Gynecologic Oncology 130 (2013) 246–251

Contents lists available at SciVerse ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review

Ovarian surface epithelium as a source of ovarian cancers: Unwarranted speculation or evidence-based hypothesis?

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HIGHLIGHTS

- Pure ovarian surface epithelium (OSE) has been transformed to serous carcinomas.
- Transitional stages in OSE-lined cysts undergoing metaplasia rule out fimbrial implants.
- Caltretinin and PAX8 don't reliably mark the origin of cysts as OSE or fimbriae.

ARTICLE INFO

Article history:
Received 20 February 2013
Accepted 23 March 2013
Available online 2 April 2013

Keywords:
Ovary
Ovarian cancer
Ovarian carcinogenesis
Ovarian surface epithelium
Origin

ABSTRACT

Objectives. There has been increasing evidence that high grade serous ovarian carcinomas (HGSOCs), the most common and most lethal of all ovarian cancers, originate in oviductal fimbriae and metastasize to the ovary. The alternate hypothesis, that ovarian carcinomas may originate within the ovarian stroma in inclusion cysts lined by ovarian surface epithelium (OSE), has been criticized and often dismissed on the basis of the OSE's embryonic origin, mesothelial phenotype, tissue-specific markers, questionable ability to undergo metaplasia, and the lack of identifiable precursor lesions. This review analyzes these criticisms and summarizes evidence indicating that OSE as a source of ovarian cancers cannot be ruled out.

Methods. The literature was reviewed and representative reports were chosen to evaluate the current criticisms of, and evidence in favor of, the OSE hypothesis.

Results. The close developmental relationship between the oviduct and OSE, both of which originate in the mesothelial coelomic epithelium, accounts for their capacity to produce similar tumors. Histopathologic and experimental data show that OSE does undergo serous metaplasia, and that transformation of pure OSE cultures produces aggressive neoplasms resembling high- and low-grade serous carcinomas, but never mesotheliomas. There is evidence of premalignant changes (e.g. p53 inactivation) in morphologically normal OSE and of rare but definitive dysplastic and early preinvasive lesions in OSE-lined inclusion cysts. Conclusions based on tissue-specific markers to identify origins of inclusion cysts usually disregard the changes in differentiation occurring when OSE is displaced to the stroma. Lastly, an explanation is offered for the rare detection of precursor lesions in OSE-lined cysts, based on the likelihood that the duration from initiation of malignant transformation to invasive growth is minimal and thus difficult to detect.

Conclusion. The likelihood that HGSOCs originate both in fimbriae and in OSE should be considered in clinical decisions involving choices between prophylactic salpingo-oophorectomies and salpingectomies.

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0090-8258/$ – see front matter
http://dx.doi.org/10.1016/j.ygyno.2013.03.021

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Introduction

The question whether, and in what proportion, different subtypes of ovarian cancer and in particular high grade serous ovarian carcinomas (HGSOCs) arise in the ovarian surface epithelium (OSE) or in the epithelium of oviductal fimbriae has not been resolved. There is considerable evidence that HGSOCs can and do originate as serous tubal intraepithelial carcinomas (STICs) which are located on distal oviductal fimbriae [1]. From there, the neoplastic cells are hypothesized to be deposited on the ovarian surface, enter the ovarian stroma by as yet unproven means and, once there, form cysts and progress to form carcinomas [2]. According to this hypothesis, HGSOCs are not ovarian in origin, but rather are metastases from the fallopian tube. There is much evidence supporting this view, though STICs have been found associated with only about 60% of these neoplasms [3]. An alternative source of ovarian carcinomas is the OSE, i.e. the pelvic mesothelium covering the ovary and lining epithelial inclusion cysts which are likely derived from surface invaginations [4]. According to this hypothesis, which was originally advanced by Scully [5], OSE is capable of metaplasia to Mullerian duct-derived epithelia (serous, endometrioid, mucinous) with subsequent progression to the respective subtypes of ovarian carcinomas. In the recent literature there is considerable support for the oviductal hypothesis, but the hypothesis that OSE-derived epithelial inclusion cysts undergo Mullerian metaplasia and subsequent malignant transformation is frequently dismissed, often without any reference to the voluminous literature to the contrary. The present review discusses these claims, and summarizes the evidence that OSE cells are capable of giving rise to ovarian carcinomas.

