Oncology

Pathways to Genome-targeted Therapies in Serous Ovarian Cancer

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Genome sequencing technologies and corresponding oncology publications have generated enormous publicly available datasets for many cancer types. While this has enabled new treatments, and in some limited cases lifetime management of the disease, the treatment options for serous ovarian cancer remain dismal. This review summarizes recent advances in our understanding of ovarian cancer, with a focus on heterogeneity, functional genomics, and actionable data.

ovarian cancer | genomics | pathway analysis | targeted therapy | heterogeneity

Gene- or mutation-targeted therapies have provided some of the most striking results in recent oncology trials. However, the clinical application of these therapies relies on an excellent understanding of molecular targets of critical importance in the biology of a targeted cancer. While major strides have been made in some cancers, few such targeted therapies are approved for use in Serous Ovarian Cancer (SOC).

SOC remains the most deadly form of ovarian cancer, with over 14,000 deaths per year from 22,000 diagnoses in the United States alone (Surveillance, Epidemiology, and End Results (SEER) Program, and [1]). The median age of diagnosis for SOC occurs in the seventh decade of life, which is about a decade later than other forms of cancer. Only about 10% of cases are germline or somatically mutated in *BRCA1* or *BRCA2*. The cancer is unfortunately commonly diagnosed in stage III or IV, once it has metastasized throughout the peritoneum and often after the disease has brought physical discomfort to the patient. Initial treatment consists of surgical resection of both ovaries, diligent removal of all macroscopic tumors within the peritoneum, and intraperitoneal chemotherapy consisting of a combination of carboplatin with a taxane such as docetaxel. While ~80% of patients will respond strongly to this treatment in the first six months, a majority of these responders will recur within two years. Second line therapy consists of further chemotherapy, often with peggylated liposomal doxorubicin. These therapies may delay progression and patients can go through five or six rounds of second line treatments before therapy is discontinued due to inefficacy.

Given the strong lethality of this disease, additional treatments are continuously sought. In the last decade SOC has attracted the focus of genomics studies seeking to understand this form of cancer in the hopes of finding its vulnerabilities. Tremendous progress has been made, but clinical progress has been limited due to a lag in understanding the wealth of new genomics data. We outline in this review how our interpretation of ovarian cancer treatment is changing with this new knowledge.

Progression of whole-ome datasets for ovarian cancer

For almost 30 years, it has been known that p53 mutations drive SOC [2]. However, very few other drivers were identified before whole-genome sequencing. Early studies found *MYC*

overexpression to be common in ovarian cancer [3]. Additionally, *BRCA1* or *BRCA2* mutations were identified largely as a result of known family trees prone to breast and ovarian cancers [4-6], however the percentage of patients fitting this criterion was below 10%. By itself, p53 mutation is insufficient to drive tumorigenesis. In normal human skin, p53 mutations accumulate in cellular micro-niches, up to 3-5% of the population of skin cells [7]. These mutations coexist with other oncogenic mutations, such as NOTCH pathway alterations [8]. Furthermore, 75% of people with Li-Fraumeni syndrome are born with germline p53 mutation, yet they develop fully into adulthood [9, 10]. Unfortunately, they are strongly pre-disposed to cancer, as are mouse models with germline p53 mutations [11]. To enable the multiple hallmarks of cancer and evolve beyond local expansion, many mutational drivers must exist in the same cell along with microenvironment vulnerabilities. The coincident driver alterations of SOC continue to remain a mystery.

In 2011, The Cancer Genome Atlas (TCGA) project released its first multi-ome dataset on SOC [12]. It was a truly monumental task: over 600 samples were processed to generate varying data types. Of those 600: 316 samples were exome sequenced for genomic DNA, 489 samples were processed by SNP arrays to generate CNA data across the whole genome, 489 samples were processed for methylation signatures and microarray RNA data, and 357 were processed for specific proteins and phosphoproteins by reverse phase protein array. Since then, further samples have been added to the publicly accessible database. Unfortunately, these data did not shed much new light on potentially targetable drivers within SOC; most drivers remained in <10% of patients. In our analyses, as many as 48% of SOC patients have zero non-*TP53* driver mutations [13]. Yet, tumors form, so driver alterations must exist.

