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REVIEW

Cells of origin of ovarian cancer: ovarian surface epithelium or fallopian tube?

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Abstract
Objective Ovarian cancer is the fifth most common cancer in women and one of the leading causes of death from gynecological malignancies. Despite of its clinical importance, ovarian tumorigenesis is poorly understood and prognosis remains poor. This is particularly true for the most common type of ovarian cancer, high-grade serous ovarian cancer.
Results Two models are considered, whether it arises from the ovarian surface epithelium or from the fallopian tube. The first model is based on (1) the pro-inflammatory environment caused by ovulation events, (2) the expression pattern of ovarian inclusion cysts, and (3) biomarkers that are shared by the ovarian surface epithelium and malignant growth. The model suggesting a non-ovarian origin is based on (1) tubal precursor lesions, (2) genetic evidence of BRCA1/2 mutation carriers, and (3) recent animal studies. Neither model has clearly demonstrated superiority over the other. Therefore, one can speculate that high-grade serous ovarian cancer may arise from two different sites that undergo similar changes. Both tissues are derived from the same embryologic origin, which may explain how progenitor cells from different sites can respond similar to stimuli within the ovaries. However, distinct molecular drivers, such as BRCA deficiency, may still preferentially arise from one site of origin as precancerous mutations are frequently seen in the fallopian tube.
Conclusions Confirming the origin of ovarian cancer has important clinical implications when deciding on cancer risk-reducing prophylactic surgery. It will be important to identify key biomarker to uncover the sequence of ovarian tumorigenesis.

Keywords Ovarian cancer · High-grade serous ovarian cancer · Fallopian tube · Ovarian surface epithelium · Lgr5

Introduction

Ovarian cancer (OC) is the leading cause of death from gynaecological malignancies. The disease consists of multiple subtypes, of which epithelial OCs account for about 90% of cases [1, 2]. These epithelial OC subtypes include endometrioid, clear cell, mucinous, and serous OC, all of which have been suggested to depend on unique sequences of tumorigenesis [3–6]. In Germany, approximately 8000 women are diagnosed with OC and about 5500 women die every year from the disease [7]; of which high-grade serous OC (HGSOC) represent the most common type with about 70% of all cases. Most patients (about 80%) that present with advanced OC are diagnosed with HGSOC [8]. HGSOC differs from low-grade serous OC (LGSOC) by having a higher mitotic index, a more aggressive behaviour and typically correlates with a poorer prognosis [9]. LGSOC is thought to sequentially arise from serous cystadenoma and borderline serous OC to invasive micropapillary serous borderline tumors, representing a distinct disease entity from HGSOC, associated with unique characteristic mutations [6].

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Despite the clinical burden of the disease, the site of origin of HGSOC is still debated [10, 11]. This is in stark contrast to the well-established sequence of tumorigenesis in other tumors, such as colorectal cancer [12]. Here, the discovery that the detection of precancerous colonic polyps correlates with clearly defined neoplastic changes has transformed diagnosis and management of colorectal cancer [13]. One could speculate that the dearth of new innovative clinical therapies may be at least partially due to the unresolved sequence of HGSOC growth [7, 14].

What are the main sites of origin of HGSOC that are debated? On the one hand, evidence suggests that this cancer arises from the ovarian surface epithelium (OSE), which is related to the mesothelium of the peritoneum [15]. It is loosely attached to the underlying ovarian stroma and separated by the tunica albuginea. The OSE harbours stem cells, which may contribute to tumor formation (Fig. 1). On the other hand, it has been suggested that HGSOC originates from the fallopian tubes, which consist of differentiated columnar epithelium composed of ciliary and secretory cells (Fig. 2). It has been suggested that the fimbriae of the fallopian tube deposit cancer cells onto the ipsilateral ovary promoting tumor formation [16].

