Nonovarian origins of ovarian cancer

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Where does the most lethal gynecological cancer in the body start? How might its development be prevented? A PNAS paper helps answer these vital questions (1). Until recently, most epithelial ovarian cancers were postulated to arise from the ovarian surface epithelium, possibly encouraged by repeat ovulation-associated cellular damage (2). Kim et al. (1) turn this notion on its head by providing experimental proof in an animal model that "ovarian cancer" may in fact originate in the fallopian tube.

Ovulation frequency in women is associated with an increased risk of developing epithelial ovarian cancer (3), which reduces under conditions that suppress ovulation, such as pregnancy, breastfeeding, and use of the oral contraceptive pill (4). Ovulation is a serial injury-repair process that repeatedly exposes ovarian surface epithelial cells to inflammatory mediators and agents of cellular and DNA damage (2, 5). A popular theory to explain the development of epithelial ovarian cancer is that postovulatory surface remodeling causes the development of epithelial inclusion cysts beneath the ovarian surface. Epithelial cells lining these cysts are thereby chronically contained in an inflammatory microenvironment, which with contributory genetic and reproductive factors predisposes them to malignant transformation (6).

Although widely accepted, the "inclusion cyst" theory of ovarian cancer pathogenesis has never been convincingly substantiated. Seemingly normal ovaries may also contain epithelial inclusion cysts (7), and premalignant changes within such structures are exceedingly rare (8). Moreover, women with high-grade peritoneal serous carcinomas, which are closely related to serous ovarian carcinomas, can have uninvolved ovaries (9). Furthermore, there is the epidemiological evidence that tubal ligation and hysterectomy with ovarian conservation substantially reduce the risk of ovarian epithelial cancer, pointing to a possible tubal origin of the disease (10).

So how can all this be explained? The Matzuk team (1) provides experimental evidence for a nonovarian cellular origin of ovarian cancer: fallopian tube epithelium. They use a double KO (DKO) genetic mouse model in which *Dicer*, a gene essential gene for microRNA synthesis (11), and *Pten*, a key negative regulator of the PI3K-Akt signaling pathway (12), are selectively inactivated throughout the Müllerian tract. All such females eventually develop fallopian tube serous carcinomas that spread to the ovaries and metastasize throughout the peritoneal cavity to cause death. However, no ovarian cancer develops if the oviduct is removed at an early age. Most tellingly, surgical removal of the oviduct prevents cancer development in the ipsilateral ovary.