The TCGA samples were universally primary, untreated tumors. Another more recent study sought to understand how genetics change upon administration of chemotherapy to help identify drivers of chemo-resistance in treated tumors. The authors also improved on the study of copy number alterations (CNAs) and other structural variants through whole-genome sequencing, a method much more sensitive than the SNP6 arrays used in the TCGA study. Their results followed similar trends; while *NF1* and *RB1* rearrangements were detected at higher frequencies (20% and 18% of tumors, respectively) than mutations (6% of tumors), the authors summarize their main conclusion regarding mutations, "We did not detect recurrent point mutations that are currently actionable in relapse samples, suggesting that, at best, only low frequency events are likely to be uncovered using personalized genomic evaluation of patients with recurrent [high-grade serous ovarian cancer]." The other unfortunate fact is like p53, targeting tumors defective in Rb and

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Nf1 has remained elusive since their discovery as tumor suppressors [14, 15]. This is in part because these genes are tumor suppressors; drugs which are clinically effective are designed to inhibit the effects of their protein targets, making this strategy illogical for tumor suppressor proteins.

However, defects in tumor suppressors alter the biology of the cell. Thus, effective strategies for targeting tumor suppressor defects involve the targeting of affected biological pathways [16]. The concept of synthetic lethality suggests some of the best drugs are efficacious since tumor cells are exquisitely reliant on a single protein or pathway, due to a mutation or pathway defect somewhere else in its genome. In practice, PARP inhibitors are showing some of the most exciting targeted-drug effects in SOC, with 2-3 months extension of overall survival in Phase II and III trials [17, 18]. SOC cells have an increased reliance on PARP-mediated DNA repair pathways due to homologous repair defects arising from *BRCA1/2* mutation or methylation-based suppression. The trapping of Parp1 on damaged DNA results in apoptosis selectively in tumor cells [19]. The success of PARP inhibitors demonstrates that targeting of tumor suppressors and biologically altered pathways is an effective way of developing new therapies for SOC.

As more sequencing data becomes available for SOC, it is becoming clear that copy-number alterations dominate the SOC genomic landscape [20]. Each CNA is a deletion or amplification of a large piece of DNA, often many kilobases and sometimes entire chromosomes or chromosome arms. Since each CNA contains dozens or hundreds of genes, its effect on the biology of the cell is cryptic. Computational studies have shown that tumors tend to delete regions of chromosomes with a higher density of tumor suppressors and amplify regions with a high density of oncogenes [21]. While each gene may be predicted to be carefully regulated by a host of transcription factors and post-translational turnover, a proteogenomic study of SOC revealed that the correlation between CNAs and protein levels was >70%, and protein correlation with mRNA was as high as 90% [22]. On average, two-thirds of all genes in SOC are affected by CNAs. What these CNAs do to create tumors or enable drug treatment is an avenue of active study.

Analysis of data is not at pace with generation of data

Despite the onslaught of new -omics information in SOC, all the way from DNA to proteomics, significant challenges have prevented sufficient progress to enable cures. The definition of "cure" is debated in oncology and often misused to imply remission [23], here we agree with the definition of "cure" to mean: a cure enables patients to survive at the same rate as their peers who have no cancer diagnosis. This would occur preferably through the mechanism of having a suppressed or eliminated cancer cell population. The primary reason for a lack of cures is obvious: cancer is not a simple disease. A few cancer types, such as blood cancers and thyroid cancer, may be driven by a single translocation or oncogene. No solid tumors have fewer than 1,000 gene-level alterations. Even after averaging millions of cells from bulk genotyping, the quantity of mutations and CNAs is staggering. Pliable epigenetics add another layer of complexity. Yet in seeking to cure these diseases, economic issues have led companies to seek "breakthrough" drugs which lead the market in targeting a single protein or "orphan" drugs which will only work in select cases. These drugs are useful in inhibiting their target; landmark studies with BRAFV600E inhibitors and PD-1 inhibitors have shown complete inhibition of their molecular target. However, the majority of solid tumors evolve resistance to these drugs and the patients succumb to the disease. While it is

absolutely critical that these drugs are developed for clinical use and enable new ways to target important alterations present in tumor cells, it is naive to predict these single drugs will ever cure complex solid tumors [24]. The status-quo "whack-a-mole" approach of targeting resistant cells with new single-protein targeted drugs is predicted to fail in mathematical modeling studies that map tumor growth in relation to observed mutational rates [25, 26]. Rather, to prevent drug evasion, multiple mutational escape routes should be blocked as early as possible during the course of therapy.

