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Wistar Scientists Identify New Mechanism Behind Chemotherapy Resistance in Ovarian Cancer

PHILADELPHIA — (JULY 23, 2026) — Scientists at The Wistar Institute have identified a new mechanism behind the chemotherapy resistance that makes ovarian cancer so lethal. In a new study, funded by top cancer research foundations and published in *The Journal for ImmunoTherapy of Cancer*, the researchers showed that chemotherapy triggers an inflammatory cascade that recruits immune cells into the tumor microenvironment, which ultimately function to protect the cancer from subsequent chemotherapy. Notably, this finding could improve outcomes for patients because the molecular pathway the researchers discovered has the potential to be blocked using drugs already in clinical use for other diseases.

"Traditionally, chemotherapy resistance has been seen as a cancer-cell problem," said **Nan Zhang, Ph.D.**, assistant professor in the Ellen and Ronald Caplan Cancer Center's Molecular and Cellular Oncogenesis Program and senior author on the study. "Our findings suggest it is also an immunology problem. The treatment meant to kill the tumor can trigger inflammatory responses that help it survive. The encouraging news is that there are already approved drugs that may be able to target this pathway and restore chemotherapy sensitivity."

High-grade serous carcinoma is the most common and deadly subtype of ovarian cancer. Many patients respond initially to first-line treatment, chemotherapy, but the majority go on to develop recurrent disease that resists subsequent chemotherapy. Although tumor-intrinsic genomic, epigenomic, and transcriptional alterations contribute to chemoresistance, prior research has found limited genomic divergence between primary and recurrent tumors, suggesting that chemoresistance is also acquired by microenvironmental mechanisms. As a result, researchers such as Zhang, have increasingly secured funding to look beyond the cancer cells themselves, to the surrounding tumor microenvironment, for answers.

For this study, which was made possible in part by funding from the Concern Foundation, the V Foundation for Cancer Research, and the Ovarian Cancer Research Alliance, Zhang, Taito Miyamoto, Yujie Ye, Marlaine Soliman, and their Wistar colleagues collaborated with gynecology pathologists at the Kyoto University Graduate School of Medicine to investigate recurring chemoresistance seen in ovarian cancer patients. Using publicly available datasets, the researchers compared patient tumor samples before and after chemotherapy. They found that interleukin-1 beta (IL-1β), a protein the body releases to signal the immune system to "send help" and promote inflammation, was significantly

elevated after chemotherapy, particularly in patients whose tumors didn't respond well to chemotherapy.

To test IL-1β's significance, the researchers used genetically engineered murine models lacking the ability to produce or to respond to IL-1β. When treated with chemotherapy, these models' tumors shrank, while models with normal immune systems stayed resistant to treatment.

Tracing the pathway further, the team postulated that when IL-1β binds to structural cells within tumors, it triggers the release of a chemical signal that attracts a type of white blood cell called neutrophils. Once recruited, the neutrophils protect tumors by exhausting cancer-fighting T cells and by undergoing a process called NETosis, in which the neutrophils rupture and release web-like structures called neutrophil extracellular traps (NETs). In the lab, the team found that NETs reduced the effectiveness of chemotherapy drugs on cancer cells and that blocking NET formation restored the drugs' effectiveness. In tumor samples from ovarian cancer patients, the researchers observed that both neutrophil infiltration and NET formation increased after chemotherapy, mirroring what they saw in preclinical models.

Building on these preclinical findings, Zhang, Soliman, and their colleagues are now exploring whether interrupting this pathway could eventually be translated into a clinical strategy to counter chemotherapy resistance.

"IL-1β therapies are already out there, and some are actually clinically approved for other conditions. So there is potential for these to be leveraged in this new context," said Marlaine Soliman, a third-year doctoral student in the Immunology Graduate Group at the University of Pennsylvania who is conducting her thesis research in the Zhang laboratory at The Wistar Institute and is a co-author of the study.

The researchers also see a possible opening for combination approaches involving immune checkpoint inhibitors, which reawaken the T cells. If T cell suppression by neutrophils turns out to be a major contributor to chemoresistance, pairing checkpoint inhibitors with IL-1β-targeted therapy could offer another route to restoring chemotherapy's effectiveness.

Several questions remain open. The team doesn't yet know what specifically triggers the increase in IL-1β production in response to chemotherapy, nor exactly how NETs impair drug sensitivity at the molecular level. Soliman, who is continuing this work as part of her doctoral research, is now investigating both avenues, along with whether T cells in this setting become truly exhausted and whether checkpoint inhibitors could reverse that.

"It's important to recognize that this is a complex tumor microenvironment, and this pathway is likely not the only reason patients experience chemoresistance," Soliman said. "But if you can significantly reduce resistance, that's important. At the end of the day, it's about how patients who have already gone through treatment once could get through it again if their cancer recurs, but with even better outcomes."

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