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Novel drug action against solid tumors explained

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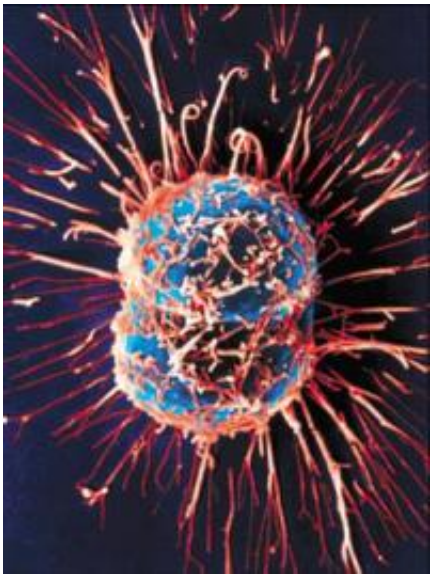

Dividing Cancer Cells. Credit: University of Birmingham

Researchers at UC Davis, City of Hope, Taipai Medical University and National Health Research Institutes in Taiwan have discovered how a drug that deprives the cells of a key amino acid specifically kills cancer cells.

Their paper, published today in *Proceedings of the National Academy of Sciences*, is the culmination of nearly a decade of research into the role of arginine – and its deprivation – in the generation of excessive autophagy, a process in which the cell dies by eating itself.

Study co-author Hsing-Jien Kung, a renowned cancer biologist and UC Davis professor emeritus who now leads the National Health Research Institutes in Taipei, Taiwan, first discovered the mechanism by which arginine deprivation works in 2009, when he led basic science research at the UC Davis Comprehensive Cancer Center.

"Traditional cancer therapies involve 'poisoning' by toxic chemicals or 'burning' by radiation cancer cells to death, which often have side effects," Kung said. "An emerging strategy is to 'starve' cancer cells to death, taking advantage of the different metabolic requirements of normal and cancer cells. This approach is generally milder, but as this study illustrates, it also utilizes a different death mechanism, which may complement the killing effects of the conventional therapy."

The discovery led to the further development of a drug now being tested in several clinical trials against melanoma, prostate, liver, sarcoma and other cancers that lack an enzyme that helps synthesize arginine, an amino acid with an essential role in cell division, immune function and hormone regulation.

The study published today describes how arginine starvation specifically kills tumor cells by a novel mechanism involving mitochondria dysfunction, reactive oxygen species generation, nuclear DNA leakage and chromatin autophagy, where leaked DNA is captured and "eaten" by giant autophagosomes.

Unlike apoptosis, a cell-death process in which the DNA is damaged within the cell nucleus, in chromatin-autophagy the nucleus is fragmented and its pieces shuttled off to the lysosome (an organelle within the cell membrane) where the fragments are degraded.

"It has long been recognized that some cancer cells are resistant to apoptosis," said Richard Bold, professor and chief of surgical oncology

at the UC Davis Comprehensive Cancer and a co-author of the study. "Now, we have another way to induce cells to undergo death that overcomes resistance to traditional apoptosis associated with cancer."

The authors suggest that using arginine-deprivation induced autophagy may also spare patients the toxicity associated with chemotherapy alone.

The drug examined in the study is ADI-PEG20, developed by Polaris Pharmaceuticals of San Diego. ADI-PEG20 is an enzyme that degrades arginine, which normally would be available to the cell, breaking it down into its precursors. The agent is currently in phase III clinical trials in liver cancer, phase II in melanoma and phase I in prostate cancer.

Primo Lara, UC Davis oncologist and associate director of translational research at the cancer center, led a phase I study of the drug in patients with advanced lung, prostate and oral cancers. He reported that combined with a chemotherapy agent, the drug was feasible and reasonably tolerated. He is currently recruiting advanced prostate cancer patients for a new phase I trial of the drug combination.

"This opens up a new field," said Bold. "Now we search for other agents that use this method and translate those into clinical trials."

More information: Arginine starvation-associated atypical cellular death involves mitochondrial dysfunction, nuclear DNA leakage, and chromatin autophagy, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1404171111

Provided by UC Davis