Researchers find experimental drug can help fight debilitating side effect of ovarian cancer

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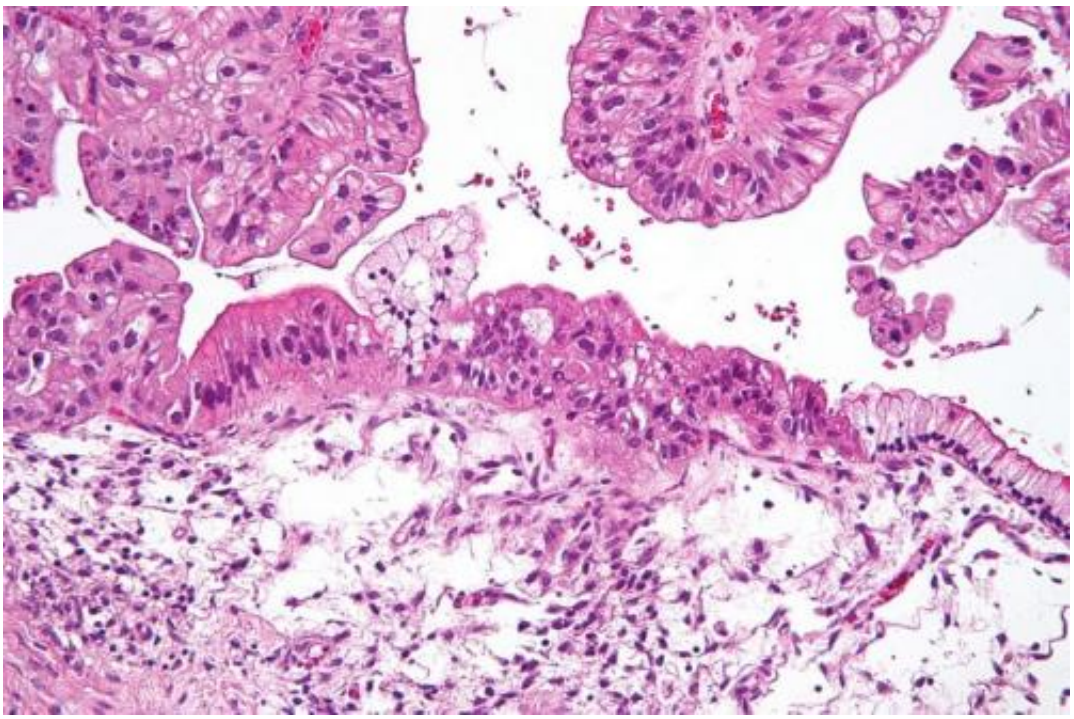

Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. H&E stain. The micrograph shows: Simple mucinous epithelium (right) and mucinous epithelium that pseudo-stratifies (left - diagnostic of a LMP tumour). Epithelium in a frond-like architecture is seen at the top of image. Credit: Nephron /Wikipedia. CC BY-SA 3.0

Women who have ovarian cancer often develop a condition called

ascites, which is a buildup of fluids in the abdomen. The most common treatment for ascites is puncturing the abdomen and manually draining the fluid, which is painful and risky and must be repeated every few weeks.

UCLA researchers have found that a drug that inhibits a receptor called the Colony-Stimulating-Factor-1 Receptor, or CSF1R, reduces ascites with minimal side effects. This inhibition therapy targets not cancer cells but macrophages, a special type of immune cell, in order to prevent them from helping the cancer take root in the abdomen.

In effect, the drug makes the abdominal cavity—where ovarian cancers often spread—into an environment less conducive to cancer growth. It may prove to be an effective treatment in combination with conventional cancer treatments such as chemotherapy.

The findings, published today in the peer-reviewed journal *Cancer Research*, may lead to a clinical trial of the drug in patients with epithelial ovarian cancer, said Dr. Lily Wu, the study's senior author and a professor of pharmacology, pediatrics and urology at UCLA.

Wu said 50 to 70 percent of the approximately 22,000 women diagnosed with epithelial ovarian cancer in the United States each year will also develop ascites.

"Trying to fight a battle on two fronts can seem hopeless, and patients fighting ascites while trying to survive a particularly deadly cancer is unacceptable," said Wu, who is also a member of UCLA's Jonsson Comprehensive Cancer Center.

Ascites is not exclusive to epithelial ovarian cancer, said Diana Moughon, the study's first author and a graduate student in pharmacology at UCLA.

"Some other cancers of the abdomen such as liver and pancreatic cancers and some highly invasive and metastatic cancers from elsewhere, such as breast cancer, can also cause ascites," Moughon said. "Macrophages have also been shown to assist in these aggressive malignancies and be a mechanism of their ascites accumulation. We are hopeful that our therapeutic strategy can eventually be broadened to include ascites induced by other cancers."

Ascites is caused by a problem with the abdominal blood and lymphatic vessels that causes the blood vessels to "leak" and the lymphatic vessels, which would otherwise drain the excess fluid, to become "plugged" with cancer cells. Previous research has focused on inhibiting a protein called VEGF, which promotes the growth of blood vessels. However, Wu said, that treatment is risky and has been reported to cause catastrophic intestinal perforation in up to 10 percent of patients in clinical trials. By contrast, people treated with CSF1R inhibitors experienced no major side effects.

"Specifically targeting the cells with CSF1R inhibitors lessens the number of pro-tumor macrophages and allows the vessels in the abdomen to become normal again, easing ascites accumulation," Wu said. "All of this is accomplished without dangerous side effects or pain."

One of the ways tumors recruit and change macrophages is through a long-distance signaling mechanism. Tumors pump out a protein called CSF-1, which floats around until it finds the receptor it is looking for—in this case CSF1R. When the signal meets the receptor, the cell in contact with the receptor receives the message from the tumor.

Macrophages express CSF1R and respond to the signaling by traveling toward the tumor and becoming pro-tumor. When CSF1R was inhibited, the number of macrophages in the ascites around the tumor was vastly

reduced, which, in turn made the ascites environment much less favorable to the tumor.

After just two weeks of treatment, the animals' blood vessels carried blood normally instead of leaking it. Wu said this caused the ascites to at least stop accumulating, and in many cases to regress.

Going forward, Wu and her team want to try the therapy in a clinical trial. They also will explore whether the CSF1R inhibition therapy can be combined with standard ovarian cancer treatments to fight both the ascites and the cancer.

More information: D. L. Moughon et al. Macrophage Blockade Using CSF1R Inhibitors Reverses the Vascular Leakage Underlying Malignant Ascites in Late-Stage Epithelial Ovarian Cancer, *Cancer Research* (2015). DOI: 10.1158/0008-5472.CAN-14-3373

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