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Revisiting ovarian cancer preclinical models: Implications for a better management of the disease

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ABSTRACT

Epithelial ovarian cancer (EOC) is the most lethal gynecologic malignancy. Despite progress in identifying "hallmark" genetic alterations associated with the main subtypes of epithelial ovarian cancer, the survival rate of women with EOC changed little since platinum-based treatment was introduced more than 30 years ago. The successful identification of new, effective anticancer drugs largely depends on appropriate preclinical experimental models that should ideally mimic the complexity of different cancer forms.

This review examines the preclinical ovarian cancer models available for a better understanding of the biological mechanisms of the development, progression, invasion and metastasis of EOC. We provide evidence that the preclinical models have been instrumental for a better understanding of the pathological events at the basis of ovarian carcinoma. The genetically engineered mouse (GEM) models of ovarian cancer have overcome some of the weaknesses of the xenograft models, such as the fact that these tumors arise orthotopically in immunologically intact mice and more closely resemble the behavior of human cancers. We envisage that in the near future these GEM models will play a key role in pre-selecting drug regimens with the greatest promise of efficacy in human clinical trials, making it easier and certainly less expensive to test new, different drug combinations.

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Introduction

Epithelial ovarian cancer (EOC) is the most lethal gynecologic malignancy.[1] Approximately 75% of woman with ovarian cancer are not diagnosed until the disease has spread beyond the ovary, contributing to a 70% mortality rate within 5 years. While the survival rate of woman with EOC has changed little since platinum-based treatment was introduced more than 30 years ago,[2,3] progress has been made in identifying "hallmark" genetic alterations associated with the main subtypes of EOC. EOC can be divided into two broad categories based on the pattern of tumor progression and molecular genetic changes: types I and II[4–6] (Table 1). Type I EOCs are low-grade, including low-grade serous, low-grade endometrioid, mucinous and a subset of clear cell carcinomas; they are relatively indolent and genetically stable. They arise from morphologically recognizable precursor lesions such as endometriosis, cortical inclusion cysts or low precursor lesions (borderline tumors) in the ovarian cortex.[7,8] Most of these tumors are slow-growing as they are generally large and confined to the ovary when diagnosed. Type II tumors include high-grade serous carcinoma (HGSC), high grade-endometrioid carcinoma, undifferentiated and some clear cell carcinomas and carcinosarcomas. They are highly aggressive and disseminate early in their clinical course. Type II tumors rarely result from morphologically recognizable precursor lesions and the epithelium lining the ovary and the fallopian tube has been advocated as their cells of origin.[9–12] Type I, generally, harbours somatic mutations (*KRAS*, *BRAF*, *CTNNB1*, *PTEN*) considered to de-regulate cell signaling pathways (AKT/MAPK), with low genomic instability. Most Type II tumors have *p53* mutation, frequent *BRCA1/2* inactivation and high level of genomic instability (Table 1).

All this information gathered in the last years has led to the idea that ovarian cancer can no longer be considered a single disease.[13,14] There is ample clinical and molecular evidence that the different histological subtypes are unique entities that do not respond uniformly to conventional chemotherapy and very likely call for exploration with novel therapeutic approaches tailored to each histological subtype.

This review looks at the preclinical ovarian cancer models available for a better understanding of the biological mechanisms of development, progression, invasion and metastasis of EOC. Particular focus will be on their use to develop rational new intervention strategies, stratified for the different molecular and histological subtypes.

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Table 1
Main features of Type I and II ovarian cancers.

	Type I	Type II
Origin	Progress from precursor lesions	*De novo* invasive tumors
Histology	Low-grade serous, low-grade endometrioid, mucinous and cell carcinomas	High-grade serous, high-grade endometrioid, clear cell carcinomas, undifferentiated, carcinosarcoma
Molecular characteristics	Genetically stable, generally *p53* wt, *BRCA* wt, RAS pathway frequently mutated	Genetically unstable, highly aberrant DNA copy number profile, *p53* mutant, *BRCA* dysfunction, *RAS* wt
Clinical course	Indolent, slow-growing	Highly aggressive with early dissemination
Response to treatment	Frequently platinum-resistant	Usually platinum-sensitive

Spontaneous models

Few animals develop ovarian tumors spontaneously, mainly the hen and the non-human primate macaque. The laying hen offers insights into the role of incessant ovulation in the development of spontaneous ovarian cancer, and even though there are differences from human anatomy, they develop ovarian adenocarcinomas.[15] In one study[16] 155 young and old laying hens were randomly selected for the presence of ovarian tumors and in 4 years of observation 32% and 8% of the birds developed ovarian and oviductal tumors, respectively; alike in humans, all the four histotypes (serous, endometrioid, mucinous and clear cell), early neoplastic lesions and a metastatic dissemination pathway were found. Molecular studies on these tumors[17] indicated that like in human ovarian cancers, *p53* alterations were common in chicken ovarian adenocarcinomas and correlated with the number of lifetime ovulations; *RAS* mutations were rare, similar to high-grade human ovarian cancers and HER-2/neu over-expression was common, as in late-stage human primary fallopian tube carcinoma and high-grade serous carcinoma (HGSC).[18,19]

