Decoding the molecular mechanisms of ovarian cancer progression

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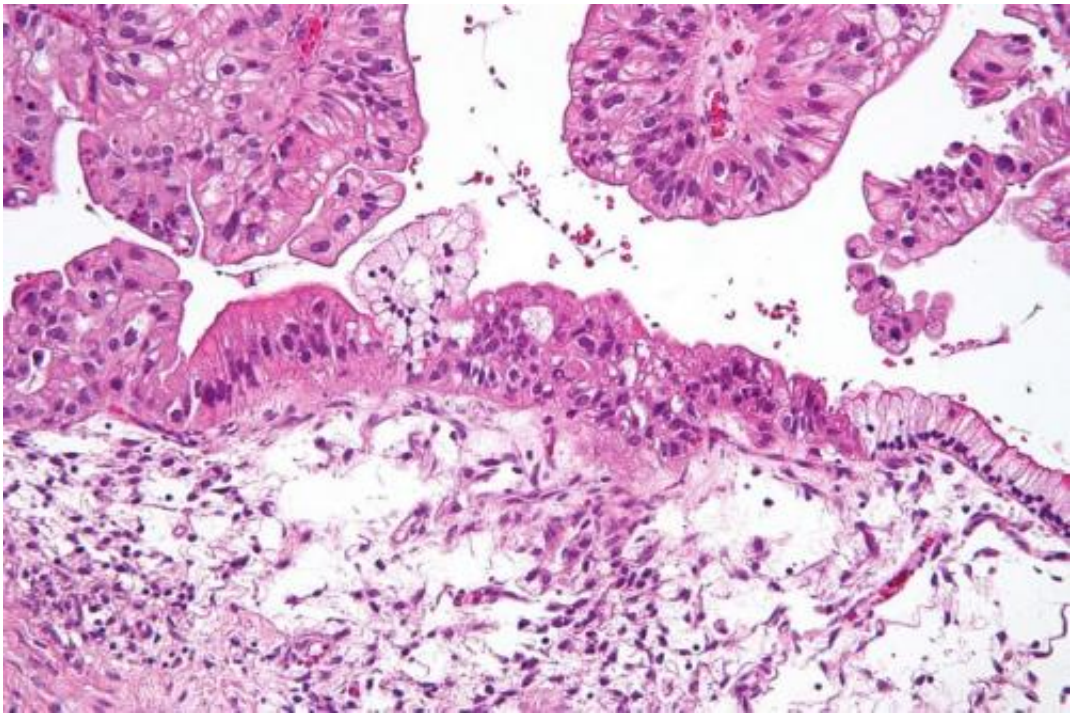

Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. H&E stain. The micrograph shows: Simple mucinous epithelium (right) and mucinous epithelium that pseudo-stratifies (left - diagnostic of a LMP tumour). Epithelium in a frond-like architecture is seen at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

Ovarian cancer is the most lethal gynecologic malignancy in the United States, resulting in an estimated 14,100 deaths and 22,500 new cases in 2017 alone. This high mortality is primarily caused by resistance to

therapy and the diagnosis of ovarian cancer after it has already metastasized, which occurs in approximately 80 percent of patients.

A new study from Sidney Kimmel Cancer Center (SKCC) at Thomas Jefferson University investigator Christine Eischen, PhD, provides new insights into the mechanisms contributing to ovarian cancer. The Eischen group focused on the role of long non-coding RNAs (lncRNAs), which have emerged as key regulators of genes. By evaluating the molecular changes that occur in large cohorts of ovarian cancer patients, the researchers were able to identify several lncRNAs that are linked to the disease. These lncRNAs were reproducibly altered in patients, and are responsible for a shift in cellular function that contributes to the metastatic properties of the cancer cells.

The research, which appears in a recent issue of *Nature Communications*, was spearheaded by lead author and bioinformatician Dr. Ramkrishna Mitra, a postdoctoral associate in the Eischen laboratory. Dr. Mitra undertook a large-scale bioinformatics approach to evaluate over 700 ovarian cancer molecular profiles from four patient cohorts. This analysis led to the identification of several lncRNAs that are overexpressed in a particular subset of ovarian cancer, those that are thought to be the most aggressive.

Further analysis revealed that overexpression of these lncRNAs in turn changed the expression of proteins that regulate a well-known developmental process, termed the epithelial-to-mesenchymal transition (EMT). EMT is important for cell migration and invasion - two characteristic of metastatic cancer cells—strongly suggesting that the link between lncRNAs and EMT contributes to the metastatic progression of ovarian cancer.

Following up on this idea, the researchers found that one of the lncRNAs was directly implicated in patient outcomes. "Overexpression of one of

the lncRNAs, DNM30S, was significantly correlated with worse overall ovarian cancer patient survival," said Dr. Eischen.

Based on these observations, the researchers suggest that targeting of the lncRNAs might represent a viable treatment strategy for ovarian cancer. To test this idea, they experimentally reduced the expression of the DNM30S lncRNA, which resulted in reduced ovarian cancer cell migration and invasion. In future work, the Eischen laboratory aims to further understand the role of lncRNAs in ovarian cancer, and potentially translate their findings into clinical applications to reduce ovarian cancer metastasis.

More information: Ramkrishna Mitra et al. Decoding critical long non-coding RNA in ovarian cancer epithelial-to-mesenchymal transition, *Nature Communications* (2017). DOI: 10.1038/s41467-017-01781-0

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