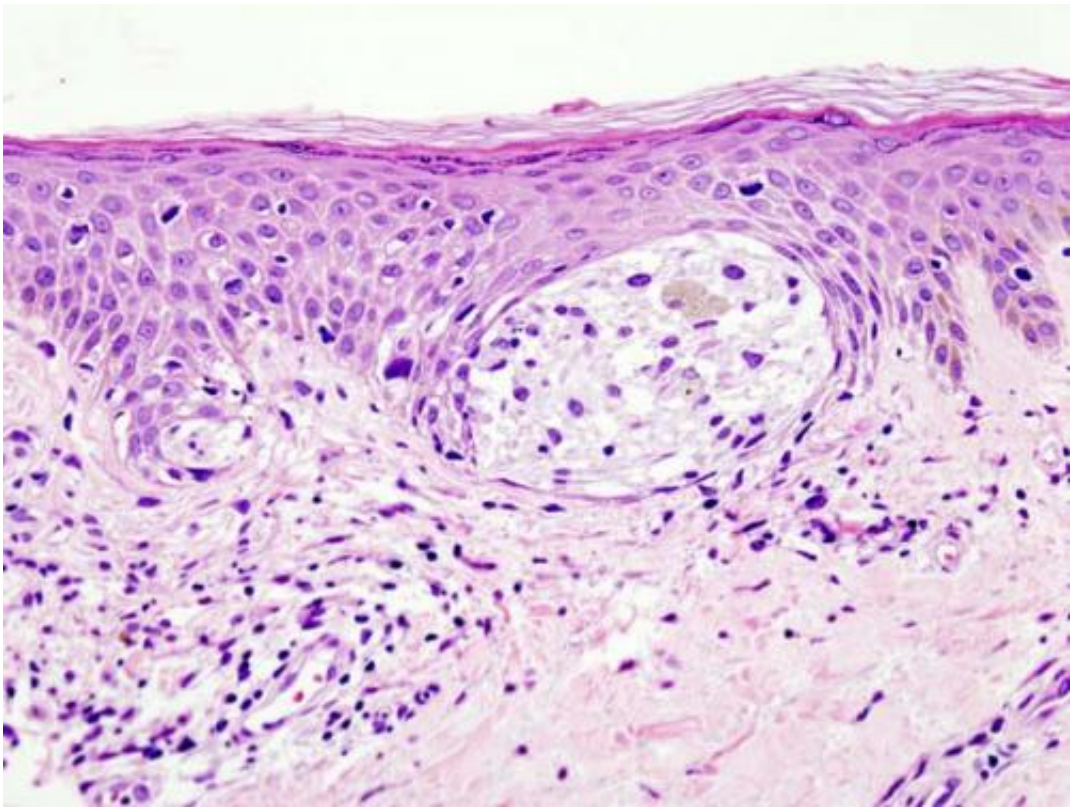

Melanoma in skin biopsy with H&E stain—this case may represent superficial spreading melanoma. Credit: Wikipedia/CC BY-SA 3.0

The development of targeted therapies has significantly improved the survival of melanoma patients over the last decade; however, patients often relapse because many therapies do not kill all of the tumor cells, and the remaining cells adapt to treatment and become resistant. Moffitt

Cancer Center researchers have discovered a novel mechanism that can lead melanoma cells to develop resistance to drugs that target the protein BRAF.

Mutations in the gene BRAF are the most common mutation found in melanoma, with up to 50 percent of tumors testing positive for the mutations. Several agents that directly target BRAF have been approved by the Food and Drug Administration for the treatment of melanoma patients who have the mutation, including dabrafenib and vemurafenib. However, many patients become resistant to BRAF inhibitors and relapse. This resistance is associated with reactivation of the BRAF protein communication pathway in tumor cells.

Another gene that is frequently mutated in melanoma is PTEN. Studies have shown that melanoma patients who have both BRAF and PTEN mutations may have a poorer response to dabrafenib and vemurafenib therapy.

Moffitt researchers wanted to determine the mechanism responsible for resistance to BRAF inhibitors. They discovered that BRAF inhibitors cause BRAF and PTEN mutant melanoma cells to increase levels of fibronectin. Fibronectin is a protein that is expressed in the space surrounding cells. The researchers found that higher levels of fibronectin allow melanoma cells to form their own protective environment that reduces the ability of BRAF inhibitors to kill tumor cells.

Importantly, the researchers discovered that melanoma patients who have PTEN mutations and higher levels of fibronectin in their tumors tend to have a lower overall survival. They also showed that targeting the tumor with BRAF inhibitors combined with a drug that targets the protective environment significantly enhances the killing effect of the BRAF inhibitor.

"This study gives important new insights into why nearly all melanoma patients fail targeted therapy," explained Keiran S. Smalley, Ph.D., associate member of the Tumor Biology Program at Moffitt.

The researchers believe that effective cancer therapy in the future will require the combined action of drugs that target both the tumor and its adaptive responses to initial therapies. This is particularly important for melanoma patients because the survival of only a single cell after initial cancer therapy is enough to allow a melanoma tumor to regrow. According to Inna Fedorenko, Ph.D., post-doctoral fellow at Moffitt, "targeting the protective environment is one way of delivering more durable therapeutic responses to our patients."

The study was published June 15 online ahead of print in the journal *Oncogene*.

More information: Fibronectin induction abrogates the BRAF inhibitor response of BRAF V600E/PTEN-null melanoma cells, *Oncogene* advance online publication 15 June 2015; DOI: 10.1038/onc.2015.188

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