In vivo tumor growth of high-grade serous ovarian cancer cell lines

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HIGHLIGHTS
• Eleven human cell models of high-grade serous ovarian cancer were tested in vivo tumor formation.
• OVCAR3, OVCAR5, and OVCAR8 were the most aggressive and OVCAR8 formed ascites.
• All six models formed peritoneal disease mimicking human cancer expressing p53, Pax8, and WT1.

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ABSTRACT
Objective. Genomic studies of ovarian cancer (OC) cell lines frequently used in research revealed that these cells do not fully represent high-grade serous ovarian cancer (HGSOC), the most common OC histologic type. However, OC lines that appear to genomically resemble HGSOC have not been extensively used and their growth characteristics in murine xenografts are essentially unknown.

Methods. To better understand growth patterns and characteristics of HGSOC cell lines in vivo, CAOV3, COV362, KURAMOCHI, NIH–OVCAR3, OVCAR4, OVCAR5, OVCAR8, OVASAO, OVKATE, SNU119 and UWB1.289 cells were assessed for tumor formation in nude mice. Cells were injected intraperitoneally (i.p.) or subcutaneously (s.c.) in female athymic nude mice and allowed to grow (maximum of 90 days) and tumor formation was analyzed. All tumors were sectioned and assessed using H&E staining and immunohistochemistry for p53, Pax8, and WT1 expression.

Results. Six lines (OVCAR3, OVCAR4, OVCAR5, OVCAR8, COV362 and OVASAO) formed i.p xenografts with HGSOC histology. OVKATE and COV362 formed s.c. tumors only. Rapid tumor formation was observed for OVCAR3, OVCAR5 and OVCAR8, but only OVCAR8 reliably formed ascites. Tumors derived from OVCAR3, OVCAR4, and OVCAR8 displayed papillary features. Of the 11 lines examined, three (Kuramochi, SNU119 and UWB1.289) were non-tumorigenic.

Conclusions. Our findings help further define which HGSOC cell models reliably generate tumors and/or ascites, critical information for preclinical drug development, validating in vitro findings, imaging and prevention studies by the OC research community.

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1. Introduction

Ovarian cancer (OC) is the fifth leading cause of cancer-related deaths among women in the US and the most lethal gynecologic malignancy [1]. The five-year survival rate has remained close to 25%, and all
women are currently treated with the same approach consisting of surgical debulking followed by chemotherapy composed of paclitaxel and carboplatin [2]. Diagnosis of OC usually occurs after metastasis at stages II–IV, and this contributes to the poor survival [3]. Targeted therapies and better strategies for early detection would increase survival, but adequate model systems to study the disease remain a major challenge facing the gynecologic oncology research field [4,5].

Ovarian cancer is a heterogeneous disease that includes at least five histotypes: clear cell, endometrioid, mucinous, low-grade serous, and high-grade serous tumors [6,7]. Heterogeneity may be a result of the cell of origin that gives rise to different forms of the disease and reflects distinct molecular alterations associated with each histotype [8–10]. High-grade serous ovarian cancer (HGSOC), the most common and deadly form of the disease, is considered the "prototype" of epithelial OC, and the recent Cancer Genome Atlas Network analysis defined the landscape of deregulated pathways characterizing HGSOC [11]. Specifically, these tumors are classified based upon mutation of p53, BRCA1/2 mutation, somatic loss, or methylation, and a variety of protein markers including PAX8 and WT1. In addition, copy number variation is a hallmark of HGSOC and less commonly found in endometrioid, clear cell, and mucinous histotypes [12]. Recent genetic signatures from primary human tumors further divided HGSOC into four molecular groups, namely immunoreactive, proliferative, differentiated, and mesenchymal [13]. While these categories are well established in primary and recurrent HGSOC tumors, the ability to correlate genomic and molecular features with useful laboratory model systems is critical for the future development of new therapies, prevention strategies, and imaging studies [14].

