

## Review

# Ovarian serous carcinogenesis from tubal secretory cells

Wenjing Zhang<sup>1,2,3\*</sup>, Linxuan Wei<sup>1,2,3\*</sup>, Lingmin Li<sup>1,4\*</sup>,  
Binlie Yang<sup>1,5</sup>, Beihua Kong<sup>3</sup>, Guang Yao<sup>2,6</sup> and Wenxin Zheng<sup>1,5,6,7</sup>

<sup>1</sup>Department of Pathology, University of Arizona College of Medicine, Tucson, AZ, USA, <sup>2</sup>Department of Molecular & Cellular Biology, University of Arizona, Tucson, AZ, USA, <sup>3</sup>Department of Obstetrics and Gynecology, Qilu Hospital, Shandong University, China, <sup>4</sup>Department of Pathology, Shanxi Medical University, China, <sup>5</sup>Department of Obstetrics and Gynecology, University of Arizona College of Medicine, Tucson, AZ, USA, <sup>6</sup>Arizona Cancer Center, University of Arizona, Tucson, AZ, USA and <sup>7</sup>Department of Pathology UTSouthwestern Medical Center, Dallas, TX, USA

\*These authors contributed equally to this work.

**Summary.** Due to a poor understanding of tumorigenesis, ovarian cancers remain the most lethal gynecologic malignancy and cause horrific deaths. In the last decade, a new dualistic model for ovarian cancer was proposed, wherein ovarian serous cancers are classified as either high-grade or low-grade, with each having different tumorigenic processes, and pathologic and clinical features. Surprisingly, both high- and low-grade ovarian serous cancers were recently found to originate not in the ovaries, but rather from the secretory cells of the fallopian tube, mostly from the tubal fimbriated ends. In this article, we review the evidentiary basis for the aforementioned paradigm shift in the cell origin of ovarian serous cancers, as well as its potential clinical implications.

**Key words:** Ovarian serous carcinoma, Secretory cell, Fallopian tube, LGSC, HGSC

## Introduction

Ovarian cancers are the most lethal gynecologic malignancy, with more than 20,000 new cases and 14,000 associated deaths each year (Siegel et al., 2013). Of all ovarian cancers, the most prevalent subgroup is ovarian epithelial cancers, accounting for ~80-90% of cases. Among ovarian epithelial cancers, ovarian serous carcinomas (OSCs) are the most common (~70%), followed by mucinous carcinomas, endometrioid carcinomas and clear cell carcinomas (McCluggage, 2011). OSCs have a poor prognosis and often present abdominopelvic metastasis at diagnosis; early detection of OSCs is thus crucial to better prognosis. However, effective methods for OSCs' early detection are currently lacking.

Histologically, OSCs are generally classified into two groups: high-grade serous carcinomas (HGSCs) and low-grade serous carcinomas (LGSCs). HGSCs account for ~90% of OSC cases and about 70% of all ovarian cancer-related deaths. LGSCs account for ~10% of OSC cases; they are less aggressive and have a much better prognosis compared to HGSCs. Based on a recently proposed dualistic model for ovarian epithelial cancers (Shih Ie and Kurman, 2004; Kurman and Shih Ie, 2008), LGSCs and other low-grade ovarian epithelial carcinomas of endometrioid, clear cell, and mucinous, as well as Brenner tumors, are classified as Type I, while HGSCs and other high-grade ovarian epithelial carcinomas of endometrioid, carcinosarcomas and undifferentiated carcinomas are classified as Type II.

*Offprint requests to:* Guang Yao, Ph.D., Assistant Professor of Molecular and Cellular Biology, University of Arizona, 1007 E. Lowell St. Tucson, AZ, 85721, USA. e-mail: [guangyao@email.arizona.edu](mailto:guangyao@email.arizona.edu). or Wenxin Zheng, M.D., Professor of Pathology, Chief, Gynecologic Pathology, UTSouthwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9073 USA. e-mail: [wenxin.zheng@utsouthwestern.edu](mailto:wenxin.zheng@utsouthwestern.edu)

DOI: 10.14670/HH-11-645

Where do OSCs originate? Recent studies suggest, surprisingly, that both ovarian HGSCs and LGSCs originate not from the ovary, but from the fallopian tube (Kurman and Shih Ie, 2008, 2010, 2011). In this review, we summarize supporting evidence for the tubal origin of OSCs, particularly in tubal secretory vs. ciliated cells. We also discuss potential clinical implications from these recent findings.

