Chemotherapy-resistant ovarian cancer cells protect their neighbors, shows study

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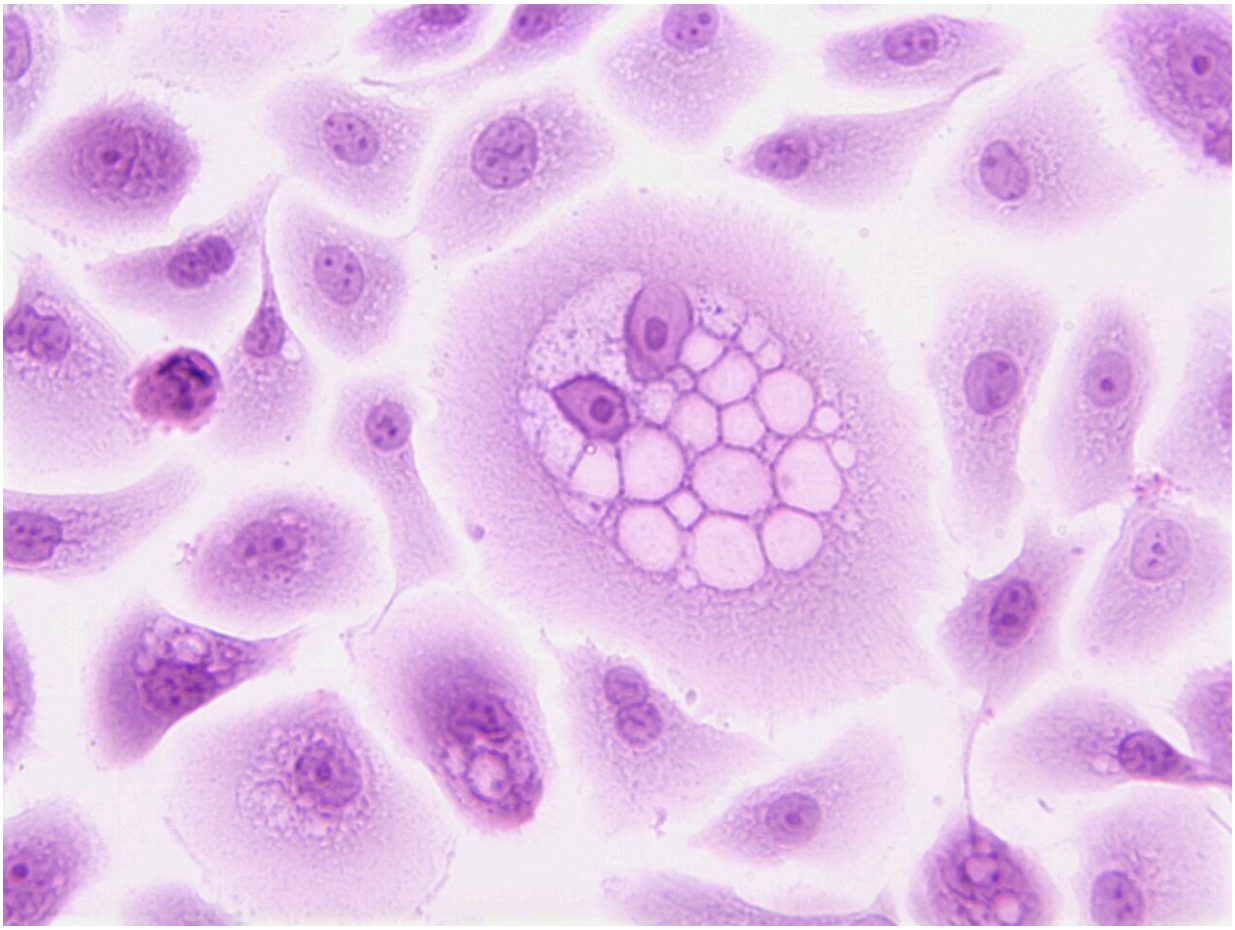

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Certain chemotherapy-resistant ovarian cancer cells protect neighboring

cancer cells by sending signals that induce resistance, according to a new study from University of Pittsburgh and UPMC researchers that may help explain why ovarian cancer patients respond poorly to chemotherapy or relapse after treatment.

