

Researchers discover mechanism leading to drug resistance, metastasis in melanoma

12 January 2015

Moffitt Cancer Center researchers have discovered a mechanism that leads to resistance to targeted therapy in melanoma patients and are investigating strategies to counteract it. Targeted biological therapy can reduce toxicity and improve outcomes for many cancer patients, when compared to the adverse effects of standard chemotherapeutic drugs. However, patients often develop resistance to these targeted therapies, resulting in more aggressive cells that can spread to other sites or cause regrowth of primary tumors.

B-Raf is a protein that is frequently mutated in human cancers, leading to increased tumor cell growth, survival and migration. Drugs that target B-Raf or another protein in the same network called MEK have proved effective in clinical trials. Several B-Raf and MEK inhibitors have been approved with the combination of a B-Raf and a MEK inhibitor being the current standard of care for patients with B-Raf mutant melanoma. However over time many patients become resistant to B-Raf and B-Raf/MEK inhibitor therapy.

Moffitt researchers found that patients who are on B-Raf inhibitor drugs develop more new metastases than patients who are on standard chemotherapy. The researchers wanted to determine how this acquired resistance develops in order to devise better treatment options for patients. They found that [melanoma cells](#) that are resistant to B-Raf inhibitors tend to be more aggressive and invasive, thereby allowing the tumor to spread to a new organ site. They used a large screening approach and discovered that this resistance and [aggressive behavior](#) was due to high activity of a cell surface protein called EphA2, which is also found on glioblastoma stem cells.

Their study found that simply withdrawing the B-Raf or MEK inhibitor drugs reversed the cells' aggressive behavior. "This suggests that alternate dose scheduling where B-Raf and MEK inhibitors are given to patients intermittently may reduce the

aggressiveness of the disease... meaning patients could stay on therapy for more time," said Keiran S. Smalley, Ph.D., scientific director of the Donald A. Adam Comprehensive Melanoma Research Center of Excellence at Moffitt.

The research also showed that targeting EphA2 reduced the aggressive behavior of the melanoma cells. This suggests that drugs that target EphA2 may prevent the development of new disease in [patients](#) who receive B-Raf and B-Raf /MEK inhibitor therapy.

More information: The study was published in the online edition of *Cancer Discovery* on Dec. 26: cancerdiscovery.aacrjournals.org/doi/10.1158/2156-8756.120152

Provided by H. Lee Moffitt Cancer Center & Research Institute

APA citation: Researchers discover mechanism leading to drug resistance, metastasis in melanoma (2015, January 12) retrieved 30 August 2022 from <https://medicalxpress.com/news/2015-01-mechanism-drug-resistance-metastasis-melanoma.html>

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