**Clinical evidence**

Previously, OSCs were thought to originate from the ovarian surface epithelium. However, mounting recent clinical and pathological evidence suggests that OSCs, particularly HGSCs, originate from the fallopian tube rather than from the ovary.

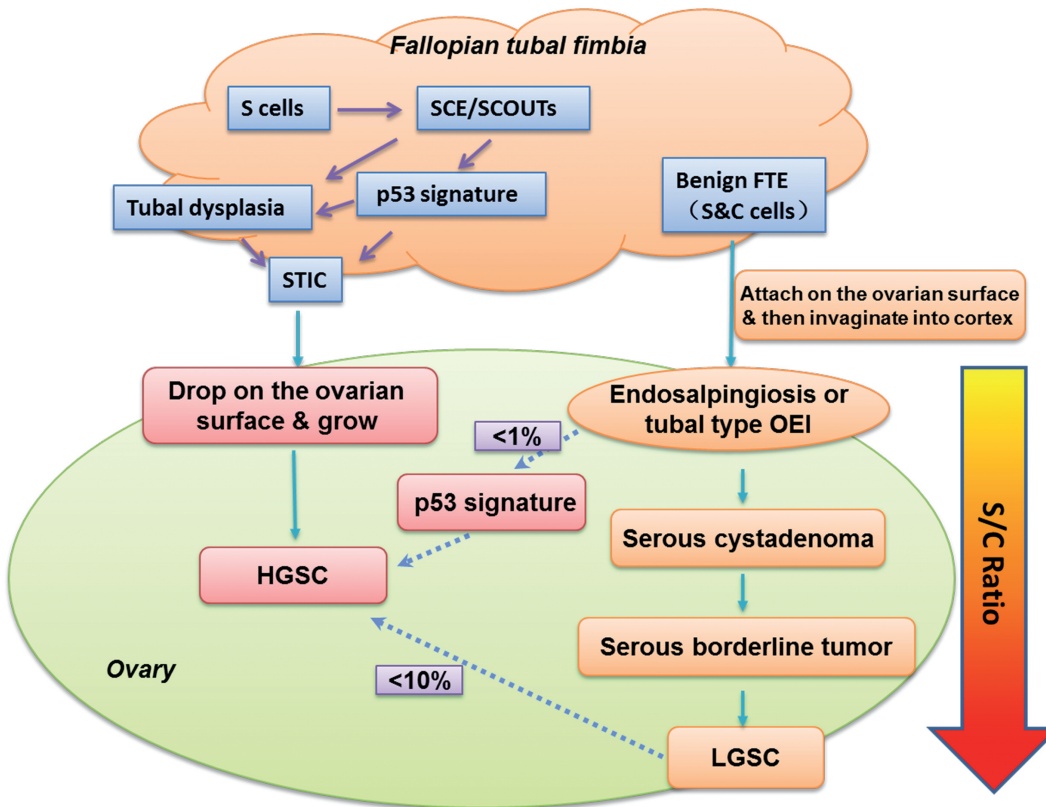
*High-grade serous carcinoma*

The pathogenesis of OSCs has perplexed researchers for decades. Until recently, the prevailing view of the origin of HGSCs was that these cancers were derived from ovarian surface epithelium or cortical inclusion cysts (Fig. 1). However, no convincing HGSC precursor has been identified in the ovary. Clinically, early stage HGSCs are rarely found in the ovary, and the majority of HGSCs at diagnosis are at stage III, with pelvic implants

or ascites. It has been thought that the ineffectiveness of standard diagnosis methods has hindered the detection of early stage HGSCs and their precursors (Buys et al., 2011). Indeed, among the standard methods, ultrasound and bimanual examination can only detect relatively large abdominopelvic masses (ultrasound: >3cm in diameter; bimanual: >~4-5cm), and CA125 examination that measures the blood level of cancer cell-secreted mucin 16 protein is not sensitive enough to detect early stage tumors.