Recent publications have characterized an expanded panel of OC cell lines at the genomic level, in 2-dimensional-cell culture (on plastic), and in regard to their in vitro response to chemotherapeutic drugs [15–17]. These reports further suggested that OC cell lines commonly used in the past (e.g., SKOV3, A2780) do not represent a good approximation of the HGSOC genotype and that a panel of recently described cell lines more closely resemble human serous tumor. However, several of the newly proposed models for HGSOC have never been characterized for the ability to form tumors in immune deficient mice, which is critical to study mechanisms of disease or therapeutic interventions in vivo. The goal of this study was to determine the tumorigenic ability of newly described HGSOC cell lines and the histologic characteristics of the xenografts derived from these cells.

2. Materials and methods

2.1. Cell culture

All reagents were obtained from Life Technologies (Carlsbad, CA) unless otherwise indicated. OVCAR4 was obtained through Material Transfer Agreement (MTA) from the National Cancer Institute for the transfer of cell lines from the Division of Cancer Treatment and Diagnosis Tumor Repository. The DCTD Tumor Repository has maintained, since the early 1960s, a low temperature repository of transplantable tumor and tumor cell lines from various species. OVCAR4 were maintained in RPMI supplemented with 10% fetal bovine serum (FBS), 2 mM l-glutamine, and 100 U/ml penicillin/streptomycin. Kuramochi, OVS-40, and OVKATE were obtained through MTA from the Japanese Collection of Research Bioresources Cell Bank (JCRB). The JCRB cells were cultured in RPMI 1640 medium with 10% FBS and 50 U/mL penicillin and 50 μg/mL streptomycin. CAOV3 were grown in Dulbecco’s Modified Eagles Medium containing 10% FBS, 0.01 mg/ml insulin and 50 U/ml penicillin, and 50 μg/ml streptomycin. CAOV3 cells were grown in Dulbecco’s Modified Eagles Medium containing 10% FBS and 50 U/Ml penicillin, and 50 μg/ml streptomycin. OVCAR5 cells were obtained from the Developmental Therapeutics Program at National Cancer Institute and cultured in DMEM, 10% FBS, 1% PSG, and 0.1 mM MEM Non-essential amino acids. OVCAR8 cells were obtained from ATCC and cultured in DMEM with 10% FBS. COV362 were from Adam Karpf, Eppley Institute for Research in Cancer and Allied Diseases, University of Nebraska Medical Center and grown in DMEM with l-glutamine (300 mg/L) and 10% heat inactivated fetal bovine serum. SNU-119 were sourced from the Korean Cell Line Bank (also obtained from Dr. Karpf) and grown in RPMI1640 with l-glutamine (300 mg/L), 25 mM HEPES and 25 mM NaHCO3, 90%; heat inactivated fetal bovine serum (FBS), 10%. UWE1289 cells were cultured in media composed of: 1:1 RPMI-1640 and Mammary Epithelial Growth Medium (MEGM, Lonza #CC-3150) supplemented by 3% FBS. Information regarding mycoplasma testing, in vitro doubling times, and STR validation is in Supplemental Table 1.

2.2. Study approval

All animals were treated in accordance with the NIH guidelines for Laboratory Animals and established Institutional Animal Use and Care protocols at the University of Illinois at Chicago, Indiana University School of Medicine, Indiana University, Bloomington, and University of Notre Dame.

2.3. Xenografting

6–7 weeks old female athymic (nude) mice were acquired from (Harlan Teklad, Indianapolis, IN) and xenografted with human OC cells 1 × 106 cells subcutaneously (s.c.) and 5 × 106 cells intraperitoneally (i.p.) in sterile PBS. Animal body weight and s.c. tumor growth (via caliper measurement) were tracked weekly and animals sacrificed when tumor burden was evident or general health was determined to be moribund. If no tumor formation was evident, animals were sacrificed after 90 days of tumor implantation.

