A comprehensively characterized cell line panel highly representative of clinical ovarian high-grade serous carcinomas

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Keywords: high-grade serous ovarian carcinoma, cell models, patient-derived xenograft, exome-sequencing, genomic characterization
Received: November 14, 2015 Accepted: May 22, 2016 Published: June 10, 2016
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ABSTRACT

Recent literature suggests that most widely used ovarian cancer (OVCA) cell models do not recapitulate the molecular features of clinical tumors. To address this limitation, we generated 18 cell lines and 3 corresponding patient-derived xenografts predominantly from high-grade serous carcinoma (HGSOC) peritoneal effusions. Comprehensive genomic characterization and comparison of each model to its parental tumor demonstrated a high degree of molecular similarity. Our characterization included whole exome-sequencing and copy number profiling for cell lines, xenografts, and matched non-malignant tissues, and DNA methylation, gene expression, and spectral karyotyping for a subset of specimens. Compared to the Cancer Genome Atlas (TCGA), our models more closely resembled HGSOC than any other tumor type, justifying their validity as OVCA models. Our meticulously characterized models provide a crucial resource for the OVCA research community that will advance translational findings and ultimately lead to clinical applications.
INTRODUCTION

Ovarian cancer (OVCA) ranks as the fifth deadliest cancer affecting women in the United States [1]. The dismal prognosis is attributable to a lack of early detection methods, effective treatment strategies, and the current inability to overcome acquired drug resistance [2]. High-grade serous ovarian carcinoma (HGSOC) is the most common and aggressive OVCA subtype [3]. Although comprehensive genomic characterization of HGSOC tumors has provided a catalogue of somatic alterations, their biological relevance and therapeutic potential remain to be thoroughly investigated [4]. An understanding of how these and prospectively discovered genetic alterations contribute to ovarian tumorigenesis is imperative for the development of new therapies targeting tumor biology [2].

To evaluate the biological significance of molecular alterations in OVCA tumorigenesis, clinically and genetically characterized cell models that recapitulate clinical OVCA are required [5, 6]. Without representative cell models, in vitro derived findings have limited potential to translate to in vivo systems in the early stages of preclinical OVCA research [6–8]. Recently, Domcke et al. compared genomic profiles of clinical HGSOC tumors with commonly used HGSOC cell lines and revealed striking dissimilarity [8]. Only 12 infrequently used cell lines were classified as suitable HGSOC models [8], which is a relatively small number compared to other cancer types [9–11]. Moreover, this number is too small to capture the broad spectrum of heterogeneity observed in HGSOC [4, 5, 7, 12, 13]. This study and other recent reports have raised awareness that additional comprehensively characterized, readily available, and representative HGSOC models are needed to facilitate translational OVCA research [6, 8, 14–17].

To address this need, we sought to generate a new panel of genomically characterized OVCA cell lines that accurately model clinical tumors. Unlike another recent group [18], we focused on generating HGSOC cell lines from malignant ascites, a common form and presentation of OVCA [19, 20], using standard media and growth conditions. We created 18 cell lines and 3 patient derived xenografts that display a high concordance in copy number, methylation, gene expression, and mutational profiles with the tumors they were derived from. These models are also highly similar to HGSOC tumors from the Cancer Genome Atlas (TCGA) cohort. Most importantly, we offer these comprehensively characterized, early passage cell lines and xenografts to the research community in hopes of providing a new resource to facilitate advances in OVCA research that will ultimately lead to improved patient outcomes.

