New drug combination has potential to significantly improve chemotherapy success

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A drug combination "could revolutionize chemotherapy by dramatically improving one of the main class of chemotherapy drugs," said Edward Kipreos, a professor at the University of Georgia. Credit: UGA
University of Georgia researchers have found a way to enhance chemotherapy's cancer-killing powers, bringing science one step closer to a more complete cancer treatment.

Chemotherapy's ultimate goal is to destroy a person's cancer, but one common type of the treatment known as antimicrotubule chemotherapy has the tendency to let cancer cells slip through at the exact time that it's supposed to kill them—during the cell division phase known as mitosis.

These dividing cells leave through a process known as mitotic slippage. It's here that UGA researchers have targeted their studies—in understanding how mitotic slippage occurs and how to prevent it. According to the study published Oct. 24 in the *Journal of Cell Biology*, they found a drug combination that caused 100 percent mitotic cell death, thereby significantly improving the killing efficiency of antimicrotubule chemotherapy drugs.

The drug combination they discovered "could revolutionize chemotherapy by dramatically improving one of the main classes of chemotherapy drugs," said the study's senior author, Edward Kipreos, a professor in the Franklin College of Arts and Sciences department of cellular biology.

To get to that treatment, they first uncovered the cause of mitotic slippage: the action of the protein complex CRL2-ZYG11. Inactivating this protein complex can significantly improve antimicrotubule chemotherapy's ability to kill mitotic cells.

By combining conventional antimicrotubule drugs with a new drug called MLN4924 that targets all CRL complexes, the researchers were able to achieve complete mitotic cell death during testing. MLN4924 has undergone phase I clinical trials, meaning that MLN4924 has been evaluated for its safety, to determine a safe dosage range and to identify
side effects.

"Because cancer arises from the unregulated division of cells, it follows that if a chemotherapy drug could kill all dividing cells, it would be able to effectively treat all cancers," Kipreos said.

The paper focuses on new insights into the regulation of mitosis, primarily on the inactivation of cyclin B1-CDK1, an enzyme complex that is essential for mitosis. Because cyclin B1-CDK1 activity promotes the mitotic program, cyclin B1 must be degraded during mitosis to allow cells to exit mitosis. Previously, the understanding was that cyclin B1 is targeted for degradation solely by the action of the anaphase-promoting complex/cyclosome, or APC/C, ubiquitin ligase.

The researchers identified a second ubiquitin ligase complex, CRL2-ZYG11, that also targets cyclin B1 for degradation. The study shows that this pathway is conserved in both humans and the small roundworm Caenorhabditis elegans. In human cells, inactivating CRL2-ZYG11 by itself does not have a large effect on a cell's passage through mitosis, because APC/C is able to handle the degradation of cyclin B1. However, when APC/C is inactivated or cyclin B1 is overexpressed, CRL2-ZYG11 becomes critical to allow cells to exit mitosis.

Antimicrotubule drugs used for chemotherapy work by preventing the formation of the mitotic spindle, which inhibits APC/C, thereby blocking APC/C's ability to degrade cyclin B1 and causing cells to arrest in mitosis. Many of the arrested mitotic cells die. However, because CRL2-ZYG11 can still degrade cyclin B1, a substantial fraction of the arrested cells are able to exit mitosis via mitotic slippage.

"Another negative aspect of mitotic slippage is that it leaves cells with twice the amount of DNA, making normal cells more susceptible to
becoming cancerous," Kipreos said. "If MLN4924 in combination with antimicrotubule chemotherapy drugs is as effective in people as it is in vitro—without significant side effects—then it could be used to treat a broad range of cancers, by killing all dividing cells."


Provided by University of Georgia

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