Origin and molecular pathogenesis of ovarian high-grade serous carcinoma

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A new paradigm for the pathogenesis of ovarian cancer has recently been proposed which helps to explain persistent problems in describing the development and diverse morphology of these neoplasms. The paradigm incorporates recent advances in our understanding of the molecular pathogenesis of epithelial ‘ovarian’ cancer with new insights into the origin of these tumors. Correlated clinicopathologic and molecular genetic studies led to the development of a dualistic model that divides all the various histlogic types of epithelial ovarian carcinomas into two broad categories designated ‘type I’ and ‘type II’. The prototypic type I tumor is low-grade serous carcinoma and the prototypic type II tumor is high-grade serous carcinomas (HGSCs). As the serous tumors comprise ~70% of all epithelial ovarian tumors and account for the majority of deaths, the serous tumors will be the subject of this review. There are marked differences between the low-grade and high-grade serous tumors. Briefly, the former are indolent, present in stage I (tumor confined to the ovary) and develop from well-established precursors, so-called ‘atypical proliferative (borderline) tumors,’ which are characterized by specific mutations, including KRAS, BRAF and ERBB2; they are relatively genetically stable. In contrast, HGSCs are aggressive, present in the advanced stage, and develop from intraepithelial carcinomas in the fallopian tube. They harbor TP53 mutations in over 95% of cases, but rarely harbor the mutations detected in the low-grade serous tumors. At the time of diagnosis they demonstrate marked chromosomal aberrations but over the course of the disease these changes remain relatively stable. Along with the recent advances in understanding the molecular pathogenesis of these tumors, studies have demonstrated that the long sought for precursor of ovarian HGSC appears to develop from an occult intraepithelial carcinoma in the fimbrial region of the fallopian tube designated ‘serous tubal intraepithelial carcinoma (STIC)’ and involves the ovary secondarily. Another possible mechanism for the development of ‘ovarian’ HGSC is implantation of normal fimbrial epithelium on the denuded ovarian surface at the site of rupture when ovulation occurs. We speculate that this tubal epithelium can result in the formation of a cortical inclusion cyst (CICs) that can then undergo malignant transformation. Thus, serous tumors may develop from inclusion cysts, as has been previously proposed, but by a process of implantation of tubal (müllerian-type) tissue rather than by a process of metaplasia from ovarian surface epithelium (OSE, mesothelial). The dualistic model serves as a framework for studying ovarian cancer and can assist investigators in organizing this complex group of neoplasms. In conjunction with the recognition that the majority of ‘ovarian’ carcinomas originate outside the ovary, this model also facilitates the development of new and novel approaches to prevention, screening and treatment of this devastating disease.

The overall survival of women with ovarian cancer, the most lethal gynecologic malignancy, has not changed in over 50 years and screening studies carried out over the past two decades have failed to provide a survival benefit. This dismal state of affairs is due to the fact that current management is directed against established cancers rather than at the mechanisms by which cancer develops. Until the processes by which ovarian cancer develops are elucidated, the prospects of reducing the burden of this devastating disease are dim. Fortunately, in the last few years important advances have occurred in the field, which have profoundly advanced our understanding of ovarian cancer, and these advances will very likely lead to a significant improvement in the outcome.

pathogenesis of ovarian serous carcinoma

The origin and pathogenesis of epithelial ovarian cancer have perplexed investigators for decades. Despite numerous studies that have carefully scrutinized the ovaries for precursor lesions, none have been found. The prevailing view of ovarian carcinogenesis can be summarized as follows: [1] the vast majority of ovarian carcinomas are high-grade serous carcinomas (HGSCs) and, therefore, ovarian cancer can be regarded as a single disease and [2] ovarian cancer originates from cortical inclusion cysts (CICs) which develop from the ovarian surface epithelium (OSE). Recent morphologic and
molecular genetic studies have illuminated our understanding of ovarian carcinogenesis in ways that have been quite unexpected and have challenged the conventional wisdom regarding their origin and development. Indeed, they have resulted in a paradigm shift that has important implications for research and for radically changing our approaches to the management of this disease. One of the major problems in elucidating the pathogenesis of ovarian cancer is that it is not a single disease, but that it is, in fact, heterogeneously composed of different types of tumors with widely differing clinicopathologic features and behavior. On the basis of a series of morphologic and molecular genetic studies, we proposed a dualistic model that grouped various types of epithelial ovarian cancer into two broad categories designated types I and II [1, 2]. Type I tumors comprise of low-grade serous, low-grade endometrioid, mucinous and clear cell carcinomas. These tumors typically present as large cystic masses confined to one ovary, have a relatively indolent course and are associated with mutations in KRAS, BRAF, PTEN, PIK3CA, CTNNB1, ARID1A and PPP2R1A [1, 3] that perturb signaling pathways. These molecular alterations result in morphologic changes, which are reflected by a step-wise progression from benign through varying degrees of atypia (borderline tumor) to noninvasive and then invasive low-grade carcinoma.

