Blocking autophagy with malaria drug may help overcome resistance to melanoma BRAF drugs

24 February 2014

Half of melanoma patients with the BRAF mutation have a positive response to treatment with BRAF inhibitors, but nearly all of those patients develop resistance to the drugs and experience disease progression.

Now, a new preclinical study published online ahead of print in the *Journal of Clinical Investigation* from Penn Medicine researchers found that in many cases the root of the resistance may lie in a never-before-seen autophagy mechanism induced by the BRAF inhibitors vermurafenib and dabrafenib. Autophagy is a process by which cancer cells recycle essential building blocks to fuel further growth. Block this pathway with the antimalarial drug hydroxycholoroquine (HCQ), the authors found, and the BRAF inhibitors will be able to do their job better.

"This study opens the door for combination therapy with BRAF inhibitors and autophagy inhibitors, which haven't been explored deeply as a therapeutic option for patients whose tumors are resistant," said Ravi K. Amaravadi, MD, assistant professor of Medicine in the division of Hematology/Oncology at the Perelman School of Medicine and co-Leader of the Cancer Therapeutics Program at Penn Medicine's Abramson Cancer Center. "Here, we show that the BRAF inhibitors induce autophagy as a way to escape cell death, which gives us clues on how to interfere with this mechanism of resistance and improve outcomes for these patients."

Based on these promising preclinical results, Dr. Amaravadi and his team have already launched a clinical trial for patients with advanced BRAF mutant melanoma to see how well-tolerated HCQ is with the BRAF inhibitor vemurafenib. "So far," he said, "we are seeing a benefit to patients and low toxicity."

BRAF inhibitors are a first line of treatment for melanoma patients who harbor the BRAF mutation, which is an abnormal change in a gene that causes some melanoma tumors to grow and spread more aggressively. While 50 percent of patients initially respond to that treatment, nearly 100 percent exhibit disease progression seven months after treatment, making it imperative to find a way to re-sensitize the tumor to treatment.

Autophagy has emerged as a key pathway that cancer cells use to survive in the face of assault by chemotherapy and radiation. However, autophagy as a potential druggable mechanism in patients who become resistant to BRAF inhibitors has not been investigated.

Using tumor biopsies from BRAF melanoma patients treated with either BRAF inhibitors or with combined BRAF and MEK inhibitors, a recently FDA-approved drug combination to fight the other mechanisms of resistance, the researchers found that tumors resistant to the BRAF inhibitors had increased levels of autophagy compared with baseline tumors. Moreover, the level of therapy-induced autophagy was correlated with lower response rates and shorter progression-free survival times.

The researchers also examined BRAF mutant melanoma cell lines, and found that BRAF inhibition induced autophagy by way of an endoplasmic reticulum (ER) stress response. The binding of a BRAF mutation to the ER stress gatekeeper GRP78 is a new and unexpected molecular interaction driving resistance, and establishes a new signaling axis that has multiple drug targets, Dr. Amaravadi said.

What's more, the researchers found that blocking this mechanism with HCQ—a drug used to treat malaria that has been shown in previous studies to block autophagy—limited BRAF inhibitor-induced autophagy and enhanced cancer cell death in mouse models.

"As the use of BRAF inhibitors become more widespread, we'll need to discover new options for our patients so they can overcome this destined resistance," said Dr. Amaravadi. "Here, we have a new pathway that links the BRAF mutation to ER stress and autophagy that could be exploited with an already-approved FDA drug, which I believe could be a game changer for this group of patients."

Next steps are to continue to enroll patients in the clinical trial investigating autophagy inhibitors in combination with BRAF inhibitors and potentially other, emerging new drug combinations proven to improve patient response.

Provided by University of Pennsylvania School of Medicine