The macaque is anatomically more like humans, with similar fallopian tubes and the outer epithelial cells in contact with the peritoneal surface and continuous with the ovarian epithelial surface (OSE). These primates develop spontaneous ovarian cancer in an age-dependent manner, like humans, though much less frequently.[20,21] However, differently from humans where the majority of tumors are epithelial, in non-human primates the most common cancers are granulosa cell and sex-cord stromal tumors.[22,23] The few carcinomas in these primates amount 23% of the tumors and show remarkable similarities to those in humans, with all four of the same histotypes and similar patterns of progression and metastasis.[22,23] No fallopian tube cancers have been observed in macaques, even though hyperplasia and nuclear atypia are found.[23]

Ovarian tumors also arise spontaneously in some strains of mice and in Wistar and Sprague–Dawley rats.[24,25] A spontaneous tumor in Lewis rats has been established and characterized as endometrioid carcinoma subtype, with an expression profile (estrogen alpha-, progesterone-, androgen receptors, her-2/neu, epithelial cell adhesion molecule, CA125, and nuclear beta-catenin) similar to that of humans.[26]

All these models, however, have a low incidence rate and a relatively long time for the appearance of tumors, so they are no use for experimental studies of ovarian carcinogenesis or therapeutic trials.

Ex vivo transformation of the ovarian surface epithelium

Based on experimental evidence that ovarian carcinoma probably arises from the single layer of epithelial cells that cover the ovary and from the fallopian tube epithelium, significant efforts have been made to isolate, propagate *in vitro* and characterize these cells. Most studies involved isolation of primary cultures of ovarian surface epithelium (OSE) from humans, rabbits, mice and more recently chickens (for a full review please refer to[27]). These primary cultures opened the way to their manipulation with the goal of inducing *in vitro* transformation and *in vivo* tumorigenicity, by culturing repeated serial passages, introducing viral oncogenes, and/or inducing specific genetic alterations. All these experiments improved our understanding of the genetic changes leading to the initiation of ovarian cancer and helped identify cooperating events in malignancy by using different combinations of genes. Rat and mouse primary ovarian cultures (ROSE and MOSE cells) could be immortalized and transformed by Kirsten murine sarcoma virus (Ki-MSV) and T antigen (SV40Tag)[28–30] and were tumorigenic when transplanted in immuno-deficient mice. Interestingly, spontaneous immortalization of cells from *p53*-deficient MOSE did not cause any transformed phenotype *in vitro* or *in vivo* tumorigenicity assays,[30] suggesting that simply silencing *p53* tumor suppressor cascade is not sufficient to start ovarian tumorigenesis. These data are in line with human EOC, in which germline mutations of *TP53* are rarely causative.[31,32]

Transfection of spontaneously immortalized ROSE cells with *c-H-RAS* and *erb-B2/neu* caused the cells to be transformed and become tumorigenic *in vivo*.[29,33] ROSE 199 cells transfected with the vascular endothelial growth factor (VEGF165) had little effect on *in vitro* cell growth and soft colony formation, but if transplanted into athymic mice they formed malignant ascites in all the animals when injected into the peritoneum, and vascularized tumors developed in 85% when injected s.c.[34] In this model system, blocking VEGF-mediated signaling by the Flk-1/KDR receptor kinase inhibitor SU5416 significantly inhibited tumor growth.[34]

Human OSEs (HOSE) are much more resistant to malignant transformation by oncogenic viruses than rodent OSEs. Populations of spontaneously immortalized cells occasionally emerged only after continuous culturing of SV40Tag or HPV16 E6/E7 transfected cells, some of which were able to form colonies in soft agar and tumors in SCID mice.[35,36] These data strongly suggested that additional genetic alterations are required to induce malignant transformation in human OSE.

Transfection of SV40- and hTERT-HOSEs with the mutant alleles of human *HRAS* ($HRAS^{V12}$) and *KRAS* ($KRAS^{V12}$) rendered cells tumorigenic *in vivo*. Tumors derived from *HRAS* cells were classified as undifferentiated adenocarcinomas with focal papillary growth, while the ones derived from *KRAS* were poorly differentiated with both sarcoma and carcinoma components, similar to the mixed Mullerian tumors in humans.[37]

Studies using retroviral transduction strategies in genetically-defined *in vivo* systems have been instrumental for a better understanding of the genes involved in ovarian tumorigenesis. This strategy is flexible and allows the generation of *in vivo* models to test the specific roles of different oncogenes and genes in EOC aetiology and the efficacy of molecular target agents.

In a seminal experiment, whole ovaries were taken from transgenic mice carrying the avian retroviral receptor (TVA), that renders cells susceptible to infection with subgroup A RCAS viruses,

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