It later turned out that efforts for HGSC early detection were focused at the wrong site. Starting in the 1990s, high-risk patients who bore germline BRCA mutations began to undergo prophylactic bilateral salpingo-oophorectomies. Upon carefully examining the resected ovaries and fallopian tubes, pathologists found no precursor lesions on the ovaries, but surprisingly, found occult carcinomas in the fallopian tubes, typically at the fimbriated end (Piek et al., 2001; Carcangiu et al., 2004; Medeiros et al., 2006; Callahan et al., 2007; Crum et al., 2007; Saleemuddin et al., 2008; Gross et al., 2010). This astonishing finding prompted researchers to reevaluate the cell origin of ovarian cancers.

Subsequently, Piek et al. hypothesized that tubal carcinomas might shed malignant cells, which would then implant and grow on the ovary, simulating ovarian cancer formation. They examined 12 BRCA+ tubal



**Fig. 1.** Schematic drawing of ovarian serous carcinogenesis. This schematic drawing summarizes our current understanding of ovarian serous carcinogenesis. Both serous cancers (LGSC and HGSC) arise in tubal epithelial cells, namely tubal secretory cells. S cells, secretory cells; C cells, ciliated cells; FTE, fallopian tube epithelium; SCE, secretory cells expansion; SCOUTs, secretory cell outgrowths; STIC, serous tubal intraepithelial carcinomas; OEI, ovarian epithelial inclusions. S/C Ratio: the ratio of secretory/ciliated cells (yellow color, low S/C ratio; red color, high S/C ratio).

## OSCs originate from tubular secretory cells

tissues, and found that six tissues showed areas of cellular dysplasia and five other tissues had early lesions with histological features favoring HGSCs (Piek et al., 2001, 2003). Consistently, gene expression profiles of tubal epithelia, but not of ovarian surface epithelia, were found to closely resemble those of HGSCs (Bonome et al., 2005). In a large clinical study in women with BRCA mutations, about ~1-5% of these patients were found to have an early tubal malignancy when they had the prophylactic surgery (Finch et al., 2006). Subsequently, in a study of pelvic HGSCs without high risk factors (i.e., from patients with no family history of ovarian and breast cancers nor BRCA mutations), early tubal malignancy was also observed with ovarian carcinoma (Crum et al., 2007; Kindelberger et al., 2007). Over 70% of sporadic (non-hereditary) ovarian and peritoneal HGSCs were found to have early tubal malignancy. Investigators of these studies named the noninvasive carcinoma identified at the fallopian tube “serous tubal intraepithelial carcinoma (STIC)”, which will be discussed in the next section on pathologic evidence. These recent studies have shifted the paradigm of ovarian cancer pathogenesis from the ovarian surface to the distal fallopian tube.

### *Low-grade serous carcinoma*

LGSCs are a relatively less common but significant type of OSCs. Unlike highly malignant HGSCs that spread early and result in relatively small primary carcinomas, LGSCs often develop into bigger masses that are easier to detect by standard screening methods. LGSC carcinogenesis progresses in a stepwise fashion through an intermediate (borderline tumor) stage, which is different from HGSC carcinogenesis. LGSCs can nevertheless transform into HGSCs, although at a low rate (<10%). Therefore, studying LGSC carcinogenesis and its connection to HGSC is important for a more complete understanding of ovarian cancer initiation and development. Similar to HGSCs, the pathogenesis of LGSCs also perplexed researchers for decades. After it was found that HGSCs were derived from the fallopian tube, not the ovary, our group was inspired to investigate whether LGSCs also originate from the fallopian tube.

We found evidence supporting the tubal origin of LGSCs. Clinically, low-grade ovarian cancers show a close relationship with ovarian epithelial inclusions (OEIs). It has been generally accepted that LGSCs are derived from OEIs (Kurman and Shih Ie, 2010). Based on our recent observations, OEIs have two subtypes, originating from ovarian surface and tubal epithelium, respectively (Li et al., 2011). It was not clear which type of OEI is the true origin of LGSCs. We then evaluated serous tumors (cystadenomas, borderline tumors and LGSCs), OEIs, ovarian surface epithelia, and distal tubal epithelia. Our results suggested that OEIs originating from the tubal epithelia (with tubal phenotype and increased proliferative index) are likely the precursor

lesions for serous borderline tumors and LGSCs (Li et al., 2011).