Type II tumors are composed of high-grade serous, high-grade endometrioid, undifferentiated carcinomas and malignant-mixed mesodermal tumors. These tumors are aggressive and typically present at an advanced stage, which contributes to their high fatality [2]. Unlike type I tumors, which are relatively genetically stable, type II tumors initially demonstrate marked chromosomal aberrations but these remain relatively stable over the course of the disease. Because the serous tumors are the most common epithelial ovarian cancer, account for the majority of deaths and have been the most extensively studied, this review will be limited to these neoplasms.

origin of HGSCs

Until recently, the prevailing view of the origin of HGSC was that these tumors were derived from the OSE or CICs, but a convincing precursor of HGSC in the ovary has not been identified. In the late 1990s and early 2000s with an increase in prophylactic salpingo-oophorectomies carried out for women at high risk of developing ovarian cancer because of a family history or because of germline mutations of BRCA1 and BRCA2, pathologists began to meticulously section the fallopian tubes and ovaries. Surprisingly, they found no ovarian lesions but instead discovered occult noninvasive and invasive carcinomas in the fallopian tubes, typically in the fimbria [4–10].

Subsequently, Piek et al. proposed that these occult tubal carcinomas might shed malignant cells, which then implant and grow on the ovary, simulating primary ovarian cancer [11]. Another argument supporting the fallopian tube as the origin of serous tumors was a gene expression study, demonstrating that the expression profiles of ovarian HGSCs more closely resembled fallopian tube epithelium (FTE) than the OSE [12]. In 2007, a study of women with pelvic (ovary, fallopian tube and primary peritoneal) HGSC who were not high risk and who did not necessarily harbor BRCA mutations reported tubal intraepithelial carcinomas in 48% [13]. Because the tubal carcinomas were associated with serous and not endometrioid, clear cell or mucinous carcinomas, these investigators proposed that the noninvasive carcinoma be designated 'serous tubal intraepithelial carcinoma (STIC). In a similar study in which the paraffin blocks of the fallopian tubes were leveled and serially sectioned, the frequency of STICs associated with pelvic HGSCs was found to be 61% [14].

Laser capture microdissection studies of STICs and concordant HGSC involving the ovary have not only shown that 92% of STICs have TP53 mutations, but that they are identical to the TP53 mutation in the ovarian carcinoma supporting a clonal relationship [15]. Parenthetically, recent studies in which the entire genome of approximately 400 ovarian HGSCs has been sequenced found TP53 mutations in >96% of cases [16]. The finding of identical TP53 mutations in the STIC and associated ovarian HGSC, however, does not exclude the possibility that STICs are metastases from a primary ovarian carcinoma. Evidence to support their primary role has been the demonstration that STICs associated with ovarian HGSCs have shortened telomeres compared with the ovarian carcinomas [17]. Shortened telomeres are one of the earliest molecular changes in carcinogenesis and lead to chromosomal instability, a cardinal feature of pelvic HGSC. Another very compelling piece of evidence supporting STICs as precursors, at least in women who are at high risk of developing ovarian cancer, is the identification of STICs in 10%–15% of fallopian tubes removed prophylactically.