2.4. Tissue collection and analysis

At the time of sacrifice, s.c. and i.p. tumors were dissected and weighed, and evidence of i.p. disease was noted by photography and charted based on organ of dissemination. Tissues were fixed in 4% paraformaldehyde before dehydration in ethanol and xylene prior to parafﬁn embedding. Immunohistochemistry and hematoxylin and eosin (H&E) staining was performed as previously described [18]. Briefly, tissues were sectioned and rehydrated in a gradient of ethanol prior to antigen retrieval and peroxidase block. Sections were incubated in primary antibody overnight at 4 °C before detection via biotinylated secondary antibody (i:200, Vector Laboratories (Burlingame, CA) and ABC peroxidase (Vector Laboratories)). Targets were visualized via 3,3’-diaminobenzidine (DAB, Vector Laboratories) and counterstained with hematoxylin. The following antibodies were used in the study: p53 (Santa Cruz Biotechnology sc-6243 dilution 1:50), Pax8 (Proteintech 10336-1-AP dilution 1:150), and WT1 (Abcam ab89901 dilution 1:50).

3. Results

To assess which HGSOC cell lines recapitulate OC clinical features in vivo, xenograft assays and pathologic characterization of resulting tumors were performed. Kuramochi, OVS-40, SNU-119, COV362, and OVCAR4 were the top five most likely to be high-grade serous ovarian cancer according to the genomic data analysis published by Domcke et al. [17]. The same report identified CAOV3, OVCAR3, and OVCAR8 as possible representatives of high-grade serous cancer. Additionally, CAOV3, Kuramochi, OVCAR3, OVCAR4, OVCAR5, and OVCAR8 were identified as high grade serous by Anglesio et al. [15]. UWE1289 was chosen because it is BRCA-null [19]. Eleven OC cell lines were injected i.p. and/or s.c. into female nu/nu mice and tumor formation was assessed after observation (up to 90 days). Six of the cell lines (OVCAR3, OVCAR4, OVCAR5, OVCAR8, CAOV3, and OVS-40) formed lu xenografts (Fig. 1, Table 1) and were considered tumorigenic. OVKATE and COV362 only
formed s.c. tumors after 90 days and 77 days respectively with no evidence of tumor formation in the i.p. grafted mice. No tumor formation (either i.p. or s.c.) was observed for Kuramochi, UWB1.289, and SNU119 after 90 days of observation, and these three OC lines were considered to be non-tumorigenic. The data in Table 1 summarizes the average survival, number of tumors per mouse, and p53 mutational status for the cell lines evaluated [19–21].

As shown in Fig. 1, the OVCAR 3 cell line formed the largest (P < 0.05) s.c. tumors by mass (460–970 mg by 36 days). OVCAR3 formed the largest i.p. tumors (1004–1509 mg by 27 days). The most rapid s.c. tumor formation was observed for OVCAR5 (26 days), OVCAR8 (27 days) and OVCAR3 (36 days), but s.c. tumor formation for the other cell lines tested took longer than 2 months (see Suppl. Fig. S1 for s.c. growth rate for tumors derived from OVCAR4, OVKATE, and COV362 cells).

For i.p. injections, 100% tumor take was seen for OVCAR3, OVCAR4, OVCAR5, OVCAR8, and CAOV3 cell lines, but only 80% for OVSAHO cells. The macroscopic appearance and distribution of i.p. tumors formed is shown in Fig. 2.

The location of metastasis in the peritoneal space after i.p. injection was also examined. Disseminated tumorigenic cells were observed on peritoneal surfaces, the gastrointestinal tract, particularly the small bowel, and the omentum (Table 2), all typical sites of metastasis encountered in women with advanced stage HGSC [5]. OVCAR3 tumors were the most widely metastatic, but interestingly malignant ascites formation was not recorded and gross metastases to the diaphragm were uncommon, despite the high tumorigenic potential of this OC line. For the models that formed i.p. disease, tumors in the GI tract were observed for all six cell lines, with the liver and reproductive tissues representing the other most common tumor sites. Only OVCAR8 consistently formed ascites fluid when grafted i.p. (within 90 days).