RESULTS

Establishment of comprehensively characterized OVCA cell lines

We generated and characterized 18 cell lines, 15 patient-matched lymphoblastoid lines, and 3 patient-derived xenografts from 18 treatment naïve OVCA tumor ascites, providing a new panel of suitable models for preclinical research. We achieved a success rate of 41% (18/44 malignant ascites were established as cell lines) with standard media and culture conditions. Of these 18 lines, 6 (33%) were capable of growth as tumor xenografts in mice: HCC5006, HCC5012, HCC5023, HCC5044, HCC5048, and HCC5076 (HCC5012X, HCC5023X, and HCC5048X were genomically characterized, Table 1). Our method enabled us to obtain, enrich and cryopreserve large numbers of original tumor cells for comparison with the corresponding cell lines. Clinical information and culture characteristics for each model are summarized in Table 1 and Supplementary Table 1. Figure 1 illustrates a malignant effusion sample after hemolysis, ascites tumor enrichment, and representative cell lines generated. For each line we have determined a short tandem repeat (STR) profile to enable cell line identification (Supplementary Table 2). Expression levels of EPCAM and the characteristic OVCA markers MUC16, WT1, and PAX8 were high in tumors, cell lines and xenografts, demonstrating that our models maintain an epithelial phenotype and typical OVCA marker expression (Supplementary Figure 1) [21–24]. Furthermore, serum CA125 was detected at high levels in all patients except for HCC5030, and mRNA levels of its gene (MUC16) in corresponding models were also high, suggesting plasma CA125 in xenograft bearing mice could be used as an indicator of therapeutic efficacy [23, 24] (Supplementary Table 3). We proceeded with comprehensive genomic characterization to 1) assess how well cell lines represent corresponding parental tumors, 2) assess similarity to HGSOC tumors in The Cancer Genome Atlas (TCGA) [4], and 3) enable researchers to select lines with the most appropriate genetic backgrounds. All but one line (HCC5075) exhibited a strong resemblance to clinical HGSOC (Table 1, Figure 1).

Cell lines and xenografts maintain the genomic landscape of patient-matched tumors

To determine whether the cell lines and xenografts we established were representative of the tumors they were derived from, we assessed concordance in their genomic profiles. We generated mutation and copy number profiles for every specimen except for two tumors and one lymphoblast line with insufficient material for exome-sequencing, as these data provide the most unique individual signatures (Supplementary Tables 4–6). Clustering and correlation analyses of single nucleotide mutations in the cell lines and xenografts were performed using the Cancer Genome Landscape (CGA) algorithm [23, 24]. We observed high correlation of mutation and copy number profiles with tumors from the Cancer Genome Atlas (TCGA) cohort. Most importantly, we offer these comprehensively characterized, early passage cell lines and xenografts to the research community in hopes of providing a new resource to facilitate advances in OVCA research that will ultimately lead to improved patient outcomes.
Table 1: Summary of the 51 UTSW specimens

| Sample      | Age | Stage | Histology          | Ethnicity         | Key Mutations*             | SKY | SNP | Methylation | Expression | Exome-sequencing |
|-------------|-----|-------|---------------------|-------------------|----------------------------|-----|-----|-------------|------------|------------------|
| HCC5006CL   | 55  | IV    | HGSOC               | Caucasian         | TP53                       |     |     |             |            |                  |
| HCC5006T    |     |       |                     |                   |                            |     |     |             |            |                  |
| HCC5011CL   | 52  | IIIC  | HGSOC arising from LGSOC | Caucasian     | TP53, BRCA1, MECOM         |     |     |             |            |                  |
| HCC5011T    |     |       |                     |                   |                            |     |     |             |            |                  |
| HCC5012CL   | 58  | IIIC  | HGSOC               | African American  | TP53                       |     |     |             |            |                  |
| HCC5012T    |     |       |                     |                   |                            |     |     |             |            |                  |
| HCC5012X (TX-OV-143X) | |       |                     |                   |                            |     |     |             |            |                  |
| HCC5018CL   | 57  | IIIC  | HGSOC               | Caucasian         | None                       |     |     |             |            |                  |
| HCC5018T    |     |       |                     |                   | Not Sequenced              |     |     |             |            |                  |
| HCC5019CL   | 59  | IV    | HGSOC               | African American  | TP53, CSMD3                |     |     |             |            |                  |
| HCC5019T    |     |       |                     |                   |                            |     |     |             |            |                  |
| HCC5020CL   | 43  | IV    | HGSOC               | African American  | TP53, NF1                  |     |     |             |            |                  |
| HCC5022CL   | 45  | IIIC  | HGSOC               | Hispanic          | TP53                       |     |     |             |            |                  |
| HCC5022T    |     |       |                     |                   |                            |     |     |             |            |                  |
| HCC5023CL   | 46  | IV    | HGSOC               | Asian             | TP53, RB1                  |     |     |             |            |                  |
| HCC5023T    |     |       |                     |                   |                            |     |     |             |            |                  |
| HCC5023X (TX-OV-075X) | |       |                     |                   |                            |     |     |             |            |                  |
| HCC5024CL   | 60  | IIIC  | HGSOC               | African American  | TP53                       |     |     |             |            |                  |
| HCC5024T    |     |       |                     |                   |                            |     |     |             |            |                  |
| HCC5030CL   | 74  | IV    | LGSOC (cytology only)* | African American | TP53                       |     |     |             |            |                  |
| HCC5030T    |     |       |                     |                   | Not Sequenced              |     |     |             |            |                  |
| *HCC5032CL  | 44  | IIIC  | *HGSC of Mullerian origin | Hispanic | TP53                       |     |     |             |            |                  |
| *HCC5032T   |     |       |                     |                   |                            |     |     |             |            |                  |
| HCC5036CL   | 47  | IIIC  | HGSOC               | Hispanic          | TP53                       |     |     |             |            |                  |
| HCC5036T    |     |       |                     |                   |                            |     |     |             |            |                  |
| HCC5044CL   | 63  | IVB   | HGSOC               | Asian             | TP53, PIK3CA               |     |     |             |            |                  |

