New combo of chemo and well-known malaria drug delivers double punch to tumors

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Blocking autophagy -- the process of "self-eating" within cells -- is turning out to be a viable way to enhance the effectiveness of a wide variety of cancer treatments.

Specifically, blocking the action of an acidic inner cell part, which acts like a stomach and chews up proteins for recycling, is the main attack strategy, says Ravi K. Amaravadi, MD, an assistant professor of Medicine at the Perelman School of Medicine and Abramson Cancer Center at the University of Pennsylvania. Amaravadi will give a presentation on the role of autophagy in fighting cancer at the annual American Association for Advancement of Science meeting in Vancouver, British Columbia.

His lab and others have demonstrated that adding hydroxychloroquine (HCQ) - an FDA-approved drug used commonly for malaria and rheumatoid arthritis -- to many cancer therapies, including chemotherapy, targeted therapy, radiation, and immunotherapy, can enhance the antitumor activity of these drugs in laboratory models of treatment-resistant cancers, and ongoing clinical trials.

Autophagy is increased in cancer cells. Normally, it is a survival pathway allowing a cell to recycle damaged proteins when it's under stress and reuse the damaged parts to fuel further growth.

Cancer cells might be addicted to autophagy, since this innate response may be a critical means by which the cells survive nutrient limitation and lack of oxygen commonly found within tumors. And, it is likely to explain how some cancer cells evade chemotherapies by using, essentially, a work around.

Nearly 30 phase I and Phase II clinical trials involving HCQ have been launched or are in planning stages in many different malignancies, including melanoma, multiple myeloma, renal cell carcinoma, colon cancer, prostate cancer, breast cancer, and others.

Preliminary results for most of the trials are encouraging. "Our assays performed on human blood and tissue samples indicate that high doses of HCQ are required to block autophagy in patients, and in some cases, such as in a brain tumor trial, these high doses, in combination with specific anticancer agents, can lead to toxicity for the tumor," says Amaravadi. "As the first phase I trials of HCQ are being completed, it is clear that in most cases the high-dose HCQ, in combination with existing cancer therapy, is well tolerated."

Randomized controlled trials using HCQ combinations to truly determine the effectiveness of the approach are planned. While these are being considered, the team will conduct additional laboratory experiments to identify more potent and specific inhibitors of autophagy and to identify biomarkers that can predict which patients are most likely to respond to this approach. To that end, the Amaravadi lab has identified a compound called Lys05, which is 10-fold more potent than HCQ at blocking the cell from giving the cancer cell a source of raw energy.

"While our knowledge of the role of autophagy in cancer is still in its infancy, the opportunity to learn about autophagy, both at the bench and the bedside, could accelerate the translation of basic advances in this

field into clinical benefit for patients with cancer," says Amaravadi.

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