

Researchers identify mechanism of resistance to BRAF inhibitors in melanoma

April 15 2019



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

Melanoma is one of the most aggressive types of skin cancer, but recent advances in targeted therapies have improved the prognosis for many patients. Unfortunately, for some patients these positive outcomes are not long lasting, due to the development of drug resistance and tumor

recurrence. Moffitt Cancer Center researchers have discovered a mechanism by which melanoma cells become resistant to the commonly used drugs that target the BRAF protein and its signaling pathway. Their study was published online today by the journal *Cancer Research*.

One of the most common genetic mutations found in melanoma is alteration of the BRAF gene. Mutations in BRAF are found in approximately 50 percent of all melanomas, leading to increased [cell proliferation](#) and survival. Several drugs are available that target BRAF and a downstream gene named MEK that cooperates with BRAF in cancer development. These drugs have resulted in significant improvements in patient outcomes; however, many patients eventually develop [drug resistance](#).

Moffitt researchers conducted a series of laboratory experiments with [cell lines](#) and mouse models to determine how melanoma becomes resistant to these commonly used drugs. They discovered that [melanoma cells](#) that are resistant to BRAF inhibitors undergo a similar response mechanism as cells treated with stress-inducing factors, such as UV radiation and low oxygen. During each of these conditions, the cells increased expression of the protein histone deacetylase 8 (HDAC8).

HDACs are proteins that regulate the expression level and activity of other proteins within the cell. HDACs are often deregulated in cancer and several drugs that target HDACs are approved for the treatment of different types of cancer. The researchers found that HDAC8 stimulated the activity of the AP-1 transcription factor that subsequently increased the expression of genes that are involved in cell motility and invasion.

"Our work provides the first evidence that HDAC8 activity is increased in responses to multiple, diverse cellular stresses, and that this in turn initiates a transcriptional program that is associated with increased melanoma cell survival," explained Keiran Smalley, Ph.D., director of

the Donald A. Adams Melanoma and Skin Cancer Center of Excellence at Moffitt.

This link between HDAC8 and drug resistance suggested to the researchers that drugs targeting HDACs may be able to overcome cellular resistance mechanisms to BRAF inhibitors. The researchers performed a series of mouse experiments and found that co-treatment with both HDAC and BRAF inhibitors inhibited melanoma tumor growth better than either agent alone.

The researchers hope their work will lead to clinical studies that will examine the potential of HDAC inhibitors to prevent the development of drug resistance in melanoma. "These findings provide a strong rationale to pursue the development of more selective and potent HDAC8 inhibitors for future evaluation as drugs that can limit phenotype switching and therapeutic escape in melanoma," said Smalley.

More information: *Cancer Research* (2019). [DOI: 10.1158/0008-5472.CAN-19-0040](https://doi.org/10.1158/0008-5472.CAN-19-0040)

Provided by H. Lee Moffitt Cancer Center & Research Institute

Citation: Researchers identify mechanism of resistance to BRAF inhibitors in melanoma (2019, April 15) retrieved 23 April 2024 from <https://medicalxpress.com/news/2019-04-mechanism-resistance-braf-inhibitors-melanoma.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.