(Continued)
variant (SNV) data confirmed that cell lines and xenografts more closely resembled patient-matched tumors than unrelated samples (Supplementary Figures 2, 3A-B, two-tailed student’s t-test, p<0.0001). The percentage of SNVs detected in tumors that were also detected in matched cell lines/xenografts ranged from 87-97%, indicating the high proportion of tumor variants retained in the cell lines/xenografts generated (Supplementary Figure 4A).

Chromosomal instability and copy number alterations (CNAs) are hallmark features of HGSOC [14, 25], and besides mutational profiles, copy number profiles were anticipated to provide the most unique signature for each tumor case. Genome-wide CNA profiles revealed 11/15 tumor-cell line pairs showed very strong concordance, with correlation coefficients, $\rho >0.6$ (Pearson test, p<0.0001, Figure 2B, Supplementary Figures 3C, 4B and 4C). The 3 tumor xenografts (HCC5012, HCC5023, and HCC5048) we profiled also showed good concordance with their corresponding tumors (Pearson correlation, $\rho >0.5$, Figure 2B, Supplementary Figures 3-4). Of the tumor-cell line pairs with lower correlation coefficients, 4 had few copy number and loss of heterozygosity (LOH) alterations detected in the tumors; this likely indicates low tumor relative to non-malignant cell content (HCC5018, HCC5022, HCC5030, and HCC5032) (Figure 2B, Supplementary Figure 4B-4D, Supplementary Table 7). We excluded these tumors from further tumor-cell line comparisons for this reason. Cell line and xenograft copy number profiles were also more correlated between patient-matched tumors than unmatched samples, as were DNA methylation and gene expression profiles generated for a subset of cases (Supplementary Figure 3C-3E; two-tailed student’s t-test, p<0.0001). Spectral karyotyping of 9 cases also revealed similarity in complex chromosomal rearrangements and tumor cell ploidy (Supplementary Figure 5, Supplementary Table 8). Collectively, our multi-dimensional genome-wide profiling supports the conclusion that the cell lines and xenografts we generated are highly representative of the tumors they were derived from. The high genomic instability, low mutational burden, specific mutations and expression of typical OVCA

| Sample     | Age | Stage | Histology | Ethnicity | Key Mutations* | SKY | SNP | Methylation | Expression | Exome-seq. |
|------------|-----|-------|-----------|-----------|----------------|-----|-----|-------------|------------|------------|
| HCC5048CL  |     |       |           |           | TP53           |     |     |             |            |            |
| HCC5048T   |     |       |           |           | TP53           |     |     |             |            |            |
| HCC5048X   | 43  | IIIB  | HGSOC     | Caucasian | TP53, CSMD3, CDK12, MECOM, ARID1A |     |     |             |            |            |
| (TX-OV-132X)|    |       |           |           |                |     |     |             |            |            |
| HCC5050CL  |     |       | HGSOC     | Hispanic  | TP53, PIK3CA, ARID1A |     |     |             |            |            |
| HCC5050T   | 46  | IIIC  | HGSOC     | Hispanic  | TP53, PIK3CA, ARID1A |     |     |             |            |            |
| HCC5075CL  | 45  | IIIC  | LGSOC     | Hispanic  | NF1, KRAS      |     |     |             |            |            |
| HCC5075T   |     |       |           |           | NF1, KRAS      |     |     |             |            |            |
| HCC5076CL  | 41  | IV    | HGSOC     | Hispanic  | TP53           |     |     |             |            |            |
| HCC5076T   |     |       |           |           | TP53           |     |     |             |            |            |
| HCC5079CL  | 61  | IIIC  | HGSOC     | Hispanic  | TP53           |     |     |             |            |            |
| HCC5079T   |     |       |           |           | TP53           |     |     |             |            |            |