The microscopic appearance of OVAR3, OVCAR4, OVCAR5, OVCAR8, CAOV3, and OVSAHO derived xenografts was consistent with HGSC histology (Fig. 3). OVKATE and COV362 were also consistent in HGSC histology, but as s.c. tumors only (neither line formed tumors i.p.). Strong nuclear staining for PAX8 and WT1, characteristic of HGSC, was observed in OVCAR3, OVCAR4, CAOV3, OVCAR8, OVSAHO and OVKATE xenografts. Patchy and fainter PAX8 and WT1 nuclear staining was seen in OVCAR5 tumors (Fig. 3 and Table 3). Strong nuclear p53 staining was observed in OVCAR3, OVCAR4, and OVKATE tumors, and faint p53 staining characterized OVSAHO, CAOV3, and OVKATE xenografts. Interestingly, OVCAR5 tumors were p53 negative (Fig. 3), and tumorigenesis was also the most rapid for this line (Table 1). The published p53 mutation present in each cellular model is reported in Table 1. COV362 s.c. tumors only stained positively for Pax8 and not for WT1 or p53.

4. Discussion

Validation and comprehensive characterization of genetically and phenotypically defined human cell models are essential for the success of biomedical research to treat and prevent ovarian carcinoma. The cellular models most commonly used in the literature, such as SKO3

<table>
<thead>
<tr>
<th>OVCAR3</th>
<th>OVCAR4</th>
<th>OVCAR5</th>
<th>OVCAR8</th>
<th>CAOV3</th>
<th>COV362</th>
<th>OVSAHO</th>
<th>OVKATE</th>
<th>Kuramochi</th>
<th>SNU119</th>
<th>UWBI.289BRCA null</th>
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<tbody>
<tr>
<td>Days until sacrifice (IP)</td>
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<td>90 days</td>
<td>26 days</td>
<td>44 days</td>
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<tr>
<td>Days until sacrifice (SC)</td>
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<td>90 days</td>
<td>26 days</td>
<td>27 days</td>
<td>100 days</td>
<td>77 days</td>
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<td>11.2</td>
<td>161.4</td>
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<td>1.4</td>
<td>0/5</td>
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<td>7-13</td>
<td>0-409</td>
<td>148-248</td>
<td>2-21</td>
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<td>0-3</td>
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<td>Tumor weight (g)</td>
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<td>1/4</td>
<td>1/3</td>
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<tr>
<td>TP53 status</td>
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<td>130*</td>
<td>224*</td>
<td>126*</td>
<td>136*</td>
<td>220*</td>
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<td>282*</td>
<td>281*</td>
<td>151*</td>
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<tr>
<td>(Base/mutation)</td>
<td>C→T</td>
<td>G→C</td>
<td>Insertion/null</td>
<td>In frame deletion</td>
<td>G→A</td>
<td>T→C</td>
<td>G→A</td>
<td>G→A</td>
<td>C→A</td>
<td>G→C</td>
</tr>
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<td>N/A</td>
<td>N/A</td>
<td>1336-splice</td>
<td>871-frame shift</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>DelAG19</td>
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<td>–</td>
<td>121*</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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</tr>
<tr>
<td>CCNE1</td>
<td>Ampli 17</td>
<td>–</td>
<td>–</td>
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and A2780, have been questioned as being valid models of the most deadly and common OC histotype, high grade serous carcinoma [15, 17]. While a few very recent publications have provided invaluable characterization of the mutational and growth characteristics of more representative cellular models of HGSOC, most of these have not been studied in terms of their growth as a xenograft [15–17], and equally importantly the tumorigenic ability of these lines as xenografts in nude mice is unknown and thus their true potential for studying human HGSOC is uncertain.

The current study is the first to compile and directly compare the in vivo xenograft characteristics of several HGSOC cellular models. Intriguingly, of the top five models suggested for use based on genomic sequencing, including Kuramochi, OVSAHO, SNU119, COV362, and OVCAR4, only two formed intraperitoneal tumors in athymic nude mice within 90 days. Furthermore, we show that of the cell models that in vivo most resemble the papillary characteristic of high-grade serous cancer (OVCAR3, OVCAR4, and OVKATE), only OVKATE formed s.c. xenograft tumors within 90 days, although it is possible that xenografting a higher number of cells for a longer period might result in i.p. disease. Of the 11 cell models examined in this study, only OVCAR8 reliably demonstrated ascites formation within 90 days, and SNU119, Kuramochi, and UWB1.298 all failed to form tumors. Overall, we demonstrate the utility of several cellular models for in vivo xenografting and illustrate their unique peritoneal dissemination pattern.

