INTERNATIONAL JOURNAL OF GYNECOLOGICAL CANCER

OPEN ACCESS

Genomics and molecular mechanisms of high grade serous ovarian cancer: the 12th Biennial Rivkin Center Ovarian Cancer Research Symposium

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Received 4 April 2019
Revised 19 June 2019
Accepted 21 June 2019

To cite: Rankin EB. *Int J Gynecol Cancer* 2019;**29**:s7–s11.

ABSTRACT

Objective The aim of this study was to review current research efforts in genomics and molecular mechanisms of high grade serous ovarian cancer, presented at the 12th Biennial Rivkin Center Ovarian Cancer Research Symposium, held at the University of Washington.

Methods The 12th Biennial Rivkin Center Ovarian Cancer Research Symposium brought together leaders in the field to discuss recent advances in ovarian cancer research and therapy.

Results The genomics and molecular mechanisms of ovarian cancer session featured invited speaker presentations by Dr Alan D' Andrea on 'Deoxyribonucleic acid (DNA) repair in ovarian cancer' and Dr Kathleen Cho on 'Modeling the genomics of high grade serous carcinoma in the mouse'. Eight additional oral presentations and 46 poster presentations were selected from the submitted abstracts that highlighted current research efforts in p53, DNA repair, genomic instability and modeling disease in mice, and organoids in high grade serous ovarian cancer.

Conclusions New technologies utilizing clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR associated protein 9 (CAS9) approaches in mice, organoids, and cell based screens continue to advance our knowledge of key molecular drivers of ovarian cancer initiation, progression, and drug resistance. Improved understanding of the mechanisms of poly ADP ribose polymerase inhibitor resistance may lead to new therapeutic strategies to enhance outcomes in women with high grade serous ovarian cancer.

INTRODUCTION

Ovarian cancer is a heterogeneous disease with multiple subtypes that are classified based on distinct histological and genetic features. The most common and lethal subtype of ovarian cancer is high grade serous ovarian cancer. Approximately 70% of women diagnosed with high grade serous ovarian cancer present with advanced disease where the tumor has disseminated beyond the ovaries and pelvic organs to the peritoneum and abdominal organs, including the diaphragm, stomach, omentum, liver, and intestines.[1 2] Common mutations associated with the development of high grade serous ovarian cancer include *TP53* mutations and *BRCA1/2* mutations.[3] At the genomic level, high grade serous ovarian cancer is also characterized by recurrent deoxyribonucleic acid (DNA) copy number alterations, making this cancer genomically unstable.[4] These clinical findings suggest an important role for p53, DNA repair, and genomic instability in the pathogenesis of high grade serous ovarian cancer, and were a focus of the research presented at the 12th Biennial Rivkin Center Ovarian Cancer Research Symposium during the session on genomics and molecular mechanisms of ovarian cancer.

Here we will summarize the key topics discussed in this session that was held on September 13–15, 2018, at the University of Washington.

P53 AND HIGH GRADE SEROUS OVARIAN CANCER

The tumor suppressor p53 is known as the guardian of the genome due to its central role in regulating DNA damage responses. A variety of stimuli, including DNA damage, nutrient starvation, and oncogenic signaling, activate p53 signaling to modulate cell cycle arrest, apoptosis, ferroptosis, senescence, oncogenic signaling, metabolic reprogramming, differentiation, invasion, and signaling within the tumor microenvironment (for a recent review see Mello and Attardi[5]). Mutations in *TP53* are found in 96% of cases of high grade serous ovarian cancer, making p53 a critical tumor suppressor for ovarian cancer.[3] *TP53* mutations are found within early serous tubal intraepithelial lesions found in the fallopian tube, suggesting that p53 loss is an early event in the pathogenesis of high grade serous ovarian cancer (for an recent review see Soong et al[6]). In the genomic and molecular mechanisms of ovarian cancer session, Dr Kathy Cho presented data from murine models of ovarian cancer demonstrating that recombination of *Trp53* inactivation along with *Brca1* and *Rb1* inactivation in fallopian tube epithelium utilizing Cre-lox technology requires a latency period of more than a year for early serous tubal intraepithelial carcinoma lesions to progress to high grade serous ovarian cancer, suggesting that tumor initiation and progression require additional events.[7 8]

