MedicalXpress

BRAF inhibitor treatment causes melanoma cells to shift how they produce energy

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A multi-institutional study has revealed that BRAF-positive metastatic malignant melanomas develop resistance to treatment with drugs targeting the BRAF/MEK growth pathway through a major change in metabolism. The findings, which will be published in *Cancer Cell* and have been released online, suggest a strategy to improve the effectiveness of currently available targeted therapies.

"We were surprised to find that melanoma cells treated with the BRAF inhibitor vemurafenib dramatically change the way they produce energy to stay alive," says David E. Fisher, MD, PhD, chief of Dermatology at Massachusetts General Hospital (MGH) and a co-corresponding author of the *Cancer Cell* paper. "While current BRAF inhibitor treatment is a major improvement – shrinking tumors in most patients and extending survival for several months – patients eventually relapse. So there is an ongoing need to improve both the magnitude and durability of these responses."

In about half the cases of malignant melanoma – the most deadly form of skin cancer – tumor growth is driven by mutations in the BRAF gene. Research by investigators at the MGH Cancer Center and elsewhere has shown that treatment with drugs that block BRAF activity temporarily halts tumor growth. Combining a BRAF inhibitor with a drug that targets MEK, another protein in the same growth pathway, strengthens and extends the antitumor response. The current study was designed to investigate how BRAF inhibition changes metabolic activity within melanoma cells and to find other possible treatment targets.

The most common way that cells convert glucose into energy is called oxidative phosphorylation and largely relies on the activity of the cellular structures called mitochondria. Many cancer cells use an alternative mechanism that produces the energy compound ATP without involving mitochondria. A series of experiments by the MGH team revealed that the elevated BRAF activity in BRAF-positive melanoma cells suppresses oxidative phosphorylation by reducing expression of a transcription factor called MITF. Suppressing production of MITF reduced levels of a protein called PGC1α that regulates the generation and function of mitochondria. But melanoma cells treated with a BRAF inhibitor showed elevated MITF activity, along with increased expression of oxidative phosphorylation genes and greater numbers of mitochondria. By switching to oxidative phosphorylation to supply the energy they need, the tumor cells increased their ability to survive in spite of BRAF inhibitor treatment.

"These findings suggest that combination treatment with mitochondrial inhibitors could improve the efficacy of BRAF inhibitors in malignant melanoma," says Fisher, the Wigglesworth Professor of Dermatology at Harvard Medical School. "Several small molecules that target mitochondrial metabolism have been identified by investigators here at the MGH and elsewhere, and laboratory investigations of specific combinations of BRAF inhibitors with mitochondrial antagonists are currently underway."

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