Editorial

Potential role of antiestrogens in treating ovarian cancer

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Ovarian cancer is the deadliest of all gynecologic malignancies and remains the fifth leading cause of cancer related deaths among women (1). High-grade serous ovarian cancer (HGSOC) is the most predominant and lethal subtype accounting for about 70% of ovarian cancer cases (2). The standard of care involves platinum and taxol based cytotoxic chemotherapy which has remained unchanged for the past 3 decades (3,4). Development of individualized targeted therapies catering to the specific tumor characteristics is needed. Andersen and colleagues report the presence of a subset of estrogen dependent HGSOC and have identified estrogen responsive features, which can be used to determine patient cohorts who can benefit from endocrine therapy. Endocrine based therapies have been found to be effective when targeting estrogen receptor (ER) in ER positive metastatic breast cancer (5). Inhibition of ER is considered as an alternative in recurrent ovarian cancer patients who are resistant to the carbo-taxol based standard chemotherapy (6). However, changes in expression of ER have been reported between matched primary and recurrent ovarian cancer (7). Therefore, it is essential to take this into account while planning therapies involving ER inhibition. In their article Andersen and colleagues suggest that many OC patients exhibit high expression of ERα and have identified an ER dependent gene expression signature (8). They further report that the selective ER-alpha down-regulator (SERD) fulvestrant is more effective than the selective ER modulator (SERM) 4-Hydroxytamoxifen (4OHT) in inhibiting the growth of ERα expressing ovarian cancer.

Despite high expression of ER-alpha in ~80% of HGSOC, the ERα gene amplification is relatively rare, occurring in about 2% of cases. Though some small but promising clinical trials of endocrine therapy having been conducted, ER-alpha has been understudied as a target in this disease. Targeting ER-alpha has shown promise in laboratory models and in clinical trials but identification of the appropriate patient subset has remained elusive. A low percentage of ER positive ovarian cancer patients respond to initial anti-estrogen therapy based on blocking ER compared to 50% responders in case of ER-positive breast cancer (9). Moreover, there are conflicting reports in the prognosis of ovarian cancer patients with high ER expression (10). Microarray analysis of gene expression of ERα regulated genes in PEO1 ovarian cancer cells revealed a signature of 1,200 cancer related genes (11). On the other hand, ERβ did not play a role in the cellular response to 17beta-estradiol treatment (11). Andersen *et al.* (8) have attempted to identify features associated with estrogen-responsive HGSOC cell line and patient derived HGSOC models. They report a subset of HGSOC xenograft models, which require estrogen for growth and survival. Estrogen-regulated transcriptome data were overlapped with public datasets to develop a comprehensive panel of ERα target genes. Prolonged endocrine therapy resulted in a significant decrease in IGFBP3. This indicated

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that effects of ERα activation were a superior indicator of endocrine therapy effectiveness since IGFBP3 is suppressed by ERα. Previous studies have attempted to identify markers of tumor endocrine response and only their IGFBP3 expression results agreed with those studies. The authors reason that this could possibly be due to the differences in the detection methods used and the sample size. To determine if estrogen regulates growth, four ERα positive HGSOC cell lines were treated with E_2 and fulvestrant or 4OHT an active metabolite of tamoxifen, which binds ERs and estrogen-related receptors. Interestingly, estrogen is metabolized differentially in ovarian cancer cells as compared to the ovarian surface epithelium. Steroid sulphatase induced by tumor micro environmental cytokines and the suppression of estrogen sulfotransferase result in an increase in E_2 (12).

Andersen and colleagues demonstrate that some HGSOC cells are E_2 responsive but the response depended on ERα and the 3D context (8). PEO1, PEO4, and OVCA432 cells expressed high levels of ERα and OVSAHO had a low expression while all of them are ERβ negative. The effects of E_2 on these cells were assayed both in 2D as well as in 3D cultures. In 2D assays, E_2 stimulated proliferation of PEO4 and PEO1 cells in a dose-dependent manner, which was abrogated by fulvestrant and 4OHT. In contrast, E_2 had no effect on growth of OVCA432 and OVSAHO cells. Whole-genome microarray analysis was performed in PEO4 and PEO1 cells after treatment with E_2 along with fulvestrant or 4OHT. E_2 was found to regulate the expression of 221 and 291 genes in PEO1 and PEO4, respectively. Notably, fulvestrant was more effective than 4OHT at blocking E_2 effects; and mitigated expression of 96% and 99.5% E_2 mediated gene expression in PEO1 and PEO4. Similar to growth in 2D, E_2 treatment increased spheroid formation in PEO4 cells but not in OVCA432 cells. Seeding on ultra low attachment plates increased ERα mRNA and protein levels versus 2-D conditions, which may mediate a novel E_2 response. The effect of E_2 on PEO1 appeared to be more through a decrease of cell death rather than increased proliferation. Survival in forced suspension typically requires induction of anoikis resistance. However, E_2 did not have any effect on caspase-3/7 activity, suggesting that E_2 may mediate its effects through other survival mechanisms. Consistent with the *in vitro* results, E_2 treatment was found to increase tumor growth in mice through the induction of GREB1 and MYC expression.

In addition, using HGSOC patient derived xenograft (PDX) models, Andersen and colleagues demonstrated that fulvestrant was more effective than 4OHT (8). Traditionally approaches to inhibit ER pathways have been using SERMs like 4OHT or its precursor tamoxifen and subsequently SERDS like fulvestrant were introduced. Aromatase inhibitors, which interfere with ER ligand synthesis, have also been tried. Based on the evidence provided by Andersen and colleagues, fulvestrant would be a potentially superior mode of endocrine therapy to be considered in the clinic. Aromatase inhibitors have not been compared and should potentially be tested in the future in a direct comparison of the effects on tumor as well as the effects on the gene signature.

Recently, the Conejo-Garcia group has reported the cancer cell independent role of estrogen signaling in cancer progression (13), which points towards the role of estrogen signaling in the tumor microenvironment. They demonstrate that the estrogen insensitive tumors were still helped by estrogen signaling through the enhancement of the intrinsic immunosuppressive activity as well as the mobilization of myeloid-derived suppressor cells. Similarly, stromal fibroblasts expressing ERα promote tumor growth in prostrate cancer (14). This opens up the possibility of targeting endocrine-based therapies to the tumor microenvironment.

There are several questions for the field including whether we have a reliable gene expression signature that will enable us to target a subset of HGSOC tumors with effective endocrine therapy? Future prospective longitudinal studies comparing pre- and post-treatment samples using larger cohorts and uniform assay techniques would result in a more robust functional signature of ERα effects. Can a similar signature be derived for the tumor microenvironment compartment? Are the tumor cell intrinsic and extrinsic effects mutually exclusive? Can patients who do not express the tumor ERα gene signature still benefit from the effects of targeting the tumor microenvironment? Addressing these questions in future studies will potentially direct the development of effective endocrine therapies to treat HGSOC.

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Footnote

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