Dr Rong Wu presented on new technologies utilizing clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR associated protein 9 (CAS9) mediated somatic gene editing in fallopian tube epithelium to model gynecologic cancers in mice. Importantly, he reported that the Cre-CRISPR/Cas9 sgRNA system could recapitulate morphology and immunophenotypic characteristics of *Apc-Pten* or *Brca1-Trp53-Rb1-Nf1* endometrioid carcinomas and high grade serous ovarian cancer produced by Cre-lox technology. Within the Rivkin Symposium, we also learnt of additional research efforts utilizing CRISPR-Cas9 mediated gene targeting in organoid cultures derived from mouse oviduct and ovarian surface epithelium to identify gene combinations that result in tumor formation in transplantation studies.[9] Future work utilizing these technologies and model systems will expedite the identification of genetic events that work in concert with p53 mutations to promote high grade serous ovarian cancer formation and metastasis within murine models.

Similar to most cancers, the majority of *TP53* mutations in high grade serous ovarian cancer are missense mutations that reside within the DNA binding domain. Mutant p53 proteins result in loss of wild type p53 function through multiple mechanisms, including loss of DNA binding and protein structural mutations. *TP53* mutations can facilitate p53 protein aggregation leading to loss of p53 function, dominant negative effects, and gain of function activities. Previous studies have shown that R248 and R280 mutant p53 proteins stimulate p53 protein aggregation *in vitro* and enhance p53 protein aggregates within the nucleus of cancer cells to inactivate p53 function.[10] Dr Nicole Heinzl discussed the development of an enzyme linked immunosorbent assay recently published by Maritschnegg et al[11] that may be utilized to detect p53 protein aggregates in high grade serous ovarian cancer patient specimens. Ongoing studies are focused on determining whether p53 aggregates correlate with patient survival and/or response to platinum based chemotherapy in high grade serous ovarian cancer.

There are likely multiple mechanisms by which p53 mediates its tumor suppressor functions in ovarian cancer. One target that may contribute to the pathogenesis of high grade serous ovarian cancer is forkhead box protein M1 (FOXM1). FOXM1 is a forkhead box transcription factor that controls cell cycle progression and cell proliferation in normal cells through activation of G2 specific genes.[12 13] In cancer cells, FOXM1 has additional functions in controlling apoptosis, angiogenesis, invasion, genomic instability, inflammation, and metabolism.[12] In ovarian cancer, aberrant activation of FOXM1 has been shown to promote tumor migration, invasion, chemoresistance, and poly ADP ribose polymerase inhibitor resistance.[14–16] The FOXM1 transcription factor network is overexpressed at the messenger ribonucleic acid (RNA) level in 87% of high grade serous ovarian cancer.[3] FOXM1 is a repressed p53 target, indicating that p53 loss may contribute to enhanced FOXM1 signaling in high grade serous ovarian cancer.[17] In support of this notion, FOXM1 expression is increased in p53 and Rb deficient murine ovarian surface epithelial cells and tumors compared with p53 and Rb wild type cells.[18] Dr Carter Barger recently demonstrated that FOXM1 is highly expressed in human cancers with p53 inactivation and Rb-E2F deregulation. Moreover, FOXM1 expression was associated with genomic instability.[18] Overall, these studies suggest that FOXM1 may be an important therapeutic target for the treatment of high grade serous ovarian cancer .