*Total: 21 36 22 20 34

A source of non-malignant cells was sequenced in all cases except HCC5048 to provide a reference for defining somatic mutations

Low confidence tumor histology due to LGSOC classification based on cytology only, however the molecular profile is consistent with HGSOC

Subsequent clinical pathology reassigned this case as endometrial cancer, although the molecular profile is consistent with HGSOC

For xenografts (X), the additional sample name (TX-OV-XXXX) indicates the identifier for these samples in the work of Reynolds et al., unpublished.
Figure 1: Representative histologies and cell lines generated from OVCA malignant effusions. A. Histological appearances of tumors. High-grade serous ovarian carcinoma HCC5012 tumor (upper left) and corresponding xenograft (upper right). The appearance of the xenograft is identical to the original tumor. Low-grade serous ovarian carcinoma HCC5075 (lower left). HCC5011 (right lower), high-grade serous ovarian carcinoma (right part of figure) arising from a low-grade serous ovarian carcinoma (left part of figure). This is a rare but well documented occurrence [41]. B. Tumor enrichment and established cell lines. Cell lines were generated from tumor cell-containing ascites obtained from malignant effusions. Images of cell preparations at various stages of cell line generation are shown.
markers observed in our cell lines were highly consistent with HGSOC, with the exception of one case [14, 21–25]. HCC5075 had pathological and molecular features consistent with a low-grade serous ovarian cancer (Table 1) [14, 25]. Additionally, one case (HCC5032) was confirmed to be of endometrial origin upon detailed histopathological review after manuscript submission (Table 1).

Established cell lines and xenografts faithfully model HGSOC tumors

We next investigated how well our models represented the TCGA’s HGSOC cohort. Mutational counts and the fraction of genome altered by CNAs (FGA) in cell lines, xenografts, and tumors were comparable to those of TCGA tumors (Figure 3A–3B, two-tailed student’s t-test, p>0.05). Our cell lines and tumors had lower mutational loads (i.e. mutations/megabase) than TCGA tumors (Figure 3C, Student’s t-test, p = 0.004 and p=0.003, respectively) although the range observed in TCGA tumors was large. Despite OVCA tumors having few recurrent mutations besides TP53 [4], we observed HGSOC-characteristic mutations among the cell lines and xenografts we derived (Table 1, Supplementary Tables 4-5). TP53 mutations were identified in 16/18 cases, and BRCA1, BRCA2, CSMD3, CDK12, NF1, RB1, and MECOM mutations were also detected among the models, illustrating the spectrum of genetic heterogeneity we captured. Furthermore, we observed significant positive correlations between our cell lines and xenografts with the mean copy number (ρ range: 0.12-0.62), methylation (ρ range: 0.39-0.70), and gene expression profiles (ρ range: 0.43-0.61) of TCGA OVCA tumors (Pearson test, p<0.0001, Supplementary Figure 6). Notably, the magnitudes of the positive correlation coefficients we observed across the various cell lines/xenografts and data dimensions were similar to those observed for the CCLE lines classified as good models of HGSOC by Domcke et al. [8]. We also observed an impressive concordance in global CNA patterns between our models and the TCGA tumors (Figure 3D, Supplementary Figure 7). GISTIC-based analysis of high magnitude CNAs [26] identified