Common criticisms of the OSE hypothesis include: 1) that the fallopian tube epithelium has a different embryonic origin from OSE and that therefore metaplasia by OSE to Mullerian duct-derived phenotypes is unlikely, 2) that evidence for metaplasia by OSE to Mullerian duct derivatives is lacking, 3) that the tissue specific markers calretinin and PAX8 indicate that most epithelial inclusion cysts (where most ovarian cancers originate) as well as HGSOCs, are derived from fimbrial epithelium, 4) that, despite numerous studies that have carefully scrutinized the ovaries for precursor lesions of HGSOCs, none have been found. 5) Papers critical of the OSE hypothesis usually omit any mention

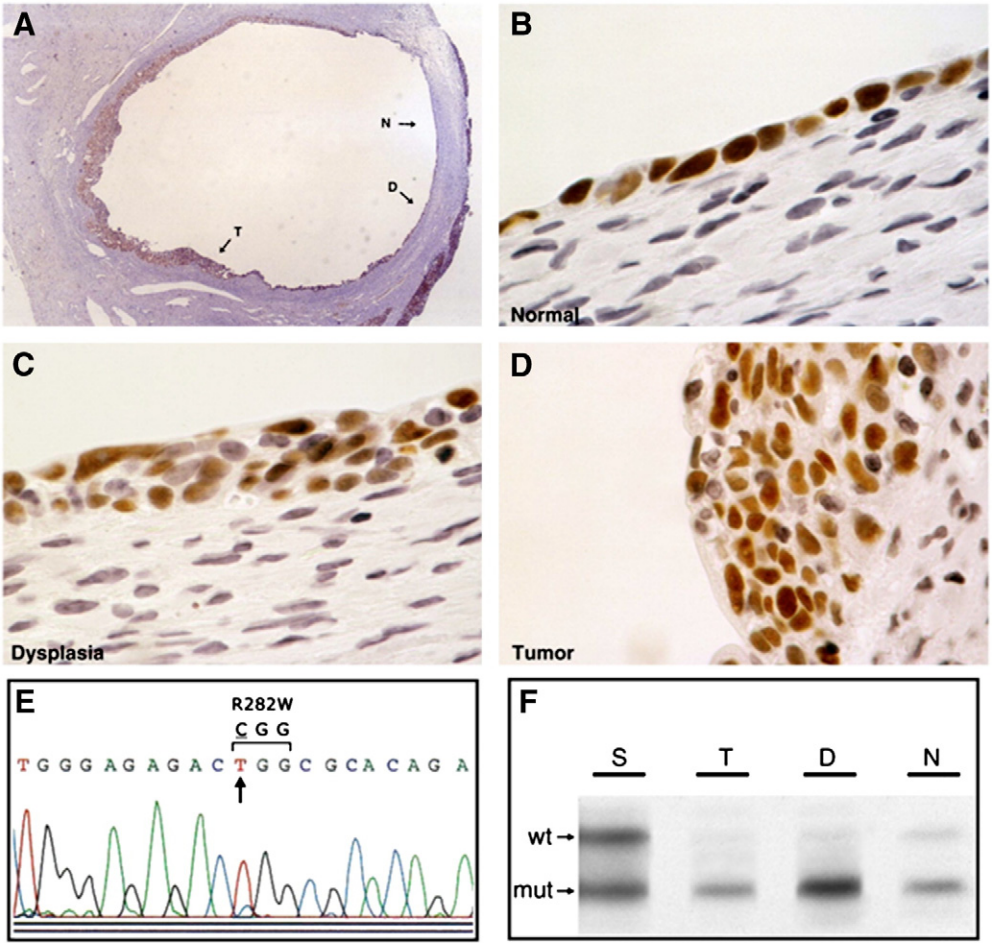

Fig. 1. Morphological, immunohistochemical, and genetic analyses of early stage ovarian carcinoma arising in a *BRCA1* 185delAG heterozygote. (A) Low-power photomicrograph of histologic progression of normal epithelium (N) to dysplastic epithelium (D) to invasive carcinoma (T) arising within an inclusion cyst. (B,C,D) High-power photomicrographs of cellular regions of normal, dysplastic, and carcinoma, respectively, as shown in panel (A). The immunostain is for p53 in panels (A–D). (E) Sequence analysis of *TP53* representative of DNA samples from all three cellular components shown in panels (B–D). A missense mutation is evident at codon 282 (CGG→TGG; R282W). (F) Loss of the wild-type (wt) *BRCA1* allele in DNA derived from normal, dysplastic, and tumor cells shown in panels (B–D), with retention of mutant (mut) and wild-type alleles in surface epithelium from the same ovary.
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