DNA REPAIR IN HIGH GRADE SEROUS OVARIAN CANCER

Defective homologous recombination plays an important role in the pathogenesis and therapeutic response of high grade serous ovarian cancer. It has been estimated that approximately 50% of high grade serous ovarian cancers have defects in DNA repair and homologous recombination. Most notably, 20% of high grade serous ovarian cancers exhibit germline or somatic mutations in the homologous recombination proteins BRCA1/2 and an additional 11% of high grade serous ovarian cancers lose BRCA1 expression through promoter methylation. Additional genomic changes within genes such as EMSY, PTEN, RAD51, ATM, ATR, and Fanconi anemia also result in defective homologous recombination occur in 25% of HGSOC tumors.[3]

The homologous recombination pathway plays an important role in repairing DNA double strand breaks that occur during DNA replication. Defects in homologous recombination result in the accumulation of chromatid breaks.[19] If chromatid breaks are not repaired, the cells become dependent on alternative end joining double strand break repair for survival. Alternative end joining will repair the breaks by joining the double strand breaks, resulting in chromosomal rearrangements and genomic instability.[20] Homologous recombination deficient tumors are particularly sensitive to intrastrand and interstrand crosslinks induced by platinum based chemotherapeutic agents.[21]

In addition to chemotherapy, homologous recombination deficient high grade serous ovarian cancers are also particularly sensitive to poly ADP ribose polymerase inhibitors. In 2014, olaparib was first approved by the Food and Drug Administration for the treatment of BRCA1/2 mutant epithelial ovarian cancer for those who have received three or more chemotherapy regimens.[22] Subsequently, rucaparib was approved for women with advanced ovarian cancer who have been treated with two or more chemotherapies and have germline or somatic BRCA mutations.[23] Niraparib was the first approved poly ADP ribose polymerase inhibitor for maintenance therapy in recurrent ovarian cancer patients who are in complete or partial response to platinum based chemotherapy, regardless of BRCA mutation status.[24] Currently, olaparib, niraparib, and rucaparib are approved by the Food and Drug Administration for maintenance therapy in patients with recurrent epithelial ovarian cancer who are in complete or partial response to platinum based chemotherapy.[25] There are a number of ongoing combination studies evaluating the safety and efficacy of poly ADP ribose polymerase inhibitors with chemotherapy, radiation therapy, immunotherapy, antiangiogenic agents, PI3K pathway inhibitors, and inhibitors of DNA damage repair.[26] Phase II clinical trials combining olaparib with paclitaxel in BRCA mutated cancers have reported improved clinical responses compared with single agent platinum or topoisomerase inhibitors.[27] However, significant myelosuppression limits the combination of poly ADP ribose polymerase inhibitors with standard doses of platinum and topoisomerase inhibitors.[28 29]

A recent study by Drs Sarah Hill and Alan D'Andrea demonstrated that independent of DNA repair gene mutational status, high grade serous ovarian cancer patient organoids with a functional defect in homologous recombination, as determined by defective RAD51 foci assembly following irradiation, correlates with response to poly ADP ribose polymerase inhibition.[30] These studies highlight the importance of homologous recombination deficiency in mediating

poly ADP ribose polymerase inhibitor response in high grade serous ovarian cancer and suggest that functional testing of homologous recombination activity may be most effective to predict which patients may respond to poly ADP ribose polymerase inhibitors. There are multiple mechanisms by which homologous recombination defective tumors are sensitive to poly ADP ribose polymerase inhibition. First, poly ADP ribose polymerase is a single strand DNA repair protein. If single strand breaks are not repaired by poly ADP ribose polymerase, they are converted into double strand breaks during replication that are repaired by RAD51 and homologous recombination.[20 31] Additional mechanisms for poly ADP ribose polymerase inhibitor mediated sensitivity of homologous recombination deficient high grade serous ovarian cancer cells may also include activation of classic non-homologous end joining and inhibition of DNA repair mediated by the accumulation of poly ADP ribose polymerase1-DNA complexes.[32]