### **Pathologic evidence**

#### *High-grade serous carcinoma*

As mentioned in the previous section, serous tubal intraepithelial carcinomas (STICs), also called tubal lesions in transition (TLIT) (Crum, 2009; Semmel et al., 2009; Mehrad et al., 2010), are noninvasive carcinomas identified at the fallopian tube. STICs are observed in ~5-7% of prophylactic salpingo-oophorectomy cases from BRCA carriers, and ~57-100% of these STICs are located in the distal portion (fimbriae) of the fallopian tube (Carlson et al., 2008; Chene et al., 2013). STICs are also observed in patients without known genetic predisposition to ovarian cancers and these STICs are almost always detected in the tubal fimbriae (Li et al., 2012). Combined, STICs are associated with about 60% of HGSCs (Kindelberger et al., 2007; Przybycin et al., 2010).

Pathologically, STICs are defined as secretory tubal cells with striking cellular atypia, positive p53 immunohistochemistry staining (in ~80-92% of cases), and a high proliferative index (with a MIB-1 labeling index >40%) (Folkins et al., 2009). Several genes that are commonly overexpressed in HGSCs (RSF-1, Cyclin E, p16 and stathmin1) are also overexpressed in STICs (Chene et al., 2013). Collectively, pathological and clinical evidence has established STICs at the distal end of the tube as precursors of ovarian HGSCs (Leeper et al., 2002; Chen et al., 2010; Leonhardt et al., 2011).

#### *Low-grade serous carcinoma*

Pathogenetically and morphologically, LGSCs appear to evolve in a stepwise fashion: OEIs, cortical inclusion cysts, serous cystadenomas, serous borderline tumors (including micropapillary formation), non-invasive and ultimately invasive LGSCs (Shih Ie and Kurman, 2004; Crum et al., 2007; Folkins et al., 2009; Kurman and Shih Ie, 2011; Li et al., 2012). OEIs were originally considered to be derived from the ovarian surface epithelium and formed by invagination. However, after the discovery that HGSCs originate from STICs at the distal tube, not on the ovarian surface, researchers began to wonder whether OEIs may originate in the fallopian tube as well.

Our group first demonstrated that the primary source of OEIs is tubal epithelia instead of ovarian epithelia (Li et al., 2011). We showed that OEIs contained epithelia of both the mesothelial phenotype (calretinin+/PAX8-/tubulin-) and tubal phenotype (calretinin-/PAX8+/tubulin+), and that the majority (78%) of OEIs displayed a tubal phenotype (Li et al., 2011). We proposed that tubal phenotype OEIs are the precursors of LGSCs, because 1) the proliferative index (MIB-1) of the tubal phenotype is much higher than that of the

mesothelial phenotype, and 2) PAX8, a marker of tubal secretory epithelial cells vs. ovarian epithelial cells, is diffusely positive in borderline serous tumor and LGSCs. This observation has been recently confirmed by another group of researchers (Banet and Kurman, 2015).

Consistent with the stepwise development from tubal-derived OEIs to LGSCs, there is a corresponding change in the “S/C ratio” during stage development. The S/C ratio is defined as the ratio between the numbers of two types of epithelial cells, secretory and ciliated cells. We found that the S/C ratio of cystadenomas was very similar to that of fallopian tube-derived OEIs, and that the S/C ratio increased slightly in serous borderline tumors and then drastically in LGSCs, whose epithelial layers are comprised almost entirely of secretory cells (Li et al., 2011). These results suggested that LGSCs are likely derived from the expansion or outgrowth of tubal secretory cells, similar to HGSCs (Jarboe et al., 2008; Chen et al., 2010; Li et al., 2013).