There are several reasons why the origin of HGSOC remained obscure. Unlike almost all other epithelial-derived tumors, HGSOC in situ is rarely found in ovaries and the identification of precursor lesions is remarkably infrequent, hindering the ability to accurately map the origin of the disease in the host tissue. The controversy of the origin of HGSOC has made it challenging to implement effective screening, prevention or develop novel therapeutic strategies for this disease. This article reviews the fascinating new insights in ovarian tumorigenesis, models

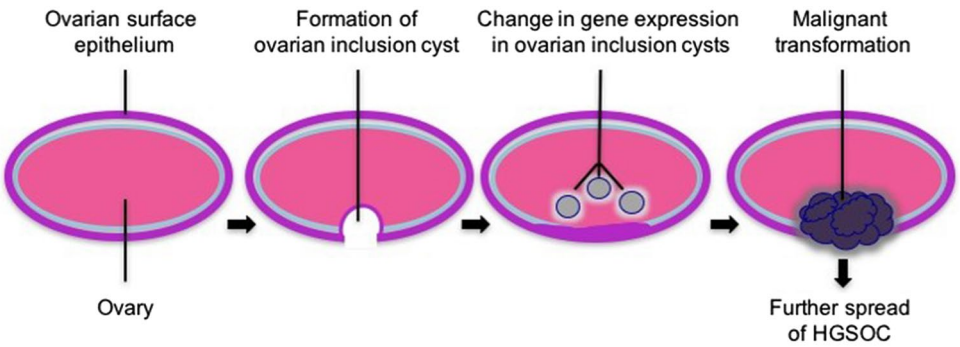

Fig. 1 Development of HGSOC arising from the OSE. The diagram shows the stepwise progression to HGSOC from the formation of ovarian inclusion cysts, their change in gene expression, and the malignant transformation, which can ultimately lead to cancer formation. Genotoxic stress through repetitive ovulatory inflammation responses may lead to malignant transformation, which is likely to be promoted by deregulation of the pluripotent stem cell activity within the OSE and/or ovarian inclusion cysts

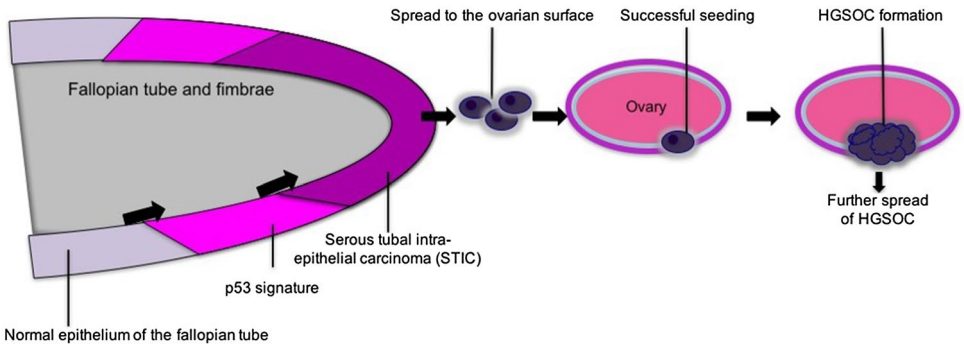

Fig. 2 Progression of normal fallopian tube epithelium to invasive HGSOC. The fallopian tube epithelium is composed of a single layer of ciliated and secretory cells that are exposed to ovulation-associated inflammatory cytokines. This repetitive genotoxic stress causes DNA damage and induces p53 mutation, leading to the clonal expansion of physiologically normal appearing epithelial cells, termed p53 signature. Further mutations enable cells to acquire a proliferative capacity, giving rise to serous tubal intraepithelial carcinoma (STIC). As STICs progress, invasive cancer cells are exfoliated from the fimbriae, whereupon they may spread rapidly to the surface of the ovary and may establish tumour formation and transformation to HGSOC. Exfoliation may also occur from STICs prior to invasion of the fimbrae (the relative size of the fallopian tube and the ovary is not representative)

of ovarian tumorigenesis, and discusses whether HGSOC originates from the OSE or the fallopian tube.