Despite the enthusiasm for the addition of poly ADP ribose polymerase inhibitors to the clinical landscape of high grade serous ovarian cancer, many patients who initially respond to poly ADP ribose polymerase inhibitors develop resistance. There are multiple mechanisms by which high grade serous ovarian cancers develop resistance to poly ADP ribose polymerase inhibitors. Dr Alan D'Andrea, an invited speaker at the Rivkin Symposium, spoke about the current research efforts investigating mechanisms that drive sensitivity and resistance to poly ADP ribose polymerase inhibitors. In BRCA1/2 deficient tumors, a common mechanism driving poly ADP ribose polymerase inhibitor resistance is the restoration of BRCA1 or BRCA2 protein activity through genetic or epigenetic events.[32] Loss of poly ADP ribose polymerase1 expression, the target of poly ADP ribose polymerase inhibitors, has also been linked to poly ADP ribose polymerase inhibitor resistance in human cancer cell lines.[33] In addition to loss of poly ADP ribose polymerase1 expression, mutations within poly ADP ribose polymerase1 that prevent poly ADP ribose polymerase trapping by poly ADP ribose polymerase inhibitors at sites of DNA damage can also contribute to drug resistance.[34] Recent studies have utilized unbiased screening methods to identify novel mediators of poly ADP ribose polymerase inhibitor resistance.

Screening for factors that mediate resistance of BRCA1 deficient tumors to poly ADP ribose polymerase inhibitors identified mitotic arrest deficient 2 like 2 (REV7) and tumor protein p53 binding protein 1 (53BP1).[35] 53BP1 is a chromatin binding protein that is rapidly recruited to double strand breaks where it regulates DNA repair choices by inhibiting DNA end resection and homologous recombination and promotes non-homologous end joining.[36] During homologous recombination, BRCA1 promotes the displacement of 53BP1 from chromatin near double strand breaks to activate DNA end resection.[37 38] Loss of 53BP1 in a *Brca1* deficient setting is sufficient to promote homologous recombination and confer poly ADP ribose polymerase inhibitor resistance.[36 39 40] REV7 has recently been identified as a component of the shieldin complex, a downstream effector of 53BP1 in DNA double strand break repair.[32 35 41] Dr Yizhou He presented data on another CRISPR mediated screen for genes that mediate poly ADP ribose polymerase inhibitor response where the multifunctional homodimeric protein hub dynein light chain LC8-type I (DYNLL1) was identified as an another important factor mediating poly ADP ribose polymerase inhibitor sensitivity. Studies revealed DYNL11 loss resulted in poly ADP ribose polymerase inhibitor resistance. In these studies, He et al found that DYNLL1 is a negative regulator of DNA end resection.[42] These findings are consistent with a recent report demonstrating that DYNLL1 acts to regulate 53BP1 non-homologous end joining by promoting 53BP1 oligomerization and chromatin interactions.[43] Overall, these findings highlight the importance of the p53BP1 pathway in poly ADP ribose polymerase inhibitor resistance and have revealed novel mechanisms governing the DNA damage response.

In addition to the p53BP1 pathway, Dr Jeremy Chien presented work ongoing in his laboratory that has identified the TP53 induced glycolysis regulatory phosphatase TIGAR as an important mediator of poly ADP ribose polymerase inhibitor response. Knockdown of TIGAR enhanced responses to olaparib in ovarian cancer cells *in vitro*. Moreover, TIGAR expression is amplified and correlates with poor overall survival in high grade serous ovarian cancer, suggesting that TIGAR may be an important therapeutic target for ovarian cancer. Overall, these data demonstrate that there are multiple mechanisms that may drive poly ADP ribose polymerase1 resistance, suggesting that analysis of each individual patient may be necessary to inform treatment strategies for these patients. Dr Elizabeth Stover performed a near genome CRISPR/Cas9 screen in BRCA2 mutant high grade serous ovarian cancer cell lines to identify genes that mediate survival to platinum based chemotherapy. In this screen, overexpression of the proapoptotic genes BCL-like 1 (BCL-XL), BCL2 apoptosis regulator (BCL-2), and MCL1 apoptosis regulator mediated resistance to platinum based chemotherapy. In preliminary studies, antiapoptotic inhibitors against BCL-XL, MCL1, or BCL2/BCL-XL synergized with cisplatin or paclitaxel, suggesting that antiapoptotic targets such as BCL-XL and MCL1 may be additional therapeutic targets driving chemotherapy resistance in high grade serous ovarian cancer. Moreover, BCL-XL, MCL1, or BCL2/BCL-XL inhibitors also synergized with the poly ADP ribose polymerase inhibitor olaparib, suggesting that BCL-XL and MCL1 may be therapeutic targets to use in combination with DNA damaging agents.