Figure 2: UTSW cell line and xenograft models recapitulate the genomic features of their parental tumors. Copy number alteration profiles were unique for each OVCA case, and highly similar between samples derived from the same patient (e.g. tumor, cell line, and xenograft). A. Examples of the high level of concordance in copy number alterations detected in primary tumors and their associated models for the HCC5012 and HCC5023 cases. Each dot represents 30 smoothed SNP array probes. Genomic coordinates are plotted on the horizontal axis versus the number of copies for each smoothed data point on the vertical axis. B. CNA profiles are plotted against genomic coordinates (horizontal axis) for each UTSW OVCA case. Correlation coefficients representing the similarity between cell lines and the tumors they were derived from are indicated.
alterations typical of clinical OVCA tumors, including MYC/AKT1 amplifications and CDKN2A/PTEN deletions (Supplementary Figure 8, Supplementary Tables 9-10) [4]. Our models exhibit low mutation loads and high levels of genomic instability which indicates that their genomic landscapes are typical of HGSOC tumors [8, 14, 27, 28]. Furthermore, we characterized the response of 8 cell lines to standard chemotherapeutics used to treat OVCA, cisplatin and paclitaxel. Adherent cell lines were assessed because they generate reproducible results in dose-response assays. The range in cell line sensitivities was consistent with those reported in the Supplementary Material of Ince et al. [18] (Supplementary Table 11). There was no correlation observed between in vitro cell line response to cisplatin or paclitaxel and clinical patient response (data not shown). However, this is not surprising given that cell lines are excellent vehicles for predicting response to relevant targeted therapies, but less predictive for response to non-targeted chemotherapeutic agents, as has been described before [5].

**UTSW ovarian cell lines are more similar to OVCA than several other TCGA tumor types**

Given the known issues of cross-contamination and poor histological annotation of cell lines from different...
tissue origins [5, 6, 16, 29], we next aimed to determine whether the lines we created were more strongly correlated to OVCA tumors than to other TCGA tumor types. We again investigated the correlations between gene copy number, methylation and expression profiles of our cell lines with the mean profiles of various TCGA tumor types. We also compared the mutation counts observed in our cell lines to other TCGA tumor types by considering somatic mutations predicted to have a functional impact. These analyses demonstrated that our cell lines most closely resemble OVCA compared to several other epithelial tumor types in each genomic dimension we assessed (Figure 4).

**DISCUSSION**

Cancer cell lines and patient-derived xenografts are invaluable tools for studying tumor biology and are widely used to test new anticancer drugs in a preclinical setting [5, 9, 10, 17, 29-31]. However, it is now appreciated that for cell lines and xenografts to be clinically relevant and reliable cancer models, they must be well characterized and recapitulate the genomic landscapes typical of clinical tumors [5-8, 29, 30]. A number of reports have articulated the need for new OVCA models to improve translational research, raising numerous concerns with currently available models including: misidentification.

![Figure 4: Pan-cancer genomic comparisons of UTSW OVCA cell lines and TCGA tumor types.](image-url)

The figure shows correlation analyses to assess the similarity between UTSW cell lines and the mean genomic profiles of various TCGA tumor types. The 2000 most variably methylated or expressed genes were assessed. For copy number, methylation, and expression plots, the horizontal dotted line indicates the average correlation coefficient observed between the TCGA OVCA tumors and UTSW cell line comparison. For mutation data, functional, somatic mutation frequencies were compared. The TCGA tumor types are indicated as follows: OVCA, bladder urothelial carcinoma (BLCA), breast invasive carcinoma (BRCA), colon adenocarcinoma (COAD), head and neck squamous cell carcinoma (HNSC), kidney renal clear cell carcinoma (KIRC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), prostate adenocarcinoma (PRAD), stomach adenocarcinoma (STAD), thyroid carcinoma (THCA), and uterine corpus endometrial carcinoma (UCEC).
and/or contamination, lack of resemblance to clinical tumors, lack of molecular characterization, and lack of availability of the most suitable models [6-8, 15-18, 32, 33]. A revealing study by Domcke et al. found that only 12 of 47 OVCA cell lines are suitable HGSOC models, and that they are used in only 1% of studies reporting on HGSOC [8]. In their report, the authors proposed that newly generated, well-characterized HGSOC cell lines from treatment naïve patients could greatly benefit the OVCA research community by improving the value of preclinical discoveries [8].