To achieve this prevention of recurrence, the biology of the disease must be understood thoroughly. Recent advances in understanding SOC have incorporated thousands of data points across all genes in each tumor to determine what molecular pathways are selectively altered in SOC. This additional layer of analysis can circumvent the problem of extremely high mutational background rates of cancer. By permuting the background mutation rate and comparing the permutations to the genes which are observed to be altered patient-to-patient, tumor-to-tumor, pathway analysis can find consistent patterns of disruption within SOC genomes. For example, our recent study using Haploinsufficient and Triplosensitive Gene (HAPTRIG) pathway analysis revealed that autophagy is universally dysregulated by copy number alterations in SOC [13]. Autophagy is a homeostatic pathway involved in clearing cellular detritus and requires over thirty genes for its normal flux. While any individual gene may only be deleted 30% of the time, what was remarkable was that every SOC has 10 or more deletions in core autophagy genes. That explains why single gene analyses have not detected the loss of this tumor suppressor pathway: an allele of an "average" gene is deleted in 33% of tumors. But the strong preponderance of deletions of genes all lying within a single pathway is statistically akin to tossing a bagful of coins and discovering every copper coin has landed heads-up, while silver and gold coins remain random.

Fully 95% of SOC are deleted in either *BECN1* and/or *MAP1LC3B*, quintessential autophagy genes. We found these genes to be dose-sensitive in regulating ovarian cancer cells' ability to handle pharmacologic stress on the autophagy system. Knowing that a "whack-a-mole" monotherapy targeting autophagy would be insufficient to cure SOC, we instead designed a multi-targeted autophagy drug cocktail designed to overwhelm the autophagic system in autophagy defective SOC. The Combination of Autophagy Selective Therapeutics, or COAST therapy, removed all visible disease from multiple mouse models, including a patient-derived xenograft model in which the cells were completely resistant to standard of care cisplatin-docetaxel chemotherapy [13]. The drug combination was found to be remarkably safe in blood chemistry and weight measures [27]. An advantage of pathway-targeted drugs like COAST is that while each tumor is unique in genotype (and therefore, single-gene-targeted drugs will only treat a small fraction of tumors, providing an economic disincentive for their use), ovarian cancer and other tumor types always have a large fraction of tumors with consistent pathway alterations. In the case of ovarian cancer, they are weakened in autophagic flux genes in 98% of cases. Thus, targeting autophagy is effective in many tumors, despite each individual tumor being variable in which specific autophagy genes are altered.

Unfortunately, there is strong negative selection against analytical papers that do not produce new genomic datasets. The preponderance of large, new data-sets in the highest-tier scientific journals may suggest some editors judge incoming manuscripts partly on the quantity of new -omics data the manuscript generates. This may be a good proxy for future citations and the

potential impact factor boost of the manuscript, but this requirement for new data pushes researchers to devote more time in acquiring and -omic processing of new samples, rather than seeking to understand data which already exists. Large genomic studies have therefore found their way into high impact journals in part due to their bulk of new data, even though the analysis within these papers can often re-affirm what is already known about the disease, without improving cancer treatment. New ideas and strategies which transcend data collection must be pursued if biology-based therapies are to reduce cancer deaths beyond what epidemiology and preventative measures have already succeeded in [28]. There is reason to believe the genomic data we need to improve the treatment of ovarian cancer already exists.

The influence of heterogeneity on treatment efficacy

There are very few examples of "cures" for cancer, despite such a term being the sought-after goal of cancer research. But the few examples in which cures or life-time management treatments exist can be highly informative. Blood cancers have had some of the most remarkable successes in new targeted chemotherapeutics which have been deemed a cure. A golden example is imatinib (Gleevec), which targets the Bcr-Abl gene fusion in chronic myelogenous leukemia (CML). Ten year survival rates surpass 80%, with the unusual recurrence often stemming from sub-standard dosing as a result of patients attempting to dilute the substantial cost of treatment [29]. Why is it that this cancer can be managed by a single kinase inhibitor, unlike the solid tumors which also may have Bcr-Abl fusions? There are two main reasons: a single mutation which is completely necessary for cancer cell division, and early detection. CML can be detected fairly early in its development due to routine blood tests which examine elevations in white blood cells. It can be readily confirmed by PCR or cytogenic tests for the Philadelphia chromosome, a chromosome 9-22 fusion, which results in the *BCR-ABL* fusion gene. This fusion gene is required to drive the cancers which have the translocation, but is not the only mutation present [30]. When treated with imatinib in chronic phase, survival nearly reaches the "cure" criterion of equivalent peer survival [31]. The chronic phase of CML can persist 3-5 years before it enters blast phase and becomes resistant to imatinib [32]. Blast phase also corresponds to an expansion of mutations and copy number alterations within CML cells, enabling drug resistance [30, 33]. Once blast phase is reached, CML prognosis remains very poor [34]. Thus, the primary reason CML with Bcr-Abl driver mutations can be effectively managed for life is that targeted treatment is administered at low mutational diversity prior to blast phase.