Ovarian surface epithelium model

The OSE model was first proposed by Fathalla [17]. The total number of ovulation events is thought to contribute to tumorigenesis by promoting a pro-inflammatory microenvironment and activation of DNA double-strand breaks (DDSBs) and subsequent repair or inadequate repair in the case of cancer growth. This is based on: firstly, the reduced risk of HGSOC formation that is associated with the long-term intake of the contraceptive (estrogen-containing) pill due to regulating ovulation [18]. Secondly, HGSOC risk is strongly associated with BRCA1/2 mutations [19, 20]. Approximately 50% of HGSOCs are characterized by dysfunction of the homologous recombination (HR) pathways, mainly because of BRCA1/2 mutations or loss of other factors of HR [21]. The identification of the BRCA1 gene has been key in the understanding of the genetic susceptibility of ovarian (and breast) cancer [22].

Mutations in BRCA1/2 impair the efficacy of DDSB repair and thus promote cancer growth, including OC [23, 24]. An international observational study of 31,481 patients with confirmed BRCA1/2 carrier status analyzed the risk of OC. This has shown that women with mutations in BRCA1/2 have a statistically significantly increased risk of OC, with an overall absolute risk of 34% for BRCA1 mutation carriers and 11% for BRCA2 mutation carriers [19, 25]. In contrast, the risk of developing OC in the general (German) population is about 0.7% by the age of 75 [7].

It can be argued that the repeated self-healing process after ovulation may increase the frequency of inadequate DDSB repair event mistakes due to malfunctioning in the repair machinery in BRCA1/2-mutation carriers, which in turn increases genotoxic stress and promotes malignant transformation of the OSE (Fig. 1).

The OSE harbor stem cells, which may suggest that dysregulated pluripotency of these stem cells, may facilitate tumor growth, particularly, under cyclical inflammatory response. It was described that stem cell maintenance activity is silenced in cancerous OSE, suggesting that deregulation contributes to HGSOC (Fig. 1) [26]. There is strong evidence from other cancers, such as colorectal cancer, suggesting that inadequate host tissue stem cell activity gives rise to malignant transformation and growth [27, 28]. A process might potentially also contribute to ovarian tumorigenesis.

It has been considered that the OSE-lined inclusion cysts are early metaplastic transformations, which would support the OSE model, because these cysts exhibit a high degree of oncogenic potential in otherwise pathologically normal ovaries (Fig. 1) [29]. However, there is also a high frequency of inclusion cysts in pathologically normal ovaries [30], and it cannot be ruled out that metastatic cancer cells, deposit onto ovaries, may promote the formation of these cysts. Despite the ovaries being the site of the disease at later stages and often at the time of clinical presentation, it has been argued that the OSE is not the actual tissue of origin of OC.

Fallopian tube model

Although it seems controversial to suggest extra-ovarian cells as the origin for HGSOC, the physiology of the female genital tract and its common types of malignancies may explain the reasoning behind this approach. The fallopian tube model was first proposed by Dubaeu [31]. A strong link between the fallopian tube and HGSOC has been suggested, because irrespective of family history, about 67% of ovarian carcinomas have also been shown to have coexisting tubal lesions [32]. Kurman and Shih further suggested that HGSOC, compared to low-grade serous, endometrioid, mucinous, or clear-cell OCs, typically arises from precursor lesions in the fallopian tube, called serous tubal intraepithelial carcinoma (STIC) [33, 34].

A histopathological study suggested a direction of this spread (Fig. 2) [35]. The histology of most HGSOC samples bears little resemblance to the OSE and ovarian tissue, but recapitulates the histological features of Müllerian epithelium that is present in the fallopian tube. In 2001, Piek et al. provided histopathological evidence that HGSOC may originate from the fallopian tube (Fig. 2) [35, 36]. They reported the presence of dysplastic changes in the fallopian tube in 11 of 12 prophylactic salpingo-oophorectomy specimens removed from suspected BRCA-mutation carriers, whereas none was identified in control subjects, i.e., not carrying BRCA mutations [35, 36]. It was shown that HGSOC is characterized by harbouring mutations in the tumor suppressor gene TP53 in the vast majority of cases [21, 37]. This is known as the p53 signature. Recent sequencing of HGSOCs has further confirmed that more than 95% of tumors have mutations in *TP53*, which is significantly different from other epithelial OCs (p value < 0.0005) [38, 39].