As STICs are found in up to 60% of cases of HGSC, the question arises as to what is the origin of the remainder? Many HGSCs extensively involve pelvic structures, and therefore, it is likely that some STICs are obscured due to overgrowth by the invasive carcinoma. We speculate that another possible site of origin of HGSCs is CICs in the ovary [18]. There appears to be two types of ovarian CICs. One type is lined by flattened epithelium which probably results from invagination of the OSE. The second type is lined by ciliated columnar epithelium, which is histologically identical to FTE. This type of cyst, like FTE, contains not only ciliated cells and secretary cells but also leukocyte populations, including CD3+ T lymphocytes, CD8+ T lymphocytes and CD68+ macrophages (Ardighieri et al. unpublished data). These immune cells are located just above the basement membrane in both FTE and the columnar-type CICs.

Thus, a subset of HGSC may indeed develop from CICs, but the latter are derived from tubal epithelium not the OSE. In support of the proposal that CICs can play a role in the development of ovarian HGSC was the report of aneuploidy in CICs [19].

serous tubal intraepithelial carcinoma

STIC is characterized by high nuclear/cytoplasmic ratio, pleomorphism, hyperchromasia, lack of ciliated cells, loss of polarity with or without epithelial stratification and occasional mitotic figures. Nuclei are rounded and enlarged, sometimes with prominent nucleoli. As previously noted, STICs have been found to harbor rTP53 mutations in over 90% of cases and stain strongly and diffusely with p53. The most common mutations...
are missense (61%), splicing/frame shift mutations, but nonsense mutations (39%) also occur [15, 20]. Strong, diffuse staining correlates with a missense mutation, whereas complete absence of staining correlates with nonsense mutations since these result in a truncated protein that is not detected by the p53 antibody [15]. In contrast, a p53 immunostain in which there is a mixture of positive and negative nuclei generally correlates with wild-type TP53. It has also been found that the Ki-67 labeling index is elevated in STICs with a mean proliferatin index of 38% and a range of 2%–95% [21–23]. The histologic diagnosis of STIC can be challenging, as the morphologic changes may at times be subtle. The morphologic features that are most helpful in the diagnosis of STIC are the presence of at least one mitotic figure, but unfortunately these are uncommon, followed by epithelial stratiﬁcation, which is relatively nonspeciﬁc. Apoptotic bodies, nuclear rounding and/or enlargement, nuclear molding, abnormal chromatin pattern and marked pleomorphism were not that helpful. Two patterns of p53 immunostaining that are useful are either strong 53 positivity in >75% of lesional cells or complete absence of staining as both patterns correlate closely with a TP53 mutation [24]. A Ki-67 labeling index of >10% is considered elevated and is a useful adjunct in diagnosis [25].

It probably strikes the reader as odd that the emergence of the fallopian tube as the most likely source of ovarian HGSC had been overlooked for so long. The failure to identify a precursor in the fallopian tube in the past can be attributed to the assumption that the precursors of ovarian cancer would be in the ovary itself. The fallopian tubes until recently were subjected to relatively limited examination, mainly to document their sectioning. Tissue was often limited to one or two cross sections in the ampulary portion of the tube with or without sections of the fimbriated end. In an effort to improve the detection of STIC the Association of Directors of Anatomic and Surgical Pathology [26] has recommended a two-tiered approach to gross examination of the fallopian tube, depending on the level of suspicion for an occult invasive or intraepithelial carcinoma. Fallopian tubes removed for benign conditions are sectioned in the ampullary and infundibular portions and a longitudinal section of the ovaries is obtained. For risk-reducing salpingo-oophorectomy specimens, the entire fallopian tube is submitted for microscopic evaluation with special attention to the fimbria, as this is where the vast majority of STIsC are detected. This approach is similar to the SEE-FIM protocol proposed by Medeiros et al. [10]. In routine practice, the SEE-FIM protocol should be used for prophylactic specimens removed from women at high risk and for pelvic (ovarian, tubal and primary peritoneal) HGSCs. For benign hysterectomy specimens cross sections through the isthmic, ampullary and infundibular portions and a longitudinal section through the fimbria suffice.

**Fallopian tube and ovarian factors influencing serous tumor development: the tube, ovary, peritoneum ecosystem**

Ovulation has long been considered to be an important factor in the development of ovarian cancer. The theory of ‘incessant ovulation’ as proposed by Fathalla [27] is thought to result in destruction and repair of the OSE which is accompanied by an inflammatory reaction. Inflammation probably is a factor in ovarian carcinogenesis, particularly as we now appreciate that a substantial number of immune cells are located normally in the fallopian tubes and in CICs (Ardighieri et al. unpublished data). In addition, follicular fluid, released at the time of ovulation, is a source of free radicals as is hemolyzed blood on the ovaries resulting from retrograde menstruation. The role of ovulation in ovarian carcinogenesis has been supported by epidemiologic studies, which have shown a significant reduction in the risk directly related to parity and the use of oral contraceptive pills (OCPs) [28].