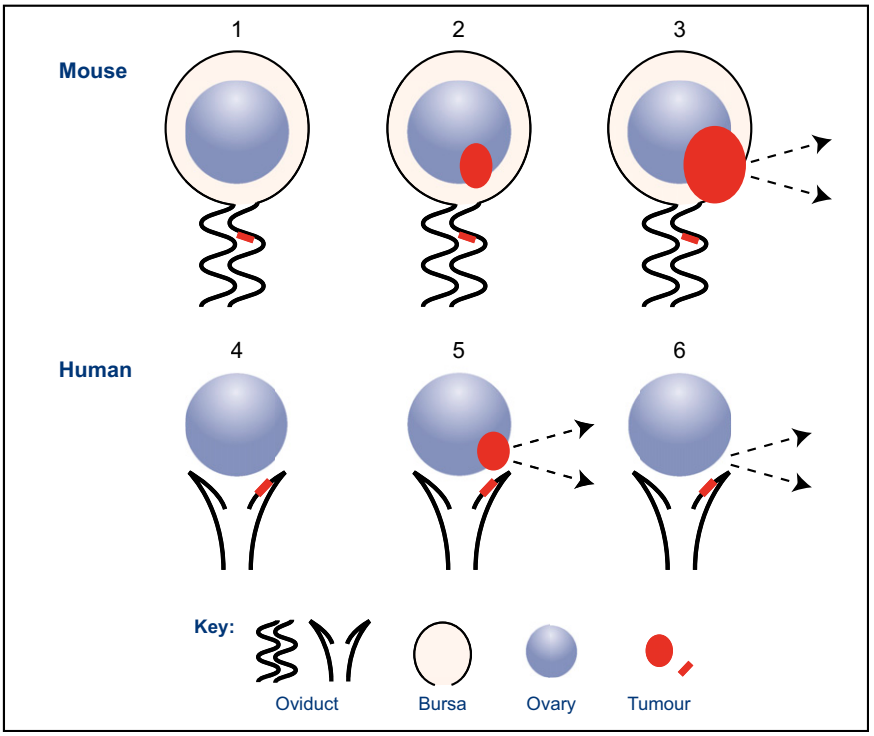

Fig. 1. Proposed fallopian tube origins of human ovarian and peritoneal epithelial carcinomas (key, *Bottom*). Studies of mice bearing dual *Pten* and *Dicer* gene KO reveal (labeled "1") epithelial tumor formation in oviducts that ("2") progresses to ipsilateral ovary, where it develops and thereafter ("3") metastasizes throughout the peritoneal cavity. Note that translocation of oviductal tumor cells is initially confined to the ovarian surface by the surrounding bursa. By analogy, human tumor cells ("4") arising in the fallopian tube epithelium can also ("5") migrate to the adjacent ovarian surface epithelium and produce a tumor. However, they would also be free ("6") to bypass the ovary and colonize other serosal surfaces in the peritoneal cavity as a result of the absence of a definite ovarian bursa. This might explain why high-grade serous peritoneal cancers can sometimes occur without macroscopic ovarian involvement.

A "fallopian tube" hypothesis of epithelial ovarian cancer origination is not new (13). There is increasing clinical evidence that cancerous cells arising in the fimbriated end of the fallopian tube can implant on the ovary and elsewhere in the peritoneal cavity to cause low-grade and high-grade serous carcinomas (14). Furthermore, studies of prophylactic oophorectomy specimens derived from women with *BRCA* mutations associated with increased lifetime risk of ovarian cancer have shown that most early ovarian carcinomas originate in the distal fallopian tube (15). The study of Kim et al. (1) is, however, remarkable in providing a surgical proof that malignant cells arising in the fallopian tube can be prevented from spreading to the ovary and producing tumors that bear hallmarks of high-grade serous ovarian cancer.

The question arises if a mouse model of ovarian cancer can adequately represent the human situation. Encouragingly, the morphology, cytology, molecular signatures, and intraabdominal pattern of spread of the murine cancer broadly mimic

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human high-grade serous ovarian and peritoneal carcinomas. The experimental results are additionally informative, given the interspecific differences that exist in ovarian anatomy and proximity to the oviduct. The mouse oviduct opens directly into a membranous periovarial sac or bursa, which completely encompasses the ovary (16). Therefore, malignant epithelial cells arriving from the oviductal lumen would be likely to be held in the region of the ovarian surface and encouraged to attach there. Metastatic spread into the peritoneal cavity following ovarian tumor growth is then a tertiary event, which necessitates breach of the bursa membrane. On the contrary, the human ovary lacks a definite bursa or rigid connection to the fallopian tube. Cellular products arising from the tubal luminal epithelium would be expected to make contact with the ovarian surface but are not required to do so, in which case malignant cells are able to bypass the ovary, disseminate into the peritoneal cavity, and implant on other serosal surfaces directly (Fig. 1). It therefore seems reasonable to propose that human serous peritoneal carcinoma without ovarian involvement may also have origins in the fallopian tube epithelium (9, 13–15).

Interestingly, the microenvironment within which cancer develops in the DKO mouse oviduct may resemble that postulated to occur in ovarian epithelial inclusion cysts. *Dicer* deletion is associated with the formation of oviductal cysts (17), and *Pten* suppresses anti-inflammatory signaling (18). Thus, the DKO oviductal luminal epithelium likely acquires a proinflammatory, cystic microenvironment, which would be expected to promote neoplasia (19).

The fallopian tube may provide a cellular source of high-grade serous ovarian and peritoneal carcinomas, at least in mouse.

We are left with a conundrum. If human ovarian epithelial cancer begins in the fallopian tube rather than the ovary, through what mechanism might ovulation frequency and related reproductive factors affect its incidence? Ovulation may damage the tubal epithelium through generating DNA damage and stimulating macrophage infiltration, but direct involvement of ovulation-associated hormones is unproven (20). Further basic research should inform, particularly by using the *Dicer-Pten* DKO mouse model.

In conclusion, we now have unambiguous scientific evidence that the fallopian tube may provide a cellular source of high-grade serous ovarian and peritoneal carcinomas, at least in mouse. These experimental data substantially strengthen the clinical evidence for a fallopian source of similar carcinomas in women. They also illuminate the curiosity that tubal ligation and hysterectomy with ovarian conservation can protect against ovarian cancer (10): no tube, no tumor.

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