To address this need, we generated a new panel of comprehensively characterized models which are highly representative of clinical HGSOC tumors with the exception of one case (HCC5075 was TP53 wild-type, KRAS mutant, and had low genomic instability which are features are consistent with low-grade serous ovarian carcinoma [14, 25, 27, 34, 35]). Further histopathological characterization after manuscript submission also revealed that one case (HCC5032) was an endometrial tumor, although its genomic landscape was strongly correlated to those of HGSOC. We have provided multi-faceted genomic evidence to demonstrate that the models we have generated genuinely resemble their parental primary tumors and clinical HGSOCs. Improving on a recently described panel of OVCA cell lines and xenografts [18], the models we have generated: i) include corresponding non-malignant lymphoblastoid cell lines (as sources of constitutional DNA), ii) can be cultured with simple media and growth conditions that are economical and highly amenable for high-throughput drug screening, and iii) include additional dimensions of genomic characterization (namely, whole-exome sequencing, genome-wide DNA methylation, and SKY profiling). Importantly, we have cryopreserved numerous vials of each cell line at low passages and we have deposited the genomic data to share with the research community (GEO Accession ID: GSE71525, SRA BioProject ID: PRJNA291290). The patient-derived xenografts we have generated will also be available for use as in vivo models of HGSOC. Finally, we have also cryopreserved multiple vials of the original tumor cell pellets to enable experiments using the primary tumor cells in addition to the corresponding cell lines or xenografts.

Our study sets an unprecedented standard for generating comprehensively characterized cancer cell lines to meet current research needs. In the era of precision medicine [36], it is essential to select representative experimental models that recapitulate the molecular features of the tumors being studied. Our preclinical models will be useful not only for studying HGSOC tumor biology, but also for assessing the efficacy of anticancer agents because of the ease with which they can be cultured and their known mutational profiles. Our new HGSOC panel is a much-needed invaluable tool that will enhance the translation potential of in vitro findings [15, 29], ultimately leading to improved therapies and outcomes for OVCA patients.

**MATERIALS AND METHODS**

Detailed methods describing OVCA model establishment and genomic profiling and analyses can be found in the Supplementary Material. Cell lines and patient-derived xenografts were generated from malignant peritoneal effusions of 18 treatment naïve OVCA patients with informed patient consent at the University of Texas Southwestern (UTSW). Subsequent pathological review revealed that one tumour (HCC5032) was of endometrial origin after manuscript submission (Table 1). Patient matched lymphoblastoid lines for 15 cases were generated from peripheral blood mononuclear cells, cultured ascites fluids, or mesothelial cells from malignant effusions. Cell line sensitivities to cisplatin and paclitaxel were determined using CellTiter 96® Aqueous One Solution Cell Proliferation Assays (Promega) performed according to the manufacturer’s instructions.

Genomic profiling including genome-wide copy number (Affymetrix SNP 6 arrays), gene expression (Illumina HT-12v4 BeadChips), DNA methylation (Illumina HM450K arrays) and exome-sequencing (SureSelect Target Enrichment System for Illumina Paired-End Sequencing) was conducted on genomic DNA or RNA extracted from tumors, cell lines, xenografts, or constitutional DNA from lymphoblastoid lines. All genomic data are available at the Gene Expression Omnibus (GSE71525) and Sequence Read Archive (PRJNA291290). Spectral karyotyping (SKY) was performed on a subset of samples as previously described [37]. Genomic data for the TCGA OVCA cohort was obtained from the TCGA Data Portal, the TCGA OVCA publication page (https://tcga-data.nci.nih.gov/docs/publications/ov_2011/) [4], cBioPortal [38, 39], and pancancer TCGA data from the Cancer Genomics Browser (CGB) [40]. Detailed materials and methods, including statistical analyses are provided in the accompanying Supplementary Material.

**ACKNOWLEDGMENTS**

The authors would like to thank Luc Girard and Emily Vucic for their assistance, and The Cancer Genome Atlas consortium for access to their datasets.

**CONFLICTS OF INTEREST**

The authors have no conflicts to disclose.

**GRANT SUPPORT**

This work was supported by grants from the Cancer Prevention Research Institute of Texas (RP10763-P1), Canadian Institutes of Health Research (CIHR, FRN 123273, FRN 110949), the Clinical and Translational Science Awards, National Institutes of Health (UL1TR001105,
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