In contrast to BRCA mutation carriers, it remains unknown whether the occurrence of the p53 signature correlates with an increased risk of HGSOC in women without BRCA1/2 mutations and whether a highly selective patient cohort overestimates the role of the p53 signature.

To explore the role of the p53 signature, Lee et al. identified that the changes identified in the tumor suppressor gene p53 in tubal epithelial cells resembled the mutations seen in STICs with morphologically intermediates between both stages [40]. Recent studies of ovarian tumorigenesis in an

animal model also provided strong evidence for the fallopian tube model [16]. Importantly, early removal of the fallopian tube prevented ipsilateral OC formation in mice [16]. A meta-analysis has also shown that BRCA1/2 mutation carriers who had undergone risk-reducing salpingo-oophorectomy have a more than 50% risk reduction of developing ovarian or fallopian tube cancer [41].

This would suggest that the fallopian tube may likely be the origin of at least a substantial number of HGSOC, particularly, in BRCA1/2 mutation carriers. However, to more accurately understand the sequence and origin of ovarian tumorigenesis, it is essential to identify key biomarkers and molecular drivers that promote HGSOC growth [42, 43]. A recently suggested biomarker could be the epithelial stem cell marker leucine-rich repeat-containing G-protein coupled receptor 5 (Lgr5) [44]. This marker has recently been shown to be expressed in stem progenitor cells of the OSE and tubal epithelia [45].

LGR5/6-positive cells as the cellular marker of the origin of ovarian cancer

Lgr5 is member of the Wnt signalling pathway, acting as receptor for a Wnt pathway agonist R-Spondin [44, 46]. Lgr5 was first discovered in stem cells of the intestine and colon in 2007 and later described a common marker in other epithelial stem cells [27, 44, 47], linking it to cancer growth in various cancers of epithelial origin [27, 48]. High Lgr5 expression has also been demonstrated to correlate with poor prognosis and advanced tumor stage in patients with OC [49]. Both sites of HGSOC are epithelial in origin, making Lgr5-positive (stem) cells an obvious candidate to contribute to ovarian tumorigenesis. Lgr5 expression has been shown in the OSE and tubal epithelium [45]. Lgr5 has been found in ovarian stem cell populations suggesting a role in ovarian stem cell regeneration and may shed light onto tumorigenesis of OSE- or tubal-derived OCs [50].

Interestingly, a recent study has shown that tubal organoids can grow in culture over several months, relying on growth factors similar to intestinal organoids. This would allow to study the stepwise progression of STICs and to identify the molecular and pathological changes that result in the formation of HGSOC. This could be achieved by selectively inducing mutations that are believed to be involved in the early stages of the disease. If Lgr5-positive cells drive regeneration of the OSE and contribute to the stemness of the fallopian tube, this may explain how the two different sites contribute to ovarian tumorigenesis by relying on similar pathways for cell growth. De-differentiated progenitor cells from the fallopian tube could receive a further growth stimulation once spread onto the OSE. On the other hand, Lgr5 expression has been shown to be present in the OSE, specifically at the cleft region of growing follicle and rupturing OSE [45]. Contributing to the cyclical self-renewal process of the OSE would predestine OC growth to be at least partially dependent on Lgr5/6-positive stem cells. More recently, a study demonstrated that human three-dimensional fallopian tube cultures could grow in laboratory conditions for many months, requiring similar signalling/growth factors to intestinal organoid cultures [51]. Intriguingly, this study suggested that Lgr5 expression was not significantly increased in fallopian tubal epithelium, whereas Lgr6 expression has been suggested as the key marker for tubal self-renewal. However, the underlying (Wnt) pathway remains the same for Lgr5- or Lgr6-positive cells, suggesting a role of Lgr5/6-positive stem cells [45, 51]. In turn, this would suggest that the fallopian tubal epithelium and the OSE share a common self-renewal mechanism.