Thyroid cancer is another example of a cancer with an available cure for the majority of patients. Like CML, this is likely possible for the same two reasons: early detection (which means less stochastic mutations resulting in a decreased chance of developing resistance) and a single exploitable weakness present in all cancerous cells. Due to its slow growth it can be detected before mutational crisis through biannual physical examinations of the neck: a simple, minimal-cost test. Since thyroid cells uptake iodine at rates exceeding that of any other cell in the body, cytotoxic radioactive iodine can eliminate all thyroid cells which were not removed by surgery, including metastatic cells. It is driven by *BRAF* and *RAS* mutations, but due to the universal iodine uptake in thyroid derived cells, targeted therapy using iodine cures 98% of patients [35]. Once again, a ubiquitous vulnerability along with low mutation rates enables the cure to this cancer.
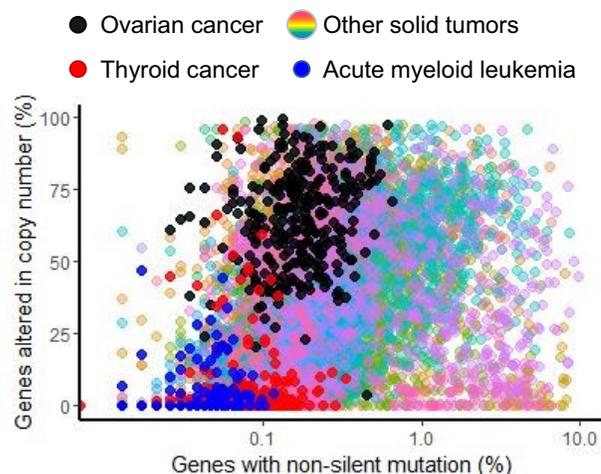
Figure 1. Cancer types able to be cured or controlled long-term with treatment are abnormally low in mutations and copy number alterations. 30 other cancers studied by the Cancer Genome Atlas are depicted for comparison.

Even with CML and thyroid cancer, improvements to survival can still be made. Yet they are cancer types with some of the most remarkable increases in patient survival due to clinical treatment with chemotherapeutics. The challenge for other tumors is this: the mutational diversity of solid tumors is 10-1000 times higher than either leukemias or thyroid cancer [20, 30, 36, 37] (Figure 1). Acute myelogenous leukemia, chronic phase myelogenous leukemia, and papillary thyroid carcinoma all present 0.1-0.4 non-synonymous mutations per megabase. Ovarian cancer, one of the least mutated cancers at the single nucleotide variant level, averages 5-10 mutations per megabase [12]. In addition, the CNAs alter two-thirds of the serous ovarian cancer genome in an average tumor. There is no known common universal weakness within every ovarian cancer cell which enables a cure, although a vulnerability in autophagy may encompass >95% of cells and patients [13]. In addition, ovarian cancer is normally diagnosed after metastasis, which may explain how even this "low" mutation rate tumor type nonetheless has 10-100X the mutations of a blood cancer. Ovarian cancer metastasizes in a sequential fashion and patients with a high degree of clonal expansion (a measure of genomic diversity in tumors) have a poor prognosis, likely due to the pre-existence of chemo-resistant mutations prior to therapy [38]. While high-hopes persist regarding precision therapy in cancer, clinicians and scientists have published editorials and reviews suggesting that precision mono-therapy for late-stage solid tumors will likely never reach the success level of imatinib in CML [24]. Given that HIV requires a minimum of three drugs to fully suppress the disease [39], there should be no illusion that cancers with orders of magnitude greater genomic diversity should require any less aggressive treatment with multi-targeted drugs.

