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Researchers examine role of hormone in response to ovarian cancer treatment

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The work comes out of the molecular therapeutic laboratory directed by Richard G. Moore, MD, of Women & Infants' Program in Women's Oncology. Entitled "HE4 expression is associated with hormonal elements and mediated by importin-dependent nuclear translocation," the research was recently published in the international science journal *Scientific Reports*.

The goal of the study was to investigate the role of the hormone HE4 in modulating an ovarian cancer's response to hormones and hormonal therapies. HE4 is a biomarker that is elevated in ovarian cancer and is known to play a role in resistance to chemotherapy.

"There is little known about the biologic functions of HE4 but we did know that there were hormonal responsive elements within the promoter region of the HE4 gene, which regulates gene expression. For this reason, we hypothesized that steroid hormones could influence expression of HE4 in ovarian cancer," Moore explains.

The study resulted in multiple findings:

- Hormonal therapies like Tamoxifen and Fulvestrant are effective because they bind the estrogen receptor. If cells have less estrogen receptor expression, these drugs can't do their job. This, the researchers believe, is due to epigenetic modifications which modify the DNA structure but not the DNA sequence itself. Overexpression led to the epigenetic modification known as

decreased DNA methylation in cell culture and in human tissue samples.

- Treatment of ovarian cancer cells with Tamoxifen and Fulvestrant all cause HE4 to translocate to the nucleaus, where it can then effect further gene expression in cancer cells.
- Using the drug Ivermectin, the researchers were able to inhibit the protein import in-4, which then inhibited HE4 from translocating to the nucleus. If HE4 can't enter the nucleus, it cannot affect gene expression. The ability to block HE4 from entering the nucleus restored sensitivity to hormonal therapy.

"We are not certain but believe this might mean there could be a subset of women whose tumors are more likely to respond to hormonal therapy. Moreover, we might be able to eventually identify which tumors these are and target treatment," Moore says.

His lab will continue to investigate the expression of estrogen receptors in both primary and recurrent ovarian cancers and how that relates to HE4 expression. In addition, he and other researchers will investigate how importin inhibitors may play a role in addressing chemoresistance to standard therapeutics, particularly in HE4 overexpressing tumors.

Provided by Women & Infants Hospital