New strategy for unleashing cancer-fighting power of p53 gene

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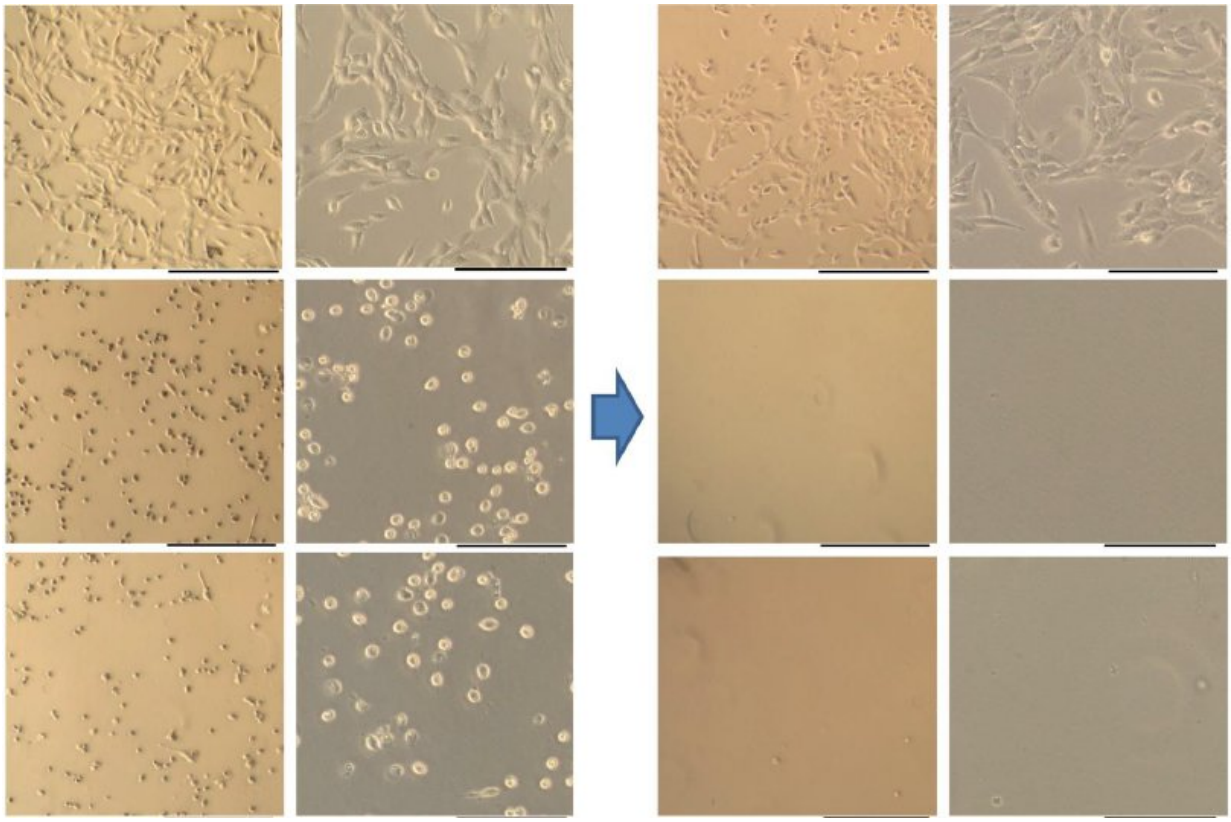

Cell-culture images excerpted from newly published Roswell Park research illustrate that disabling the protein peptidase is an effective strategy for killing cancer cells. Credit: Roswell Park Cancer Institute

Tumor protein p53 is one of the most critical determinants of the fate of cancer cells, as it can determine whether a cell lives or dies in response

to stress. In a new study published today in the journal *Nature Communications*, a research team from the Department of Pharmacology and Therapeutics at Roswell Park Cancer Institute reports their discovery of a major mechanism by which cells regulate this important and multifunctional tumor suppressor, opening up new avenues for cancer research and treatment.

p53 is stimulated by various forms of cellular stress, such as exposure to radiation or carcinogens. Yuesheng Zhang, MD, PhD, and a team of colleagues found that more than half of all nuclear and cytoplasmic p53 is bound to and suppressed by the protein peptidase D (PEPD), also known as prolidase. Under normal conditions, PEPD's suppression of p53 is essential for cell survival, but in cancer cells, PEPD is essential for tumor growth. The complex that is formed between PEPD and p53 is critical for cell survival.

Using the stressors doxorubicin and hydrogen peroxide as examples, Dr. Zhang and team found that the PEPD-p53 complex serves as a "p53 depot" designed to rapidly mobilize a large amount of p53 in response to cell stress. The team discovered that releasing p53 from the PEPD-p53 complex resulted in the death or growth inhibition of cancer cells. This study demonstrates that disrupting the association between PEPD and p53 causes cell death and tumor regression and also raises the possibility that tumor cells overexpress PEPD in order to enhance p53 inhibition.

"This study uncovers a very important physiological function of PEPD and a critical new regulatory mechanism of p53," says Dr. Zhang, a Professor of Oncology at Roswell Park and senior author on the new study. "The interaction between PEPD and p53 likely operates in most if not all cells, since both proteins are expressed ubiquitously. Therefore, disrupting the way in which PEPD suppresses p53 represents an important new therapeutic strategy for controlling many different types of cancer."

The research also reveals a previously unrecognized anticancer mechanism of doxorubicin, which is widely used as a chemotherapy drug.

"We have shown that p53 separation from PEPD is critical for doxorubicin-induced p53 activation and cancer cell killing, raising the intriguing question of whether other stress-inducing anticancer agents may also activate p53 by disrupting the PEPD-p53 complex. We also demonstrate that antioxidant N-acetylcystine markedly reduces the cancer-cell-killing activity of doxorubicin by preventing p53 disassociation from PEPD, adding to the evidence that antioxidants may limit the effectiveness of chemotherapy," notes Lu Yang, PhD, a Roswell Park Research Associate and first author on the new paper.

More information: Lu Yang et al. PEPD is a pivotal regulator of p53 tumor suppressor, *Nature Communications* (2017). DOI: 10.1038/s41467-017-02097-9

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