It will be important to identify the molecular steps that lead to a loss of appropriate stem cell function and promote distinct changes in gene expression in the OSE and tubal epithelium. This could also shed light on the well-established link between (sporadic and hereditary) gynaecological and colorectal cancer, which is typically seen in hereditary non-polyposis colon cancer (Lynch syndrome) [52].

Discussion

It is remarkable that despite decades of research the cells of origin of HGSOC have not been identified. This could be explained, because the two models are supported by unique yet equally valid findings, and there is no evidence that clearly excludes one of the two models. However, in BRCA mutation carriers, the presence of a p53 signature in the fallopian tubes may strongly suggest that, at least in this patient cohort, a tubal origin of HGSOC seems favourable [35, 36], reflecting proven cancer risk reduction and the advice of prophylactic risk-reducing salpingo-oophorectomy in these individuals [53].

If both models are true, the question remains of how the ovarian tissue environment forms a hotspot for cancer formation from (at least) two different origins [14]. This could (at least partially) be explained developmentally, because the OSE and the fallopian tube share the same embryonic origin. Therefore, one could imagine that ovaries offer the same growth-promoting environment for cells form both tissue types, which would explain the similarities of HGSOCs that arise from different origins.

Interestingly, risk factors for tubal and ovarian origin of HGSOC have been shown to differ by looking at the tumor dominance as a surrogate for the cell of origin. This study, based on a case–control study (New England Case–Control Study) and two cohort studies (Nurses' Health Study/Nurses' Health Study II), classified dominant tumors, as

being either restricted to one ovary or at least twice as large on one ovary than on the other [54]. These dominant tumors were thought to arise from the ovary, whereas non-dominant tumors were thought to arise from the fallopian tube. Two or more pregnancies were more likely to be associated with a tubal origin, whereas endometriosis and age were more likely to be associated with an ovarian origin of cancer [54].

Neither of the two models can uniquely explain how cancer cells grow into or reach the ovarian tissue and how these cells, once established in the ovary, are stimulated to rapidly form HGSOC. One could speculate that the rapid tumor growth relies on the growth-stimulating environment established by the OSE. Likewise, it has also been suggested that endocrine dysregulation and/or inadequate hormonal exposure is linked to ovarian tumorigenesis [55]. This hypothesis stems from the increased risk of ovarian cancer after hormonal replacement therapy and the potential role of sex hormone receptors in ovarian tumorigenesis [55, 56].

It is also known that tumor heterogeneity is widespread, having been already described in OC more than 30 years ago [57, 58]. One could assume that ovarian tumor heterogeneity may also partially reflect the tissue origin of HGSOC. Recent advances in culturing normal human epithelial cells from the fallopian tube and ovaries from the same donors argue that ovarian tumor heterogeneity may reflect the different cells of origin [59]. However, this study relied on immortalized cell lines with ectopic hTERT expression [59]. Interestingly, a recent publication compared frequently used OC cell lines and compared the genomic profile of cell lines to 500 tissue samples from HGSOC [60]. This alarmingly suggested that particularly, the most frequently used OC cell lines (SKOV3 and A2780) bear little molecular resemblance to the actual disease, i.e., most significantly not harbouring TP53 mutations [60]. Importantly, a newly published technique showed promising results, describing the routine isolation of primary cell lines from human OC with > 95% efficiency [61]. The authors described the isolation of 25 new OC cell lines that showed constant growth in a newly developed cell culture medium while maintaining their genomic profile. It remains to be seen whether this new culturing technique may allow the establishment of more representative and closely disease-related cell cultures, avoiding the alterations inadvertently seen in long-term cultured cancer cell lines.

