Review Article

Tubal origin of ovarian low-grade serous carcinoma

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Abstract: Our understanding of the carcinogenesis and histogenesis of ovarian cancer has undergone a paradigm shift in recent years, after accumulating evidence from morphologic and molecular genetic studies. Findings from these studies suggest that both high-grade and low-grade serous ovarian cancers, traditionally believed to start from the ovarian surface, may originate from the distal fallopian tube. This article reviews recent evidence for the tubal origin of serous ovarian cancers, especially the low-grade serous carcinomas.

Keywords: Ovarian cancer, serous carcinoma, fallopian tube, cell of origin

Introduction

Ovarian cancers are the 5th leading cause of cancer-related deaths in women and the most lethal gynecologic malignancy. In 2013, it is estimated that 22,240 new cases of ovarian cancers will be diagnosed, with 14,030 associated deaths from this disease [1]. Ovarian epithelial cancers (OECs) account for 80–90% of all ovarian cancers. Among OECs, serous carcinomas are the most common, accounting for ~70% of all cases [2].

Serous ovarian cancers can be divided into two broad groups: type I or low-grade serous carcinomas (LG-SCs), and type II or high-grade serous carcinomas (HG-SCs). LG-SCs are generally present at early stages and clinically less aggressive; they rarely harbor TP53 mutations, instead, contain other specific mutations (e.g. KRAS and BRAF) and are genetically relatively stable. On the contrary, HG-SCs are clinically aggressive; they frequently display TP53 mutations and are genetically unstable [3]. HG-SCs account for the majority (~90%) of ovarian serous cancers while LG-SCs account for ~10%.

How do ovarian serous cancers originate and develop? Last decade has seen a paradigm shift in ovarian cancer carcinogenesis. Rather than starting from the ovarian surface, many ovarian HG-SCs have been surprisingly found to originate from the distal fallopian tube, possibly from expansion of secretory cells, as shown by a large body of recent clinical-pathological and molecular studies [4-9].

The cell of origin of LG-SCs is less clear compared with that of HG-SCs. LG-SCs are thought to evolve in a stepwise fashion, from ovarian epithelial inclusions (OEI) to benign cystadenomas and borderline tumors, and finally to LG-SCs [3, 10]. Li, et al. recently suggested that the majority of OEIs are derived from the fallopian tube rather than ovarian surface epithelium (OSE), and that the tubal secretory cells are likely the cell origin of LG-SCs [11]. This central role of the fallopian tube in LG-SC development has received further support [12, 13]. Here we summarize evidence for the fallopian tube as the site of origin for ovarian LG-SCs.

LG-SCs evolve from OEIs

The stepwise development of LG-SCs from OEIs is supported by several morphological and histological observations. First, the majority of benign cystadenomas seem to derive from
OEs, as cystadenomas display an epithelial lining similar to that of OEs morphologically and immunophenotypically. Actually, the diagnostic criterion that separates cystadenomas from OEs is merely an arbitrary threshold made at the 1 cm size [14]. Second, histological transitions from cystadenomas to borderline tumors are observed at high frequency in nearly 75% of cases [15]. Third, borderline tumors are found associated with the majority of LG-SCs [16]. It is seen that, foci of true early invasion in borderline tumors resemble LG-SCs [15, 17-19], and, invasive implants mostly associated with micropapillary serous borderline tumors, which has been recently defined as LS-SC [20-22], are histologically identical to LG-SCs [23, 24]. All these morphological and histological observations support a model wherein LG-SCs evolve from OEs, via intermediate stages of serous cystadenomas and borderline tumors.

OEIs’ tubal origin

Since OEs may represent the earliest putative precursor for LG-SCs, origination of OEs may provide cues of the LG-SC origin. Recently, the morphologic and immunophenotypic features of OEs, serous tumors (cystadenomas, borderline tumors, and LG-SCs), ovarian surface epithelium (OSE), and distal tubal epithelium were evaluated [11]. Two types of OSE were found: the vast majority of OSE displayed a mesothelial phenotype (calretinin+/PAX8-/tubulin-) and a low proliferative index (0.012), while about 4% of cases displayed foci with tubal phenotype (calretinin-/PAX8+/tubulin+). Although the OSE with tubal phenotype were found in only 4% of the cases, it did show that benign tubal epithelia can possibly implant on the ovarian surface and architecturally simulate ‘OSE’ microscopically. Meanwhile, there were also two types of OEs: most (78%) of the OEs displayed a tubal phenotype (vs. mesothelial phenotype) and had a significantly higher proliferative index than OSE’s, suggesting that OEs and OSE are mostly of different cellular lineages. The fact that significantly more tubal-like epithelia were found in OEs than in OSE argues that most OEs are not derived from the OSE, rather, bear a tubal origin. One straightforward explanation is that the fallopian-derived OEs represent intraovarian endosalpingiosis, which is well in line with the ideas expressed by Duboeau and Crum [25, 26]. Regarding the possibility that tubal-phenotype OEs (78%) originate from mesothelium-derived OEs through a müllerian metaplasia, if it were true, the metaplastic process must result in a hybrid type of OEs in the ovary. The fact that the hybrid or intermediate type of OEs with both mesothelial and tubal phenotypes were rarely found makes the müllerian metaplasia hypothesis unlikely. Furthermore, mesothelium-derived OEs may not be able to grow into a tumor mass due to their extremely low cellular proliferative index (similar to OSE’s), while fallopian-derived OEs showed proliferative activities and immunophenotypes similar to ovarian serous tumors. The above findings suggest that OEs with tubal phenotype and increased proliferative index [11] are likely originated from tubal epithelia, and are likely the precursors of LG-SCs.