### Cytologic evidence

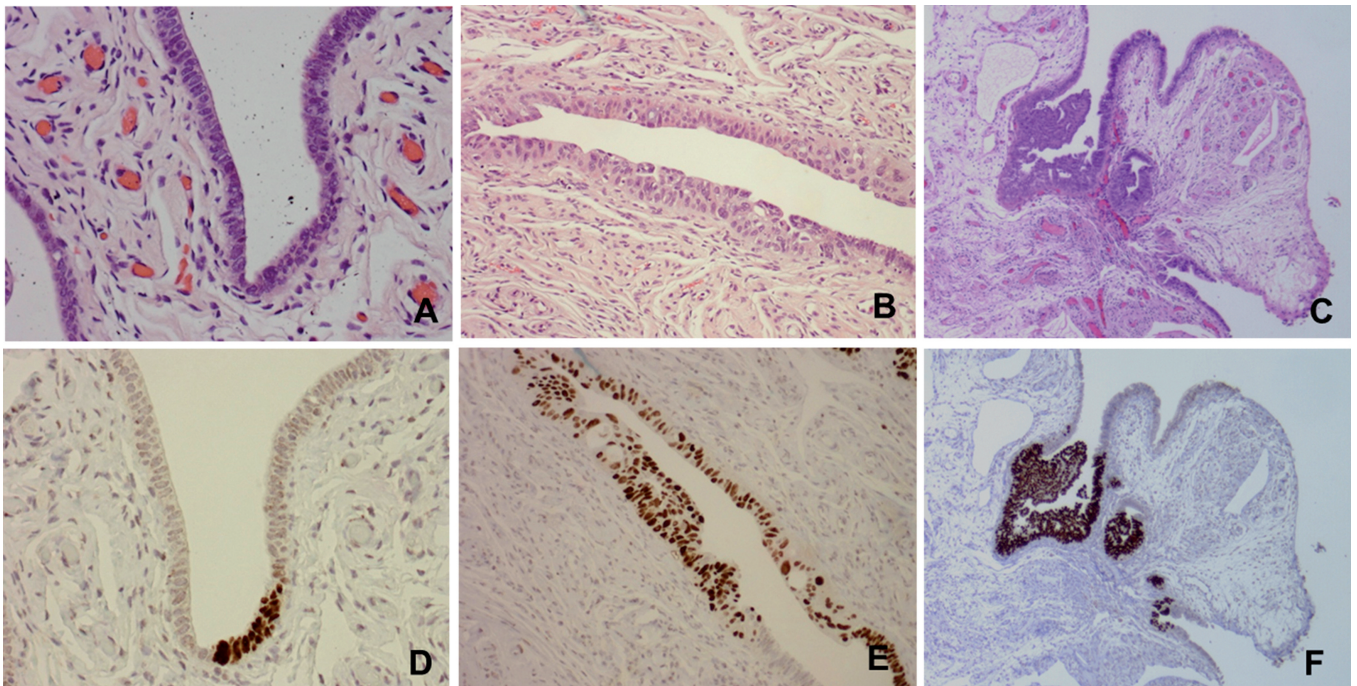
In reproductive women, normal fallopian tubal mucosa is composed of at least three types of cells: ciliated, secretory and intercalary. Ciliated cells account for ~20-30% of the mucosal cells, and secretory cells account for ~50%-60%. Intercalary, or peg, cells are a columnar cell type with no cilia, whose cell body is primarily occupied by a thin, dark-staining nucleus.

Intercalary cells are considered a morphologic variant of secretory cells, sharing the same PAX8 cellular marker. Different from normal tubal mucosa, the epithelia of OSCs contain just one single cell type: secretory cells. Also, the proliferation of benign-looking secretory cells can be frequently identified, as discussed below, in tubal p53 signatures and secretory cell expansion or outgrowth (SCE/SCOUTs) (Chen et al., 2010; Leonhardt et al., 2011; Mehra et al., 2011).