Examples of the problem of heterogeneity are widespread in the ovarian cancer literature. The very origin of the disease remains unclear: some tumors may arise in serous tubal intraepithelial carcinomas (STICs) in the fallopian tube, others from the ovarian epithelium, and perhaps others from a currently unidentified microenvironment [40]. In all these areas where disease is found, the majority of the mutational lesions are already present. Yet, during metastasis and following chemotherapy treatment and recurrence, the number of single nucleotide variants and CNAs continues to rise [41]. *TP53* mutations are universal and one of the earliest driver mutations, but unfortunately are not yet well-targeted by any therapy [38]. *BRCA1/2* mutation and
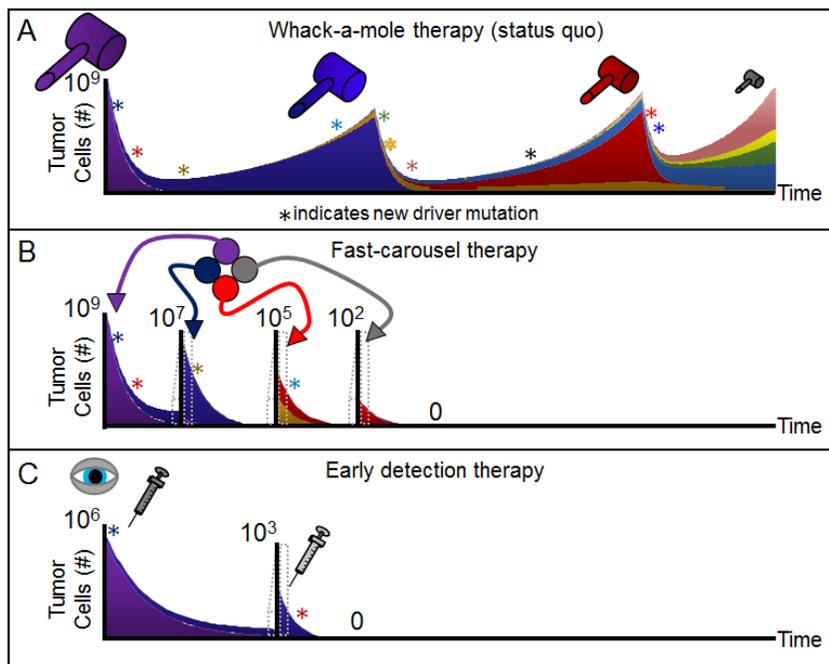
Figure 2. Methods of therapeutic management of the heterogeneity in cancer. (A) The status quo is to treat cancers with a single or pair of drugs each time an observable tumor burden arises. Each treatment removes the vast majority of cells in early stages, but resistant subclones are allowed to expand and stochastically create a large diversity of alternate-therapy resistant clones. (B) An option to prevent resistant clones from growing and creating newly resistant clones is to presume resistant clones already exist in the patient, and rotate therapies until all good options are attempted before tumor outgrowth. (C) Optimally, if early detection methods are perfected, the quantity of tumor cells will be much reduced from the beginning, allowing for a much lower chance of stochastically acquired resistance mutations.

suppression by methylation may suppress homologous repair efficiency in as many as half of serous ovarian cancers [41]. BRCA-targeted therapy using PARP inhibitors has extended progression free survival by over a year and overall survival by months [17, 18]. Yet targeted therapy is by no means a cure. Following normal chemotherapy-surgery initial treatment, recurrent tumors are observed to have multiple independent *BRCA1* reversion mutations in a single patient [41]. The interpretation of this is that the number of cells surviving chemotherapy is sufficient to enable further diversification of the genomic mutations which may circumvent any single or dual drug combination therapy (Figure 2A). To cure serous ovarian cancer, this leaves two possible routes. One is to accept the fact that this tumor type is extremely heterogeneous and to treat late-stage tumors, multiple rounds of alternate therapies must be utilized before re-expansion occurs to avoid escaping cells (Figure 2B). Another is to develop methods, potentially through circulating cell-free DNA or circulating tumor cells in simple blood draws, to detect serous ovarian cancer early at >99.9% specificity to enable clinical usage of the test as a diagnostic. This would enable treatment long before diversity of the tumor cells is established and similarly prevent resistant cells from coming into existence (Figure 2C).

