Letter to the Editor

Article by Natalie Banet and Robert J. Kurman: Two Types of Ovarian Cortical Inclusion Cysts: Proposed Origin and Possible Role in Ovarian Serous Carcinogenesis; Int. J. Gynecol. Pathol. 2015;34:3–8.

In Reply:

The above publication is very interesting and deals with an important topic, that is, the source of high-grade serous ovarian carcinomas. The authors propose that all of these highly malignant tumors originate from oviductal fimбриa, or from ovarian cortical inclusion cysts (CICs) that are derived from fimбриa, rather than from CICs derived from ovarian surface epithelium (OSE). Several points in the publication require clarification before this conclusion can be accepted:

The authors used calretinin and PAX8 as the specific histochemical markers for OSE-derived and fimбриa-derived CICs, respectively. However, while calretinin is a consistently positive marker for mesothelial cells including OSE, and is absent in fimбриa, PAX8 is found in both cell types. In the ovary, PAX8 is mainly, although not completely absent in OSE on the ovarian surface, but it is expressed by most OSE-lined CICs (1–3). This shift in gene expression parallels the general tendency of OSE to acquire epithelial characteristics when translocated from the surface to the ovarian stroma (4). Panels J–O in figure 2, meant to illustrate the specificity of calretinin and PAX8, are of such poor quality as to be inconclusive.

The authors assume that all “mixed” CICs (those being lined partially by flat, OSE-like epithelium and partially by columnar, ciliated epithelium) are derived from fimбриa, and speculate that “expansion” (not further defined) causes flattening of some of the ciliated cells to resemble OSE. However, the flat component of mixed CICs does not only resemble OSE morphologically but also by differentiation: it expresses calretinin and lacks several epithelial markers (eg, EPCA, EMA, cilia) present in the ciliated cells within the same CICs (2,3). Therefore, mixed CICs do not result simply through distortion of cell shapes but, rather, through altered gene expression, that is, metaplasia from an OSE-like to a fimбриa-like phenotype. The only alternative interpretation of the coexistence of OSE-like and fimбриa-like cells within the same CICs would be metaplasia from a fimбриal to a mesothelial phenotype, which is unlikely. Metaplasia of OSE to fimбриa-like epithelium is more likely to occur because (1) OSE cells are pluripotent stem cells with the capacity to differentiate along more than one pathway (5–7) and (2) metaplasia tends to lead to developmentally related cell types, and OSE originates from the same embryonic field as the fimбриal epithelium (8,9). It is misleading that, in figure 1, the authors pooled the mixed CICs with ciliated CICs. As mixed CICs include OSE-derived CICs undergoing metaplasia, it is impossible to determine the true proportion of ciliated CICs from figure 1. In the Results section the authors report that 60% of CICs are ciliated, which is closer to results by others (4) and is significantly lower than suggested by figure 1.

The article is based on the assumption that fragments of fimbral epithelium enter the ovarian stroma through ovulatory ruptures of the ovarian surface. This idea has been suggested in many publications but there seems to be no evidence supporting it. In contrast, there are indications contrary to this hypothesis: (1) Immediately after ovulation, the site of follicular rupture is filled with a mass of cells, coagulated fluids and blood, which must impede displacement of any fimbral epithelial fragments. It would be expected, therefore, that such fragments would occasionally be found within or near freshly ovulated follicles and that ciliated CICs would be located predominantly in or near ovulated follicles or c. lutea. No such spatial relationships have been reported. (2) The authors conclude, based on table 1, that the number of CICs increases with age. Interestingly though, in this table, the highest number of total ciliated CICs occurs in the 71+ age group, that is, in women long past menopause and ovulations. (3) CICs are significantly more numerous in women with polycystic disease who ovulate rarely or not at all, and the number of CICs is proportional to parity, that is, it is inversely proportional to the number of ovulations (10,11). These reports support the hypothesis that CICs arise from invaginations of surface OSE (11).

In conclusion, the hypothesis that all high-grade serous ovarian carcinomas arise from fimbral cells requires further studies.
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The authors declare no conflict of interest.

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To the Editor:

We appreciate Dr Auersperg’s letter regarding our paper as it gives us the opportunity to address and clarify issues which she raises. As we understand from her letter, Dr Auersperg primarily takes issue with the view that all high-grade ovarian serous carcinomas are derived from fallopian tube-type epithelium. Although we do subscribe to this view, this was not the primary aim of our study. The specific aim was to try to characterize the nature and presumed origin of ovarian cortical inclusion cysts (CICs) because they have been proposed to be the source of these ovarian carcinomas. To explain how flat nondescript epithelium observed in CICs undergoing malignant transformation to high-grade serous carcinoma, which has a fallopian tube phenotype, it has been proposed that the OSE undergoes tubal-type metaplasia. Dr Auersperg, in fact, has been one of the main proponents of this theory.

