Blocking melanoma's escape: Avatars break theraping resistance in relapsed cancers

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Meenhard Herlyn, D.V.M., D.Sc., is director of the Melanoma Research Center at The Wistar Institute. Credit: The Wistar Institute

Melanoma patients who receive treatment with targeted therapies experience an initial response that feels like a cure, but that early

excitement is quickly dampened when patients relapse as their cancers find alternative pathways in our cells to grow and spread. With melanoma so good at escaping targeted treatments, there's a dire need to halt these cancers in their tracks to prolong good responses and promote longer, healthier lives.

Now, by utilizing a revolutionary method that allows mice to serve as "avatars" for patients, scientists at The Wistar Institute have shown that a previously ineffective targeted drug for melanoma may actually be quite potent in halting the progression of disease in certain patients.

The findings were published by the journal *Clinical Cancer Research*.

Personalized medicine holds enormous promise for melanoma patients. Melanoma accounts for only about five percent of all skin cancer cases, yet the disease is responsible for about 75 percent of all skin cancer deaths. Since specific mutations are responsible for melanoma growth and proliferation, drugs that target mutated skin cancer cells are an attractive treatment option. For example, the gene BRAF is mutated in about half of all melanomas, leading to aberrant activation of an important growth pathway. Drugs that inhibit activated BRAF can extend the lives of patients.

However, almost every patient who receives drugs eventually relapses and no longer responds to initial treatments. That's because the melanoma cells become aware of the blockade and find an alternative survival mechanism. Researchers are now studying these melanoma "escape routes" in the hope of cornering cancerous cells with combination treatments that don't allow them to survive.

"There are about fifteen routes of escape that we've identified in melanoma patients, and it is never easy to predict which one will be used in any given patient," said Meenhard Herlyn, D.V.M., D.Sc., director of

the Melanoma Research Center and Caspar Wistar Professor in Melanoma Research at The Wistar Institute, and lead author of this study. "These melanoma cells will do anything to get reactivated."

To identify escape routes and test therapeutic treatments that block the spread of the disease, researchers at Wistar are using a revolutionary method called patient-derived xenograft (PDX) mouse models. Researchers implant tumor samples from patients into mice, thereby creating avatars for individual patients. One tumor can be studied in a pool of mouse avatars. This allows researchers to study different drugs and combinations of drugs to see how one type of tumor will respond.

In this latest study, the team at Wistar used PDX models to test tumors from patients who had received a BRAF inhibitor and then relapsed after treatment. In addition, observing mutations in genes such as NRAS and MAP2K1 - which are known escape route genes for previously treated BRAF-mutated melanomas - the scientists also observed amplification of MET, which suggested a possible new mechanism of resistance.

Wistar's team used this information to test a combination of targeted therapies as a means of halting disease progression. A MET inhibitor called capmatinib, currently in clinical trials, showed significant tumor regression when used by itself to treat melanoma, but the results were only temporary, meaning that an amplification of MET was not the sole driver of tumor growth. However, when capmatinib was given in combination with encorafenib (a BRAF inhibitor) and binimetinib (a MEK inhibitor hitting the BRAF pathway), the researchers observed complete and sustained tumor regression in all animals who received this combination.

"Historically, MET inhibitors have not shown much activity in melanoma patients," said Clemens Krepler, M.D., research assistant

professor in the Herlyn Lab at The Wistar Institute and first author of the study. "While our findings need to be validated in more robust trials, this study provides evidence than MET inhibitors given either after or at the same time as BRAF inhibitors appear to successfully halt the progression of the disease and may considerably lengthen response and overall survival in melanoma patients."

More information: clincancerres.aacrjournals.org … 5-1762.full.pdf+html

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