GENOMIC INSTABILITY OF HIGH GRADE SEROUS OVARIAN CANCER

High grade serous ovarian cancer ranks among the top cancers with chromosome structural variants.[1 4] In addition to recurrent mutations in *TP53* and the homologous recombination pathway, high grade serous ovarian cancer exhibits a high degree of somatic copy number alterations. Dr James Brenton presented work from his laboratory where they utilized copy number signatures derived from whole genome sequencing of core biopsies as a novel approach to identify mutational processes in high grade serous ovarian cancer. Their study identified seven distinct copy number signatures that are present in high grade serous ovarian cancer patient specimens at the time of diagnosis. Importantly, a copy number signature associated with oncogenic RAS signaling (neurofibromin 1, NF1; KRAS proto-oncogene GTPase, KRAS; and NRAS proto-oncogene GTPase, NRAS) predicts platinum resistant relapse and poor survival in high grade serous ovarian cancer patients. Moreover, they identified a copy number signature associated with BRCA1/2 related homologous recombination defects

that is associated with improved patient survival.[44] Their study also reveals the majority of high grade serous ovarian cancer patients have a mixture of copy number signatures, suggesting multiple mutational processes may coevolve during the pathogenesis of high grade serous ovarian cancer.[44] These studies reveal new information regarding mutational processes that occur during the evolution of high grade serous ovarian cancer and have important therapeutic implications in the use of copy number signatures for patient stratification to targeted therapies in high grade serous ovarian cancer.

EMERGING AREAS WITHIN HIGH GRADE SEROUS OVARIAN CANCER

The analysis and identification of driver non-coding somatic mutations in epithelial ovarian cancer is an emerging area of research in the ovarian cancer field. Whole genome sequencing studies within epithelial ovarian cancer have identified thousands of non-coding somatic mutations.[45] Dr Rosario Corona presented ongoing work in the Lawrenson laboratory analyzing non-coding somatic mutations in epithelial ovarian cancer to distinguish between driver and passenger non-coding mutations. They hypothesized that driver non-coding mutations may localize to regulatory elements (promoters, enhancers) of genes known to be involved in the pathogenesis of ovarian cancer. They utilized genome wide histone 3 methylates Lys27 (H3K27) acetylation ChIP-sequencing of fresh primary ovarian cancer tissue samples from each major ovarian cancer histotype combined with RNA sequencing to identify common active regulatory elements across all histotypes. They then integrated these data with whole genome sequencing data to identify common non-coding mutations within active regulatory elements in ovarian cancer. Preliminary data identify several commonly mutated regulatory elements within each ovarian cancer histotype, including RNA polymerase III subunit E (POLR3E) and coiled-coil-helix-coiled-coil-helix (CHCHD6) for high grade serous ovarian cancer. Future studies are needed to further explore the identification and validation of these novel non-coding somatic mutation in epithelial ovarian cancer.

SUMMARY

In summary, new technologies utilizing CRISPR-CAS9 approaches in mice, organoids, and cell based screens continue to advance our knowledge of key molecular drivers of ovarian cancer initiation, progression, and drug resistance. Poly ADP ribose polymerase inhibitors, targeting homologous recombination defects in high grade serous ovarian cancer, have significantly altered the clinical management of ovarian cancer. However, resistance to these agents has emerged as an important clinical challenge. The development of predictive biomarkers for single agent poly ADP ribose polymerase inhibitors are needed for patient stratification. Additionally, improved understanding of the mechanisms of poly ADP ribose polymerase inhibitor resistance may lead to new therapeutic strategies to enhance outcomes in women with high grade serous ovarian cancer.

Contributors EBR wrote the research summary.

Funding This study was supported by US Department of Defense (W81XWH-15-1-0097).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

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