HR deficiency and cancer stem cells in serous ovarian and endometrial carcinomas

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Background

In vitro fertilization (IVF) is an effective tool for couples experiencing infertility but biomarkers for prediction of treatment outcome are lacking. A better understanding of mechanisms underlying relapse and treatment resistance in high-grade serous ovarian carcinoma (HGSOC) has led to research in cancer stem cells (CSC) and homologous recombination deficiency (HRD). While mutations in BRCA1/2 have been studied in relation to HRD in HGSOC to evaluate the benefit of targeted therapeutics, i.e. PARP inhibitors (PARPi) this has not been explored in serous endometrial carcinoma (SEC), a cancer type genetically and histologically similar to HGSOC.

Materials and methods

Response to hormonal stimulation and pregnancy outcome in IVF patients was investigated by assessment of polymorphisms in the LHCG and FSHR genes in a cohort of 384 women. The prognostic role of the CSC marker SOX2 was investigated using immunohistochemistry in a cohort of 130 patients diagnosed with HGSOC.

The prevalence of HRD was explored in twenty-nine women with SEC using SNP-arrays, targeted sequencing and immunohistochemistry. Twenty-five HGSOC cases have also been HRD-scored and to complement these data we will investigate HRD and stem cell factors in relation to chemotherapy in parental and resistant HGSOC cell lines.

Results

Paper I

A combination of two common SNPs in LHCG and FSHR could predict the clinical pregnancy outcome after IVF.

Paper II
The level of SOX2 expression could predict the risk of relapse and death in HGSOC patients with tumor tissue remaining after surgery.

Paper III

HRD and copy number signatures associated with HRD in HGSOC were a common feature of SEC, whereas mutations in BRCA1/2 were rare.

**Significance**

The possibility to predict pregnancy chances for couples experiencing infertility could help in planning IVF treatment.

The connection between SOX2 expression and prognosis could help surgeons make decisions regarding surgical aggressiveness and encourages more studies of CSCs in HGSOC.

Elucidating the prevalence of HRD in SEC could lead to clinical studies evaluating the effect of PARPi in this cancer type. Analyses of HRD and CSC factors before and after chemotherapy and the development of resistance may help in identifying targets for treatment of primary tumors.

**Included papers**


Bååth, M., Westbom Fremer, S., Martín de la Fuente, L., Ebbesson, A., Davis, J., Malander, S., Måsbäck, A., Kannisto, P., Hedenfalk, I. SOX2 is a promising predictor of relapse and death in advanced stage high-grade serous ovarian cancer patients with residual disease after debulking surgery. *In revision.*

Jönsson, J-M., Bååth, M., Björnheden, I., Durmaz Sahin, I., Måsbäck, A., Staaf, J., Hedenfalk, I. Frequent homologous recombination repair deficiency in serous endometrial carcinoma. *In preparation.*