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Editorial

The evolving pathogenesis model of high-grade pelvic serous carcinoma

Although high-grade serous carcinoma involving the ovary historically was thought to originate from the ovarian surface epithelium, a growing body of literature suggests that a large proportion may arise from fallopian tube secretory epithelial cells (FTSECs) and be better termed high-grade pelvic serous carcinoma (HGPSC). The clinical ramifications of clearly understanding tumorigenesis are highlighted in the successful screening, early detection, and treatment of colon cancer, in which there is a well-described sequence of mutational events that characterize the transition from normal epithelium to premalignant adenoma and eventually invasive carcinoma. In stark contrast, the origins of ovarian cancer are only now being elucidated, and thus it remains the most aggressive gynecologic malignancy, with the majority of women diagnosed at an advanced stage, in which treatment is more challenging.

Developing a model of high-grade serous ovarian carcinoma pathogenesis is critical, and biomarkers of early tumorigenesis may guide effective screening and treatment. A model described by Bowtell and supported by others describes primary events that include early TP53 loss followed by BRCA loss, leading to chromosomal instability and widespread copy number changes [1–3]. Secondary and tertiary events then cause global changes in gene expression followed by mutations to facilitate tumor evolution. Importantly, most models incorporate early loss of TP53 and BRCA. Potential biomarkers or therapeutic targets must consider the driver mutations and genomic events in these models that take place before the full development of carcinoma, when a multitude of subsequent mutations and copy number alterations occur to shape each individual tumor.

In support of FTSECs as the origin of HGPSC, Jarboe et al. and others have described a histologic continuum of epithelial changes that have been observed in the distal fallopian tube [4,5]. The transition is postulated to occur as follows: normal fallopian tube epithelium, overexpression of TP53, serous tubal intraepithelial carcinoma (STIC), and finally, invasive serous carcinoma. Clonality of the precursor cells in both the areas that overexpress TP53, so-called p53 signature, and the STICs provide the strongest support for the distal fallopian tube as a site of origin for HGPSC [6]. Other morphologic and anatomic evidence supports this hypothesis. However, a precursor lesion within the fallopian tube can only be identified in approximately half of all advanced cases of HGPSC. Therefore, the site of origin may lie outside of the fallopian tube in some cases, or premalignant cells may be shed onto the ovary or into the peritoneum prior to a neoplastic lesion developing within the distal fallopian tube. The data to suggest that the ovarian cortical inclusion cyst is a site of origin for some HGPSCs represent the union of these concepts, with FTSEC being shed onto the ovarian surface and subsequently undergoing invagination into a cortical inclusion cyst, which serves as a site for malignant transformation [2].

In this issue of *Gynecologic Oncology*, Karst et al. report on *Stathmin 1* (*STMN1*) as a novel marker of early serous carcinoma that may play a role in tumorigenesis [7]. STMN1 is a multifunctional protein that is critically important in the regulation of cell-cycle progression and microtubule dynamics and has been shown to mediate the effects of p27 on cell proliferation and invasion [8,9]. With recent literature showing that p27 expression was lost in preneoplastic lesions of the fallopian tube epithelium [3] and STMN1 being a downstream target of p27, Karst et al. investigated STMN1 as a marker of early neoplasia in the fallopian tube. Immunohistochemistry (IHC) was used to examine STMN1 and p27 expression in 12 benign and 13 malignant fallopian tubes that contained representative sections of the histologic continuum from benign fallopian tube epithelium to invasive serous carcinoma [7]. In addition, they used IHC and Western blot to assess STMN1 expression in 131 late-stage HGPSCs and 6 ovarian cancer cell lines, respectively. They found that STMN1 expression was negative in the epithelium of all 25 normal fallopian tubes and in 13 (72%) of 18 p53 signatures, yet positive in 6 (86%) of 7 proliferative p53 signatures and in all 13 tubal intraepithelial carcinomas and invasive tumors. STMN1 expression was also negatively correlated with its regulator p27. Finally, they demonstrated that STMN1 was expressed in 110 (84%) of 131 primary late-stage HGPSCs and 5 (83%) of 6 ovarian cancer cell lines.

The lack of effective screening and prevention measures for HGPSC reflect the crucial need to better understand the origins of this disease. Karst et al. have identified STMN1 as another potential player in the evolving model of the pathogenesis of high-grade serous ovarian carcinoma. The discovery that STMN1 is strongly expressed in tubal intraepithelial carcinoma and that it may play a critical role in serous carcinogenesis lends itself well to previous work conducted by the same team of investigators, in which they used nonviral, clinically relevant genetic alterations to transform human FTSECs and successfully produced high-grade serous carcinoma with a Müllerian phenotype in a mouse model [10]. The authors demonstrate that transformed FTSECs are morphologically similar to HGPSC of apparent ovarian origin. This model system is well suited to investigate other candidate oncogenes and tumor suppressor genes, including *STMN1*.

The work by Karst et al. sheds more light on the pathogenesis of high-grade serous ovarian carcinoma but also leaves a number of questions unanswered. Although STMN1 was strongly expressed in all putative precursor lesions (STICs), it was expressed in 84% of HGPSCs, leading to the conclusion that some fraction of HGPSCs may not arise in the fallopian tube. It would be of interest to survey the immunostaining of STMN1 in other pelvic tissues such as the ovarian surface epithelium, cortical inclusion cysts, and pelvic peritoneum. Alternatively, the loss of STMN1 in established tumors may reflect its importance in tumor initiation to the exclusion tumor maintenance once genomic instability is firmly established. The identification of

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these essential early changes demonstrates that drivers of tumor initiation and progression are more effectively identified in precursor lesions rather than frank carcinoma, in which additional events have already occurred. Additionally, due to the relatively small sample of cases with STIC, there are likely some tumors that may develop without the intervening over-expression of STMN1. It is unclear whether STMN1 is simply a marker of cellular transformation or if it directly participates in the transformation of normal fallopian tube epithelium along the proposed continuum toward carcinoma.

A final issue is the penetrance of p53 signature and STIC lesions. p53 signature lesions have been found in 15–25% of normal fallopian tubes removed from women without cancer or genetic predisposition [7,11]. TP53 mutations can be identified in about half of the p53 signatures [6]. STMN1 here has been demonstrated to be expressed in all STIC lesions but no p53 signature lesions, suggesting that it plays a critical role in the early transformation after p53 overexpression has occurred. It would be interesting to see if TP53 mutations are present more commonly in the 28% (5 of 18, considering all samples) of the p53 signature lesions in this report with STMN1 over-expression. Answers to these and other questions may help us to figure out which precursor lesions (p53 signatures and STICs) are most likely to develop into advanced HGPSC.

In an effort to more effectively prevent and treat HGPSC, the model of pathogenesis must continue to evolve, and the authors have demonstrated that STMN1, a downstream target of p27, is a promising new player. As more attention turns toward the fallopian tube as a likely site of origin for most HGPSCs, a larger number of precursor lesions will be identified to confirm the authors' findings. As models to explain the origins of HGPSC develop, we will continue to discover targets that may help in our efforts to identify effective approaches to screening and improved therapies. *Stathmin 1* is a promising gene of interest whose role in the tumorigenesis model will continue to be elucidated.

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