### p53 signature

P53 plays a pivotal role in mediating cell cycle arrest and apoptosis in response to DNA damage. P53 mutations often result in deregulation of the cell cycle and apoptosis control (Gorgoulis et al., 2005; Latonen and Laiho, 2005). In previous studies, p53 mutations were identified as a primary genetic lesion in ovarian tumorigenesis (Berchuck, 1995; Shih Ie and Kurman, 2004; Bonome et al., 2005; Latonen and Laiho, 2005). Mutations of p53 can be seen as early as in the stages of preinvasive neoplasia and clonal epithelial expansion (Ren et al., 1997). P53 protein levels are low in normal cells due to p53-MDM2 negative feedback regulation. In contrast, p53 mutants often disrupt p53-MDM2 negative regulation, resulting in their high accumulation levels in the cell (Lee et al., 2007).

In benign mucosa of the distal fallopian tube, small segments of strong p53 staining can sometimes be identified, indicating an early lesion with arising p53



**Fig. 2.** Tubal epithelia with secretory cell expansion. **A** shows focal area of p53 signature (**D**). Tubal epithelial dysplasia with all secretory cells (**B**) shows many p53 positive nuclei (**E**). Tubal intraepithelial carcinoma (**C**), comprising pure secretory cells, is diffusely positive for p53 staining (**F**).

## OSCs originate from tubular secretory cells

mutations. Correspondingly, a “p53 signature” is defined as loci on tubal epithelium that exhibit p53 immunoreactivity and a low proliferative index, with each locus being a stretch of at least 12 primarily secretory cells with few intervening ciliated cells (Lee et al., 2007; Carlson et al., 2008). The “p53 signature” shares several attributes with tubal intraepithelial carcinoma, including: 1) location in the fimbria (80%), 2) secretory cell phenotype, 3) evidence of DNA damage, 4) strong nuclear localization of p53 protein, 5) p53 mutation, and 6) occasional direct continuity with tubal intraepithelial carcinoma (Lee et al., 2007). Based on these findings, the tubal p53 signature was proposed as a precursor of OSCs.

### IMP3 signature

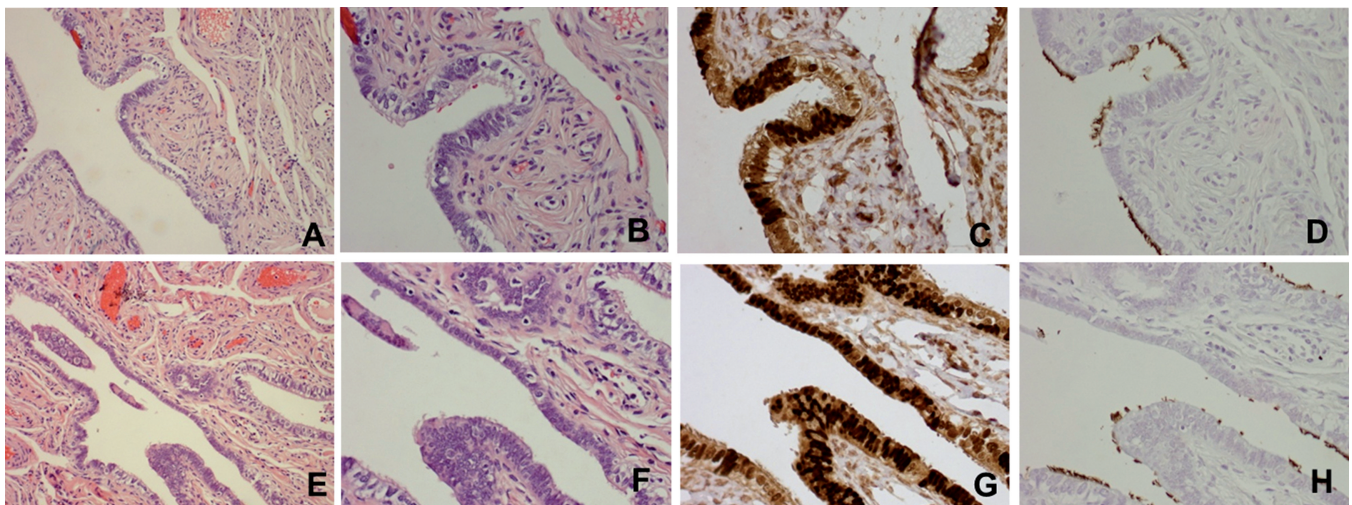
We recently found that an “IMP3 signature” can serve as an additional biomarker in serous carcinogenesis. “IMP3 signature” is defined as 10 or more consecutive secretory cells in benign tubal mucosa stained positively for insulin-like growth factor II mRNA-binding protein (IMP3) and showing growth advantage (Wang et al., 2014a,b). IMP3 is an oncofetal protein involved in embryogenesis and is rarely expressed in normal adult tissue. IMP3 overexpression in benign tubal epithelia suggests a potential precursor lesion. Correspondingly, IMP3 is overexpressed in ~55% of STICs in high-risk patients, ~58% of STICs in pelvic serous carcinomas (PSCs), and in ~63% of PSCs (Wang et al., 2014a,b). Interestingly, the IMP3 signature often occurs in anatomic continuity with STICs, suggesting a stepwise development from IMP3 signature to STICs, then to serous carcinoma. This observation suggests that

