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Massive screen of drug combinations may find treatment for resistant, BRAF-mutant melanoma

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A team of Massachusetts General Hospital (MGH) investigators has discovered a new combination of drugs that may be effective against one of the deadliest cancers, malignant melanoma. The combination - pairing a drug targeted against mutations in the BRAF gene with a second drug that targets another important signaling pathway - was discovered through one of the largest screens of cancer drug combinations conducted to date. Findings from the study conducted at the MGH Cutaneous Biology Research Center and Center for Molecular Therapeutics have been published in the open-access journal *PLOS ONE.*

"We wanted to see whether very-large-scale screening across a diverse collection of cancer cell lines and a large number of drugs could yield new combinations for patients with cancer," says Adam Friedman, MD, PhD, of the CBRC and the MGH Cancer Center, who led the study. "By conducting such a screen, we found one specific combination of agents that are already being used clinically that potentially could be used for a specific group of patients - those with BRAF-mutant cancers."

Friedman notes that, even with the increasing number of drugs targeting specific molecular abnormalities that drive tumor growth, most patients are only treated with one such drug at a time. Most of those treated with targeted-therapy drugs will relapse within a year, often because their tumors have become resistant, and some tumors never respond to the targeted drugs. While combining anti-cancer drugs appears a promising

strategy, the sheer volume of drugs currently in use or in development - more than 500, which could make up more than 100,000 two-drug combinations - makes testing each potential combination in clinical trials challenging.

Previous efforts to screen potential drug combinations only analyzed use of a few drugs against a limited number of cell lines or lines in which genomic variations were poorly understood. This study utilized 36 well-characterized melanoma cell lines assembled by the MGH Center for Molecular Therapeutics to test all possible combinations of more than 100 oncology drugs, two-thirds of which are currently in clinical use. More than 5,775 potential drug combinations, as well as each single drug, were screened against each cell line, looking for effects on the number and viability of tumor cells. While several combinations showed synergistic effects - with some drugs sensitizing the cells against several other drugs - most combinations increased the response of only one or two cell lines, implying that the vulnerability of an individual patient's tumor to these combinations depends on its unique genetic signature.

Since around half the cases of malignant melanoma are driven by mutation in the BRAF gene, the team focused on combinations that might address intrinsic resistance to the BRAF inhibitor vemurafenib. They found that combining that drug with the cediranib, an investigational drug that targets a group of proteins known to be involved in blood vessel formation, had synergistic effects against cell lines that were resistant to treatment with vemurafenib alone but not those sensitive to single-agent therapy. They also tested this combination in animal models into which two resistant cell lines had been grafted, and found significant synergistic effects against both tumor models.

"We need to confirm this synergistic activity of vemurafenib and cediranib across a broader range of melanoma models, investigate why the particular combination is effective, and find biomarkers that predict

which patients with BRAF-mutant melanoma should receive this combination," says Friedman, who is a research fellow in Dermatology at Harvard Medical School. "What is really exciting is that these drugs are already in the clinic; in fact a clinical trial for a similar combination is already underway at another research center. We may be able to quickly improve on the selection criteria for this trial and identify patients whose tumors might respond."

He adds, "This study was actually a pilot project for a much larger effort within the Center for Molecular Therapeutics to map responses against drug combinations across hundreds of cancer cell lines, not just melanoma, and look for novel combinations that will benefit subsets of patients regardless of the particular type of tumor they have. Since our collection of cell lines is completely genetically annotated - which means that mutations and expression changes in each line's genes have been documented - we should be able to identify in advance patients who will benefit from specific combinations. Beyond the specific combination we focused on, this study should help others understand the technical challenges of analyzing such a large combination dataset."

More information: *PLOS ONE*, journals.plos.org/plosone/arti … journal.pone.0140310

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