Another obvious question concerning the tubal/ovarian relationship is why do tumors that apparently arise in the fallopian tube more commonly develop in the ovary? Recently, we have detected ovarian stromal cells that are strongly positive for inhibin, calretinin and steroid factor 1 (SF1) immediately surrounding nests of tumor cells and in the stroma of the tumor itself. These tumors include HGSC as well as endometrioid, clear cell, mucinous carcinomas and corresponding adenomas and atypical proliferative (borderline) tumors (Kuhn et al., unpublished data). We speculate that following implantation of epithelium in the ovary, the adjacent stromal cells are ‘activated’ and secrete steroid hormones that may in turn stimulate the epithelium of the carcinoma. Moreover we and others [29] have localized an enzyme, steroidogenic acute regulatory (STAR) protein which transfers cholesterol from the outer to the inner mitochondrial membrane and plays an important role in steroidogenesis in these activated stromal cells. Functioning ovarian stroma in association with metastatic tumors in the ovary was first described in the 1961 by Scully and Richardson [30] and subsequently expanded to include primary epithelial ovarian tumors, in which endocrine studies revealed elevated urinary 17-ketosteroids as well as increased serum testosterone and estrogen levels. [31]. These observations provide a possible explanation for why the ovary as opposed to the fallopian tube is a preferential site for growth of a carcinoma that is located in both sites. Indeed, many of these neoplasms in the ovary contain estrogen, progesterone and androgen receptors.

**Molecular pathogenesis of pelvic serous cancer**

Despite considerable effort aimed at elucidating the molecular mechanisms of ovarian serous carcinoma, much remains to be known about its exact pathogenesis. Traditionally, serous carcinomas have been graded as well, moderately and poorly differentiated. Implicit in this grading system was the notion that well differentiated tumors progressed to moderate and ultimately poorly differentiated carcinoma. In recent years, however, correlated morphologic and molecular genetic studies have shown that there are distinctly different molecular pathways that lead to the development of low- and high-grade serous [18]. Interestingly, Malpica et al. developed a two tier grading system to replace the three tier grading system for serous carcinoma based on morphologic features and clinical outcome independent of our studies [32]. It should be noted that although most low-grade and high-grade serous tumors develop independently, on rare occasion low-grade serous...
tumors progress to HGSCs [33, 34]. It was the correlated morphologic and molecular genetic studies of serous tumors that led to the proposal of a dualistic model for the development of all epithelial ovarian cancers that divides them into two broad categories designated types I and II. Initially, attention was directed at correlating specific mutations with specific histologic types but it has become evident that it is not a matter of discrete molecular alterations but rather signaling pathways that are perturbed by different types of molecular aberrations that lead to the development of specific tumor types.

clinical implications

For the last two decades, numerous studies, including large clinical trials, have been conducted in an effort to develop screening tests (serum CA 125 and transvaginal ultrasound) to detect ovarian cancer when confined to the ovaries, thereby reducing mortality by detecting early stage disease. These screening studies have not provided a survival benefit. An appreciation of the dualistic model of serous carcinogenesis and the new concepts of origin suggest new approaches to early detection of this heterogeneous group of tumors that may be more effective.