overexpression of IMP3 may be involved in the initial process of tubal or pelvic serous carcinogenesis (Fig. 2). Therefore, an IMP3 signature may serve as a latent precancer biomarker for tubal or pelvic serous carcinomas in women (Wang et al., 2014a,b).

### SCOUTs or SCE

Normal tubal mucosa consists of both secretory and ciliated cells, appearing in a recurring pattern of alternating secretory and ciliated cell stretches of typically fewer than 10 cells each. A secretory cell outgrowth (SCOUT) is defined as the expansion of tubal secretory cells to 30 or more, forming a morphologically distinct stretch of the secretory cell population. SCOUTs have been linked to serous neoplasia and serve as an OSC biomarker (Chen et al., 2010; Li et al., 2011; Quick et al., 2012).

Similarly to SCOUTs, we also examined the phenomenon of secretory cell expansion (SCE) in our previous study (Li et al., 2013). SCE is defined as a linear stretch of more than 10 secretory cells without intervening ciliated cells (Figs. 2, 3). We found that SCE occurs more commonly than SCOUTs (Li et al., 2013). Both SCE and SCOUTs occur more frequently in tubal segments of patients with either high-risk factors or PSCs than in normal tubal controls. However, SCE is more strongly associated with serous neoplasia than SCOUTs are (Li et al., 2013). Comparable to SCOUTs, SCE is morphologically distinct and it can be used as an early biomarker in the process of serous carcinogenesis (Li et al., 2013). Mechanistic studies of SCE initiation and development are likely to facilitate strategies for OSCs’ prevention and early intervention.



**Fig. 3.** Representative pictures of secretory cell expansion (SCE) and outgrowth (SCOUT). An example of SCE is illustrated in the top panel, while SCOUT is shown in the bottom panel. Regular H&E stain shows a mixture of tubal secretory cells and ciliated cells, visible under routine microscopy (**A and B**). The areas with SCE are highlighted by PAX8 staining (**C**), while the intermixed ciliated cells are highlighted by tubulin staining (**D**). Another tubal sample contains areas of SCOUT with an increased number of secretory cells and fewer ciliated cells (**E and F**). These two cell types are better viewed by PAX8 (**G**) and tubulin stains (**H**). A, E, x 40; B-D, F-H, x 100.

How and why do SCE and SCOUTs occur? Compared to ciliated cells, secretory cells show a limited ability to resolve DNA damage over time, which may leave them more susceptible to accumulating mutations and more vulnerable to tumorigenesis (Levanon et al., 2010). Consistently, it has been shown that secretory cells play an important role in several gynecological diseases related to OSCs, such as endometrioid ovarian carcinomas, ovarian clear cell carcinomas and endometriosis (Folkens et al., 2009; Chen et al., 2010; Wiegand et al., 2010; Li et al., 2011, 2012). Further studies are underway in our and other laboratories to elucidate the molecular mechanisms underlying SCE and SCOUTs in fallopian tubal mucosa at the gene, pathway and functional levels.