Influence of stem cell populations in ovarian cancer

Another confounding variable for developing an effective treatment is the alterations present within a small subset of tumor cells: the cancer stem cells (CSCs). These add another layer of heterogeneity on top of the already heterogeneous genetics. Early evidence has indicated SOC originates from stem/progenitor cells on the ovary surface epithelium. Cells in the hilum region of the ovarian surface epithelium in mice were found to express stem and progenitor cell markers Aldh1, Lgr5, Lef1, CD133 and CK6B. These proteins were found to have transformation potential following inactivation of tumor suppressor genes Trp53 and Rb1 [42]. While this evidence suggests cells in stem cell rich hilum region are precursors in ovarian cancer, more recent evidence has shown a significant number SOCs to originate in tissues outside the ovary such as the regions in the Fallopian tubes [43]. The initiating CSC niche within the fallopian tube may involve cells expressing the Lgr5 marker [44]. It is unclear how to target pre-cancerous CSCs, but this will be an important avenue of research to enable less invasive or toxic late-stage cancer therapies.

In general, CSCs are subpopulations of tumor cells which share characteristics common among stem cells and progenitor cells. These characteristics include the capacity for self-renewal, the ability to differentiate through asymmetric division, an enhanced resistance to DNA damaging small molecules, and inhibition of anoikis, the triggering of apoptosis through loss of cell adhesion or anchorage [45]. Because of these characteristics, CSC populations are hypothesized to have an involvement in primary tumorigenesis, maintenance of heterogeneity, chemotherapy resistance, metastasis, and tumor relapse. It is important to note that the definition of CSC is distinct from the definition of tissue of origin since tumor initiating events are not required to be of stem cell or stem cell pathway in origin [46, 47]. Additional evidence has shown non-CSC tumor cells may revert or acquire CSC characteristics, opening the possibility that CSC populations may not always be of stem cell origin.

In SOC, stem cell multidrug resistance (MDR) drug efflux pathways have been widely found to be associated with chemotherapy resistance through drug efflux. Dye excluding CSC side populations, a marker for cells expressing the MDR

ABC transporters, in ovarian cancer were first observed in genetically engineered mouse ovarian carcinoma cell lines [48]. These side population cells were also found to be doxorubicin resistant. SP populations taken from patient ascites were also found to be more chemotherapy resistant, and express higher levels of Abcg2 protein than the non-SP cells [49]. In patients with SOC, recurrent fusions of *ABCB1* promoters, which lead to an upregulation of Abcb1 transport proteins, have been observed [41]. In addition to enhancing drug efflux mechanisms, CSCs also have been found to upregulate pathways involved in the detoxification of molecules, such as reactive oxygen species and reactive aldehydes, which can injure cellular components. Aldehyde dehydrogenase pathways have been implicated as a mechanism for CSCs to remove cell damaging agents and enhance resistance in a wide variety of tumors. In SOC, studies have observed an enrichment of cells positive in Aldh1a1 in patient derived xenografts (PDX) treated with chemotherapeutics [50].

In addition to drug resistance mechanisms, ovarian cancer CSCs are known to display stem cell surface markers. CD44 has been associated with self-renewal, tumor sphere formation, and the ability to recapitulate tumors from single cell. CD133 was observed to be significantly enriched in recurrent patient tumors in comparison to their primary counterparts [51]. The same study has found no significant differences in tumor expression of Aldh1a1 and CD44. CD133 but not CD44 expression was also found to be significantly increased in PDX cells treated with chemotherapeutics [50].

Traditional developmental pathways are also altered in SOC cancer stem cells. The notch signaling pathway is known to control cell differentiation pathways during embryonic development, but has been found to be widely dysregulated in cancer. Notch signaling was found to be altered in 22% of SOC samples [12]. Notch3 pathway was found to be linked with chemotherapy resistance in SOC human cell lines, SOC murine cell lines and SOC patient ascites [52]. Additional PDX studies have found Wnt/β-Catenin signaling to be upregulated in platinum resistant SOC tumors derived from patients [53]. An understanding of how to best target all these CSC pathways will remain critical in developing cures for SOC.

Addressing heterogeneity in sequencing studies

To enable cure options for SOC (Figure 2B or 2C), our knowledge of ovarian cancer must extend to understanding: (1) what copy number alterations are true vulnerabilities and/or drivers of the disease, (2) how many different populations of cells exist in ovarian tumors, at the genetic and phenotypic level, and (3) which of these genetic differences are specific to ovarian cancer and not present in any normal tissue cells, enabling early detection and treatment? CRISPR-mediated controlled experimentation of copy number alterations is theoretically possible [54], though this is rarely attempted. Studies which complement strong bioinformatic calculations and sequencing with adequately supportive cell biology and vice versa are necessary to enable effective control of this incredibly complex disease. In particular, an understanding of pathway-level genetic changes in tumors may best enable a new generation of successful targeted therapeutics.

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