Low-grade serous carcinomas are slow growing, generally remain confined to the ovary for long periods of time and attain a size that allows them to be relatively easily detected by pelvic examination and/or transvaginal ultrasound. They constitute, however, only 10% of all serous cancers and result in a relatively small number of deaths. Therefore, the development of a biomarker screening test for low-grade serous carcinoma is not urgently needed. In contrast, HGSC accounts for approximately 75% of all ovarian cancers and accounts for the vast majority of deaths. Unfortunately these tumors are rarely confined to the ovary, even at their inception. In a study of nearly 400 patients who were carefully staged from the Washington Center Hospital in Washington DC, which is largely a primary care hospital, less than 1.25% of HGSCs were confined to the ovary (Seidman et al, unpublished data). Similarly, the British Columbia Tumor Registry reported that only 0.5% of HGSCs were limited to the ovary at diagnosis. The futility of detecting early-stage ovarian cancer was recently underscored in a large multi-institutional prospective study [35] in which, despite intensive annual screening of nearly 35 000 women with CA 125 and transvaginal ultrasound, 70% of the women presented with advanced stage disease. This was no different from unscreened populations. A more recent study from the same group showed that morbidity was significantly higher in the screened population because false-positive tests led to unnecessary surgical intervention [36]. Accordingly, a sensitive and specific screening test is needed for HGSC but the goal should be the detection of low volume, not low stage disease. This can only be accomplished by developing a panel of sensitive and specific biomarkers that are expressed early in ovarian carcinogenesis. A novel test has recently been described in which DNA obtained from liquid cervical cytology specimens is analyzed for the presence of somatic mutations in rare tumor cells that accumulate in the cervix. Using new whole-exome sequencing, a panel of genes that are commonly mutated in endometrial and ovarian carcinomas was assembled and with a highly sensitive massively parallel sequencing method the same mutations in the liquid cytology specimen and the patient’s tumor were detected in 100% of 24 endometrial and 41% of 22 ovarian carcinomas [37]. These results are very encouraging but large population studies must be carried out to validate the findings.

Treatment of low-grade and high-grade serous carcinoma, like early detection, should be different based on their distinctive molecular pathways. Low-grade serous tumors are slow growing and are confined to the ovary at diagnosis usually spreading late in their evolution. Accordingly, when confined to the ovary, oophorectomy may suffice. On the other hand, when they have spread beyond the ovary, chemotherapeutic agents that are effective against the more rapidly proliferating HGSCs are not effective against the low-grade tumors, because the latter are slow growing. Therefore, new approaches for advanced-stage low-grade serous tumors are needed. Deregulation of protein kinase activity as a result of somatic mutation in these genes occurs in many low-grade serous tumors. Mutations in these genes constitutively activate the signaling pathways they control, and tumor cells with mutations become dependent on those mutations for progression. Therefore, these genes could provide potential targets for therapeutic intervention. For example, many low-grade serous carcinomas constitutively activate the MAPK signaling pathway because of mutations in ERBB2, KRAS or BRAF, the upstream regulators of MAPK. It is, therefore, conceivable that BRAF inhibitors and other MAPK kinase inhibitors could prolong disease-free interval and improve overall survival in patients with these types of advanced stage low-grade serous tumors. In contrast, treatment of HGSC should be initiated on the basis of detection of sensitive and specific biomarkers before the appearance of morphologically recognizable disease, when therapy will likely be more effective [18]. A precedent exists for this approach, as women with hereditary BRCA mutations are treated on the basis of that information only. Another important treatment issue that needs to be considered is whether patients found to have a STIC require adjuvant chemotherapy. The finding of positive pelvic washings in patients with only a STIC indicates that these microscopic lesions can shed malignant cells. At present there is no consensus as to whether or not these women should be treated. This will have to be determined by a randomized clinical trial.

Finally, the mounting evidence that ovarian cancer does not develop in the ovary and the lack of success of ovarian cancer screening provides a strong rationale for directing efforts at primary prevention. It has been well established in epidemiologic studies that the use of oral contraceptives reduces the risk of ovarian cancer substantially. In an epidemiologic analysis of 100 000 women it was shown that the longer women used oral contraceptives, the greater the reduction in ovarian cancer risk (P < 0.0001). This reduction in risk persisted for more than 30 years after oral contraceptive use had ceased. Based on these findings, it was estimated that since the introduction of these drugs, nearly 50 years ago, 200 000 ovarian cancers and 100 000 deaths were prevented [38]. Accordingly, the entire approach to prophylaxis, not only for women at high risk of developing ovarian cancer but also for the general female population, needs to be reevaluated in the light
of the evolving new paradigm of ovarian carcinogenesis as discussed here. The traditional approach for reducing the risk women with a family history of ovarian carcinoma or who are found to have BRCA1/2 mutations has been bilateral salpingooophorectomy. If it can be unequivocally shown that the serous carcinomas in these women develop almost exclusively in the fimbria, then salpingectomy or fimbriectomy alone would be sufficient. This approach would have to be evaluated in a randomized, clinical trial comparing it with the standard treatment of bilateral salpingo-oophorectomy.