Although a significant number of women present with bilateral HGSOC, it is still poorly understood how cancer arises at both ovaries at the same time or whether the same precursor lesion spreads to the contralateral ovary. Interestingly, the mouse model described by Kim et al. shows that there is no cancer formation after removal of the ipsilateral fallopian tube [16]. This model may be utilized to identify signaling pathways that may contribute to bilateral OC formation.

The understanding of LGR5/6-positive stem cells in regulating the stemness of the OSE and fallopian tubal epithelium may shed light onto the origin of HGSOC. If both epithelia rely on the same key mechanism for self-renewal, this could explain how precancerous tubal lesions may give rise to HGSOC once implanted on the OSE. Using tubal (and ovarian) organoids may aid to model the origin of the disease.

Conclusion

It is evident that some OCs are a result of p53 inactivation and mutations in the epithelial cell lining of the fallopian tube, from which cancerous cells are then subsequently deposit onto the ovaries and promote cancer formation. This is particularly true for the subset of HGSOCs that arise in BRCA mutation carriers. However, it is unclear whether the OSE may contribute to this process or whether the OSE itself undergoes metaplastic changes and gives rise to HGSOC independently. Both models (OSE and fallopian tube) offer compelling evidence for the origin of HGSOC and future studies on the biology of STICs, and the OSE and biomarkers may shed light onto how HGSOC originates and how the tissue microenvironment itself drives ovarian tumorigenesis. Ovarian and tubal organoids represent a promising tool to investigate the influence of the tubal epithelium or the OSE contributing to HGSOC growth.

In addition, establishing the sequence of ovarian tumorigenesis and confirming the origin of HGSOC raise important questions regarding the clinical management of the disease. If some HGSOCs arise from tubal precursor lesions, how can one explain that the prolonged treatment with the combined oral contraceptive pill decreases the risk of OC? It may potentially reduce the incidence of cytotoxic stress during ovulation events or hormonal dysregulation potentially plays a role in ovarian tumorigenesis.

Another important clinical decision will be the usefulness of prophylactic or opportunistic surgical procedures, i.e., is there a clear incentive to perform a salpingectomy or a salpingo-oophorectomy to reduce the risk of HGSOC? On the one hand, clinicians should reconsider whether irreversible contraception should rather be performed by bilateral salpingectomy than tubal ligation if it reduces the risk of developing OC [53]. On the other hand, there is evidence of the beneficial effect of prophylactic bilateral salpingo-oophorectomy in patients with BRCA1/2 mutations, which should be performed at the age of 40–45 [53]. In this high-risk patient group, it was shown that prophylactic bilateral salpingo-oophorectomy significantly reduces the risk of developing both breast cancer and BRCA-related gynaecological cancer (hazard ratio 0.25, 95% CI 0.08–0.74) [62]. Despite the clear evidence in BRCA mutation carriers,

the potential benefits of a bilateral salpingectomy are less clearly defined in patients without an increased genetic risk. Opportunistic bilateral salpingectomy is typically discussed with patients undergoing abdominal surgical procedures for other indications, such as hysterectomy. It remains to be seen whether prophylactic bilateral salpingectomy is an effective cancer prevention in women with low genetic risk. Interestingly, a recent multi-centre randomised controlled trial ($n = 64$) showed that opportunistic salpingectomy in patients undergoing laparoscopic hysterectomy did neither decrease ovarian reserve, measured as pre- and post-operative antimüllerian hormone (p values > 0.2), nor increased surgical risk [63]. This is a relatively small trial, but it suggests that salpingectomy does not affect ovarian function while potentially reducing the risk of OC. This would have major clinical implications for the management of HGSOC and it will require carefully designed clinical trials, given the unclear benefit of opportunistic bilateral salpingectomy and the yet still uncertain origin of HGSOC [53].

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Compliance with ethical standards

Conflict of interest We declare that we have no conflict of interest.

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