### Mouse and cell model

Perets et al. successfully established a *de novo* HGSC mouse model (Perets et al., 2013). This model targets frequently mutated genes in tubal secretory cells that contribute to the transformation from STIC to HGSC. As PAX8 is actively expressed in secretory cells at the fallopian epithelium but is silent in ovarian epithelium, a PAX8 promoter was chosen as the locus to drive Cre recombinase that mediated the inactivation of different combinations of the BRCA1 or BRCA2, Tp53 and PTEN genes in tubal epithelium (Perets et al., 2013). Consequently, the development of STICs and HGSCs and the progression of advanced stages (ovarian and peritoneal metastases) were observed in this mouse model with the same morphologic characterizations as corresponding human lesions. The results strongly support that HGSCs can arise from the fallopian tube and that secretory cells can serve as the cell origin of HGSCs.

Levanon et al. established an *ex vivo* culture of primary human fallopian tube epithelial cells which faithfully recapitulates the *in vivo* epithelium (Levanon et al., 2010). This cell model behaves as a phenocopy of tubal epithelium, expressing lineage-specific markers such as PAX8, Bcl-2 and TNF $\alpha$ IP2 for secretory cells, and Foxj1, Sall2 and SELENBP1 for ciliated cells (Rusiniak et al., 2000; Piek et al., 2001; Bowen et al., 2007; Levanon et al., 2010). This *ex vivo* culture model was found to secrete a panel of proteins previously identified as ovarian cancer biomarkers and it has been used to study tubal pathobiology and ovarian carcinogenesis.

### Clinical implications in ovarian cancer prevention

Clinically, ovarian cancer is the most difficult to screen among all gynecologic tumors, due to its physical location deep inside the body, its asymptomatic early stage and its unknown oncogenesis. In the last few decades, numerous methods for screening for ovarian cancers had been tried, in hopes of intercepting the disease at an early, treatable stage. However, these attempts failed because they incorrectly focused on the

ovarian surface. In the 2000s, the fallopian tube was found to be the site of origin of most ovarian cancers, including the majority of serous, clear cell and endometrioid carcinomas. This new understanding of ovarian cancer's origin laid a foundation for developing new approaches for early detection and prevention.

### Risk-reducing salpingectomy

Based on the findings above, it has become clear that bilateral salpingectomy or removal of the bilateral tubal fimbriated end can be effective in reducing the risk of ovarian cancers. Risk-reducing salpingectomies can be performed regularly when women undergo hysterectomies for benign lesions or tubal ligations for sterilization. This prophylactic procedure preserves the function of the ovary to produce female sex hormones, to avoid sequelae such as cardiovascular disease and osteoporosis.

A potential limitation of the risk-reducing salpingectomy is that it is likely ineffective when ovaries already have endosalpingiosis. Endosalpingiosis is now considered a precursor of ovarian cancer and may develop into OEIs and cystadenomas, borderline tumors and finally to LGSCs (Kurman et al., 2011; Li et al., 2011; Gruessner et al., 2014).

### Tubal cytology as a tool for early detection

Considering that early detection is the key to improving ovarian cancer prognoses, we are attempting to find a feasible method to detect ovarian precursors or cancerous lesions at an early stage. Tubal cytology, which detects exfoliative epithelial cells of the tubal fimbriated end, may be an effective method for ovarian cancer early detection. We have been performing tubal cytology on voluntary patients, with or without ovarian cancers, who received a bilateral salpingectomy. However, this method is currently limited by the lack of standard tubal cytology and an effective, minimally-invasive means of accessing the fallopian tube.

### Conclusion

Recent studies have determined the fallopian tube as the origin of both LGSCs and HGSCs. This new paradigm has profound clinical implications in ovarian cancer prevention strategies. Prophylactic bilateral salpingectomy is now being considered an effective method to prevent ovarian cancer. Cytology of tubal epithelia is another approach that might help with early detection of ovarian cancer in the future.

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*Acknowledgements.* This work was partially supported by funds from a NCI Cancer Center Support Grant (P30CA023074-34), National Science Foundation (DMS1418172) and the Better Than Ever (BTE) program at the University of Arizona. This work was partially supported by the American Cancer Society (G.Y.; IRG7400134).

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## *OSCs originate from tubular secretory cells*

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## *OSCs originate from tubular secretory cells*

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