conclusions

A new paradigm for the pathogenesis of ovarian serous cancer based on a dualistic model and the recognition that the majority of these tumors originate outside the ovary assist in organizing the complex group of epithelial ovarian neoplasms and facilitates the development of new and novel approaches to prevention, screening and treatment. The low-grade serous tumors (type I) are generally indolent, present in stage I (tumor confined to the ovary) and develop from well-established precursors, so-called ‘atypical proliferative (borderline) tumors and are characterized by specific mutations, including KRAS, BRAF and ERBB2, but rarely TP53. They are relatively genetically stable. In contrast, the HGSCs (type II) are aggressive, present in advanced stage and develop from STICs. They have a very high frequency of TP53 mutations but rarely harbor the mutations detected in the low-grade serous tumors. At the time of presentation they exhibit marked chromosomal aberrations but subsequently remain relatively stable throughout the course of the disease. Although low-grade serous and HGSCs develop independently along different molecular pathways, both types develop from FTE and involve the ovary secondarily.

The proposal implicating the fallopian tube as the primary site of ovarian serous carcinoma is supported by several lines of evidence. First, STICs are detected in more than half the cases of sporadic pelvic HGSCs and in ~10%–15% of fallopian tubes prophylactically removed from women at high risk of developing ovarian carcinoma because of germline BRCA mutations. In these latter cases the STIC morphologically resembles ovarian HGSC and importantly there are no similar lesions in the ovary. Second, in an analysis of 342 consecutive gynecologic cases that were entirely submitted for histologic examination, Tang et al. reported that STICs were only associated with cases in which there was either an ovarian or pelvic HGSC but not with endometrioid, clear cell or mucinous ovarian carcinomas. Third, STICs frequently up regulate oncogene products, such as cyclin E1, Rsf-1 and fatty acid synthase, that are over-expressed in HGSC. Fourth, in cases in which there is a STIC and a concordant ovarian HGSC, TP53 mutational analysis has demonstrated the identical TP53 mutation in both the STIC and the associated ovarian neoplasm indicating that the two lesions are clonally related. Fifth, STICs have been reported to contain relatively shorter telomeres compared with normal-appearing FTE and the associated ovarian HGSC as occurs in precursor lesions of other cancer types. This latter finding and the presence of STICs in prophylactic salpingectomy specimens in the absence of carcinoma are among the most important pieces of evidence that argue against the view that STIC represents lateral extension or metastasis from the adjacent HGSC. Finally, another possible mechanism for the development of serous carcinoma (low- and high-grade) carcinoma is implantation of normal FTE from the fimbria, at the site of rupture of the OSE when ovulation occurs resulting in the formation of a CIC that may then undergo malignant transformation. Thus, serous tumors may develop from CICs, as has been thought, but by a process of implantation of tubal (müllerian-type) tissue rather than by a process of metaplasia from OSE (mesothelial).

This new model of ovarian carcinogenesis explains why current screening strategies designed to detect ovarian cancer, when it is confined to the ovary, are ineffective. Although the recently reported novel method of early detection of mutations in liquid cervical cytology specimens is very promising [37], attention should be directed to primary prevention. This takes on particular relevance with the recognition that the majority of ovarian carcinomas are derived from cells in the fallopian tube and the important role of ovulation in ovarian carcinogenesis. Salpingectomy alone may be sufficient to accomplish this, as removal of the fallopian tubes would reduce the risk of ovarian cancer while preserving ovarian function. Ovarian conservation seems to be particularly important for a woman’s health, as it has been shown that oophorectomy is associated with increased overall mortality and a higher frequency of nonfatal coronary heart disease. Other approaches such as greater use of oral contraceptives should be explored. As previously noted, the use of these agents dramatically reduces the risk of ovarian cancer and it has been estimated, based on the current usage that oral contraceptives can result in the prevention of at least 30 000 cases of ovarian cancer per year over the next several decades [38]. Accordingly, new diagnostic, prevention and therapeutic approaches must be developed on the basis of our evolving understanding of ovarian carcinogenesis.

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