Published in *Clinical Cancer Research*, the study investigated chemotherapy-resistant cancer cells called quiescent cells. As chemotherapy primarily targets rapidly dividing cells, quiescent cells are resistant because they divide slowly.

The researchers found that quiescent cells secrete a protein called follistatin that prompts neighbors to become resistant to chemotherapy too. By targeting this protein, they improved response to chemotherapy and boosted survival in a mouse model of aggressive ovarian cancer, paving the way for future human clinical trials.

"I think about quiescent cancer cells like the yellow center of a daisy and neighboring cells as the surrounding white petals," said Ronald Buckanovich, M.D., Ph.D., professor of medicine at Pitt and co-director of the Women's Cancer Research Center—a collaboration between UPMC Hillman Cancer Center and Magee-Womens Research Institute.

"In response to chemotherapy, quiescent cells secrete follistatin that acts like a signal to protect the whole flower. When chemotherapy stops, follistatin levels drop and cells start proliferating again, almost like a barometer that says, 'Conditions are good to grow.' This might explain why ovarian cancers often come back so quickly."

Ovarian cancer is the deadliest form of gynecologic cancer in the U.S. More than 70% of patients who are treated for this disease will have the cancer return, and it is rarely curable in this form. According to Buckanovich, there is an urgent need for therapies to combat resistant cancer cells and reduce recurrence rates.

In the new study, Buckanovich and his team found that quiescent cells ramp up production of follistatin in response to chemotherapy drugs in both lab-grown human cells and mice.

Next, they showed that quiescent cells halt the growth of actively dividing cancer cells, making them resistant to chemotherapy drugs. When they blocked follistatin with an antibody, this effect was lost, demonstrating that follistatin drives chemotherapy resistance.

"We thought that quiescent cells would produce factors to make themselves resistant to chemotherapy, but the fact they also protect their neighbors and amplify chemoresistance was surprising," said Buckanovich. "If some of these neighbors learn to be quiescent themselves, which in turn protect their own neighbors, more and more resistant cells will persist and lead to cancer recurrence."

To further confirm the role of follistatin in driving chemoresistance, the team genetically deleted the gene encoding follistatin in tumor cells that initiate an aggressive and incurable form of ovarian cancer in mice. The results were dramatic: After chemotherapy, 30% of mice with tumors lacking follistatin were cured, while all mice with normal tumors died.

Next, the team analyzed Cancer Genome Atlas data from hundreds of ovarian cancer patients. They showed that higher levels follistatin levels were associated with worse survival rates, indicating that follistatin is also relevant in people.

Finally, they compared samples from ovarian cancer patients before and after chemotherapy. Follistatin levels doubled or tripled in just 24 hours after treatment.

"To me, the most exciting thing about this study was the fact that we saw this incredible response to chemotherapy in patients within 24 hours,"

said Buckanovich. "These data reinforce our findings in mice and suggest that follistatin is a new target to improve ovarian cancer response to chemotherapy."

Buckanovich is now working with Pitt's Center for Antibody Therapeutics to develop antibodies for follistatin in humans with the eventual goal of moving this approach into clinical trials.

"If we're able to reverse chemoresistance and fewer patients relapse, we might be able to increase cure rates," he said. "Even if this approach works for 20% of patients, that would be huge because approximately 14,000 patients each year are dying from ovarian cancer."

According to Buckanovich, other recent research has suggested that follistatin also drives immunotherapy resistance in ovarian cancer, suggesting that an antibody targeting this protein could potentially be used to augment both chemotherapy and immunotherapy.

The team also plans to investigate how follistatin causes chemotherapy resistance in cancer cells. Blocking these signals by developing new drugs or repurposing existing drugs could be another promising avenue to improve treatments for ovarian cancer in the future.

More information: Alexander J. Cole et al, Quiescent ovarian cancer cells secrete follistatin to induce chemotherapy resistance in surrounding cells in response to chemotherapy, *Clinical Cancer Research* (2023). DOI: 10.1158/1078-0432.CCR-22-2254

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