In vivo growth characteristics of HGSOC cell models may help dictate their application. For example, OVCAR3, OVCAR5, and OVCAR8, the most aggressive lines based on their rapid growth in vivo, may be useful to reduce the length and cost of xenograft studies. However, because OVCAR5 and OVCAR8 i.p. tumor growth is widely disseminated, it may be a challenge to quantitate initial tumor burden as well as changes in tumor growth in response to therapy. Take rates were remarkably consistent between the cell models that produced tumors, suggesting that if grafted, these models are reliable. OVSAHO and OVKATE were both very slow growing in vivo and in vitro, and it seems reasonable to suggest that they would both form i.p. disease with more cells or more time. OVCAR3 and OVCAR8 formed the largest tumor masses and these lines may be extremely useful in conjunction with in vivo optical imaging technologies or drug accumulation and biodistribution studies with nanocarriers. For the cells that formed tumors, there was a remarkable divergence in organs colonized, although the organs were similar to those seen in human disease. All cell models colonized the GI tract and liver and the second most common site of tumor formation was the reproductive tract, suggesting that these models may be appropriate to study interactions between tumor cells and the microenvironment, in general as well as at specific sites in vivo.

In this initial analysis, there was no apparent correlation between the mutational spectrum of the cell lines and in vivo growth characteristics. All of the models in this study have p53 mutations except for OVCAR5, which is p53 null. Otherwise the mutational spectrum for these lines is dramatically different, and each could therefore be a model for a specific target, such as BRCA1 (for COV362 as a s.c. model), c-myc (COV362 as a s.c. model), cyclin E (OVCAR3), mutation in ERBB2 (OVCAR8) or loss of Rb (OVSAHO) [17]. Interestingly, previous reports based on in vitro immunocytochemistry studies performed on the cell lines found CAOV3 and OVCAR4 to be negative for p53 and WT1. In contrast, our in vivo study found that these markers are expressed in tumors from both of these cell lines [16]. OVCAR5 and OVCAR3 were identical at the cellular and tumor level for p53 and WT1 expression. OVCAR8 expressed WT1...

**Table 2** Sites of HGSOC peritoneal colonization.

<table>
<thead>
<tr>
<th>Line</th>
<th>Reproductive tract</th>
<th>G.I. tract</th>
<th>Omentum</th>
<th>Peritoneal wall</th>
<th>Diaphragm</th>
<th>Pancreas</th>
<th>Kidney</th>
<th>Liver</th>
<th>Injection site</th>
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<tbody>
<tr>
<td>OVCAR3</td>
<td>1/6</td>
<td>2/5</td>
<td>2/5</td>
<td>5/5</td>
<td>2/6</td>
<td>0/5</td>
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<td>2/6</td>
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<tr>
<td>OVCAR4</td>
<td>4/6</td>
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<td>3/6</td>
<td>3/5</td>
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<td>6/6</td>
<td>0/5</td>
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<td>3/6</td>
<td>0/5</td>
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<tr>
<td>OVSAHO</td>
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Fig. 3. Human ovarian cancer cell models form high-grade serous tumors based on histology and protein expression. Cell models that formed intraperitoneal tumors are shown except for OVKATE and COV362, which only grew subcutaneous tumors. Histology and immunohistochemical staining of PAX8, WT1, and p53 are shown for human cell models. Scale bars equal 50 μm.
mostly in the nucleolar compartment, which has previously been described in mucinous tumors [22]. Only three of the models tested here were screened for chemotherapy sensitivity in vitro [16]. All three models appeared to be relatively sensitive to chemotherapy and also had almost exactly the same doubling time in vitro, between 51–56 h [16], yet in vivo OVCA3 was much more aggressive (Fig. 1). In summary, the development of more reliable and authenticated models of HGSOc has been dramatically improved by recent reports characterizing their genomes, behavior in vitro, and sensitivity to drugs. This report adds to the growing information and helps to define which HGSOc models reliably generate tumors and/or ascites, essential information for their use in drug discovery, imaging, and prevention studies.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2015.05.040.

Transparency Document

The Transparency document associated with this article can be found in the online version.

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References