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Follicular fluid has more to offer: Insulin-like growth factor axis on ovarian carcinogenesis

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Ovarian cancer is a highly lethal gynecological malignancy because it is almost always diagnosed at a late stage [1,2]. Despite the best efforts of researchers and clinicians alike, survival rates for women diagnosed with this devastating disease have improved by only 8.5% in the last twenty years since the introduction of carboplatin/paclitaxel-based chemotherapy, which remains the standard of care [1]. Prevention and early detection followed by appropriate surgical intervention, therefore, are the best strategies to significantly improve the mortality and morbidity of women suffering from this disease. The success of both tasks relies on a better understanding of the carcinogenesis pathway so that biomarkers can be identified and detected before ovarian cancer advances, and the risk factors can be validated and eliminated at the earliest stage possible.

Current research into the etiology of ovarian cancer suggests that the most common subtype, high grade serous carcinoma (HGSC), which makes up about 75% of ovarian cancer cases, actually originates in the fallopian tube epithelium [3,4]. Precursor lesions in the fallopian tubes such as the morphologically normal p53 signature and proliferative but still non-invasive serous tubal intraepithelial carcinoma (STIC) have significant molecular similarities with high grade serous carcinoma, including a high frequency of TP53 driver mutations [3,4].

Temporary cessation of ovulation such as during pregnancy or while taking birth control is known to have a significant protective effect on ovarian cancer [5], but the mechanism of this effect is still unclear. Previous studies have examined the link between ovulation and cancer development by examining fallopian tube follicular fluid (FF), which bathes fallopian tubes after each ovulation and is a required process during ovulation [6,7]. They found that FF in high concentrations could cause significant DNA damage, double-stranded breaks, and TP53 nuclear accumulation that created an immunostaining pattern similar to that seen in p53 signature. Reactive oxygen species (ROS) were implicated in this mutagenesis [7]. However, DNA damage alone does not fully explain the tumorigenic effect of FF.

This new and timely study by Hsu et al. expands upon what has been know on early ovarian cancer development by interrogating the other potential carcinogenic factors present in FF. They were able to collect FF samples from a large sample of women undergoing *in vitro* fertilization ($n = 31$), which was fractionated to identify key proteins. Pooled samples of diluted FF were also used to treat immortalized non-cancerous fallopian tube epithelium cell cultures in combination with protein inhibitors to determine which, if any, of these key proteins had carcinogenic activity [8]. In this study, the researchers were able to identify insulin-like growth factor (IGF)-axis proteins present in FF which have a tumorigenic effect on immortalized cell culture. They demonstrate that IGF-axis proteins play a key role in repairing tissue damage after ovulation by inducing stemness through activation of the IGF-1R/AKT/NANOG pathway. However, in the presence of ROS-caused mutations, this same process can lead to clonal expansion and tumor proliferation, as well as copy number variations.

These results provide valuable new insight into the molecular events behind the still poorly understood process of early ovarian cancer development and link together many separate observations from ovarian cancer research such as the link between ovarian cancer and incessant ovulation, and the presence of mutated but normal-appearing, non-proliferative p53 signature lesions in women at risk of developing ovarian cancer [9,10]. This creates a two-hit model, where mutations in p53 and/or Rb, while leading to cell cycle arrest on their own, can be activated by IGF2 in order to cause a stem-like tumor phenotype. The researchers' decision to pool and dilute FF during testing allows duplicate cell cultures to be compared with much greater efficacy; however, it creates uncertainty whether these observations are universal across all patients, or if this is only relevant to a subset of women. Future research should endeavor to compare samples from the fallopian tubes of multiple women and perform the proteomic analyses on the samples separately, in order to allow for the identification of any subsets of women that might be particularly vulnerable to ovarian cancer and identify candidates for ovarian cancer prevention opportunities. Though Hsu et al. do not directly discuss the clinical implications of this research, future studies could capitalize on the results of this study by investigating the potential for treatments targeting the IGF-1R/AKT/NANOG pathway, thus arresting or preventing the development of malignancy in mutated tissues.

Contributions

Both authors developed the concept and wrote the commentary.

Disclosure

The authors declare no conflict of interest.

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