development model from tubal epithelia to OEs

Based on the connection between the tubal epithelium and LG-SCs, Li et al. proposed a two-step model of LG-SC development as following [11]. First, fallopian tubal epithelia, mostly from fimbriated end, may detach and implant on the ovarian surface. This step could occur via two possibilities: 1) the close spatial relationship between the tubal fimbriated end and the ovarian surface may allow detached tubal epithelium to implant in the ovarian stroma, especially when ovulation or non-ovulation induced disruption of the ovarian surface occurs [27]; and 2) adhesion of tubal epithelium on the ovarian surface (due to inflammation or other factors) and dynamic stromal growth around it may result in tubal derived OEs formation. During the second step, the acquisition of mutations such as KRAS or BRAF in tubal derived OEs results in their transformation to cystadenomas, borderline tumors and ultimately to LG-SCs [28-32]. Notably, the further acquisition of additional mutations such as TP53 in LG-SCs may contribute to the development of a small proportion of HG-SCs [27].

There are other recent studies linking LG-SC origin to the fallopian tube. Kurman et al identified a fallopian tube lesion, designated as papillary tubal hyperplasia (PTH) whose cytological appearance is essentially identical to that of atypical proliferating serous tumor (APST), non-invasive implants, and endosalpingiosis [13]. The authors hypothesized both a PTH-pathway and a non-PTH pathway model [9] for the origin.
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and development of the pelvic low-grade serous proliferations. The PTH process begins with chronic inflammation, leading to tubal hyperplasia, which, if progresses to PTH, can shed and implant tubal epithelium on ovarian and peritoneal surfaces, resulting in a variety of low-grade serous proliferations including serous borderline tumors and eventually LG-SCs. Some OEs may derive from OSE. However, those OSE-derived OEs are thought to have limited proliferative index and rarely develop into LG-SCs. Less than 10% of LG-SCs might develop into HG-SCs upon the acquisition of p53 mutation. HG-SCs also mainly originate from the TFE, starting from serous tubal intraepithelial carcinoma (STIC). This figure is adapted from REF [48].

Cell origin of LG-SCs

There are two types of epithelial cells within the fallopian tubal mucosa: ciliated and non-ciliated, the latter are also called secretory cells. Both types of the cells are also present in fallopian tube-derived OSE, fallopian tube-derived OEs, serous cystadenomas, and borderline tumors, with a significant increase in secretory-to-ciliated cell ratio (S/C ratio) observed during the apparent transition from the normal fallopian tube to fallopian tube-derived OEs (P<0.001) [11]. Fallopian tube-derived OEs and cystadenomas displayed very similar S/C ratios (consistent with their arbitrary pathologic difference, size threshold of 1 cm), while the S/C ratio of serous borderline tumors was slightly higher. In contrast, LG-SCs contained almost entirely secretory cells in their epithelial components and displayed a strikingly high S/C ratio [11]. These results suggested that LG-SCs are likely derived from the expansion [33] or outgrowth of tubal secretory cells, similar to HG-SCs [34, 35]. The significant increase of the S/C ratio between normal tubal epithelium to fallopian tube-derived OEs suggests that during this transition step some molecular event(s) occurred, either facilitating secretory cell expansion or ciliated cell suppression. The reduction in cilia with advancing tumor development could indicate an impaired maturation program. Overall, the progressive increase of S/C ratio from fallopian tube-derived OEs all the way to LG-SCs is consistent with the concept of a stepwise progression, and the secretory cells in fallopian tube appear to be the cell of origin of LG-SCs.

Emerging concept of mesothelial-müllerian junction as a potential source of LG-SC originination

Another model for the origination of ovarian serous carcinomas has been gradually emerg-
Figure 1

References

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