Dr Auersperg first disputes the use of PAX8 as a marker of tubal-type epithelium as opposed to OSE asserting that “PAX8 is mainly, although not completely absent in OSE on the ovarian surface, but it is expressed by most OSE-lined cysts.” She supports her argument with 3 references, 2 of which are her own. In our search we found only 2 other papers describing PAX8 expression in CICs which we had cited in our report. Neither of these indicated whether the CICs were flat or ciliated. In our study, none of the 5 CICs lined by flat epithelium (OSE) were positive for PAX8 and 4 of the 5 were positive for calretinin. We did find focal PAX8 expression in OSE on the ovarian surface in 2/20 cases. Admittedly, the numbers are small and, although in general surgical pathology practice PAX8 is used as a müllerian marker and calretinin as a mesothelial marker, we recognize that no one marker is perfect so we used a constellation of markers. Accordingly, in addition to PAX8 expression, we interpreted absence of calretinin expression, presence of estrogen receptor (ER) and progesterone receptor (PR), and expression of CD45 (lymphocyte marker) as markers of tubal-type epithelium. Lymphocytes are always present in fallopian tube epithelium but rarely in OSE (3). Taking into account all of these markers, we found a much closer “family resemblance” of CICs lined by ciliated epithelium to fallopian tube epithelium as opposed to OSE. Dr Auersperg also states that “Panels J-O in figure 2 of our paper, meant to illustrate the specificity of calretinin and PAX8, are of such poor quality as to be inconclusive.” Obviously, the reviewers and the Editor did not share this view as figure 2 was featured on the cover of the Journal in which our article appeared.

Dr Auersperg’s next argument is that our interpretation that CICs lined partially by ciliated epithelium and flattened epithelium (so-called hybrid cysts) are of tubal-type is incorrect. Again she
attributes this to metaplasia from OSE. We concluded that the flattened portion may have resulted from expansion of the cyst and flattening of the epithelium thereby obliterating the cilia because we found that the immunoprofile of the ciliated epithelium and the flattened epithelium in the hybrid cysts was the same. PAX8 was expressed in all 11 hybrid cysts, but only 4 expressed calretinin. In addition, ER and PR were expressed in 5% and 67%, respectively, of ciliated cysts and in 9% and 45%, respectively, of hybrid cysts. ER and PR were not expressed in the flat cysts. Finally, lymphocytes were present in all hybrid cysts as in ciliated cysts; however, it was present in only 1/3 of flat cysts. Because we found that the ciliated and hybrid cysts were so similar we combined them in figure 1. Dr Auersperg says that as a result of combining the 2 groups it is “impossible to determine the true proportion of ciliated CICs.” The 2 types of cysts are split out in the Results section and therefore the proportion can be easily calculated as she herself does in the next sentence of her letter.

Next, Dr Auersperg disputes our proposal that fimbrial epithelium can be implanted on the ovary at the site of rupture during ovulation. She says there is no evidence for this (we agree that this is speculative, but biologically plausible) and then goes through a number of reasons why this could not possibly occur concluding that if implantation of tubal epithelium were the source of the CICs they would be located in or near ovulated follicles. Over time atretic follicles and corpora lutea are resorbed as evidenced by the finding that the number of corpora albicans in middle-aged and older women is far lower than would be expected from the number of ovulatory cycles that would have occurred during their reproductive years. In any event, none of Dr Auersperg’s reasons are supported by any evidence and hence Dr Auersperg’s criticism is as speculative as our proposal is.

In our study, we found a trend of increased ciliated cysts in older women and suggested that this indirectly provided support to our hypothesis that they resulted from ovulatory cycles as older women were likely to have more numerous ovulatory cycles. Dr Auersperg disputes this in favor of the opposite scenario, namely that CICs are significantly more numerous in women who ovulate rarely indicating that CICs result from invagination of the OSE. The logic of this statement eludes us. Why do women who ovulate less frequently develop invaginations of OSE? She offers no explanation. Dr Auersperg concludes by saying that 2 studies (citations 11 and 12 in her letter) support the hypothesis that CICs arise from invaginations of OSE. One of the pieces of evidence cited in reference #11 was the frequent identification of tubal metaplasia in CICs in the normal ovary of women with ovarian carcinoma on the contralateral side. “Tubal metaplasia” in a CIC is simply the presence of tubal tissue lining the CIC and is therefore morphologically identical to a CIC arising from implanted tubal epithelium. The latter interpretation simply eliminates the need to invoke metaplasia to account for the presence of ciliated tubal epithelium. Parenthetically, other types of metaplasia in CICs are very rare (personal observations, R.J.K. 2014).

Our proposal that there are 2 pathways for the development of CICs does not negate the hypothesis of invagination of OSE but rather builds on it. In fact, as stated by Brian Greene in The Hidden Reality. Parallel Universes and the Deep Laws of the Cosmos “successful new theories do not render past theories irrelevant, instead they embrace and extend them” (4).

In conclusion, the morphologic and immunohistochemical features of CICs suggest that they are derived either from invagination of OSE leading to the development of flat cysts or from implanted fallopian tube epithelium leading to the development of ciliated cysts.

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The authors declare no conflict of interest.

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