Profiles of Genomic Instability in High-Grade Serous Ovarian Cancer Predict Treatment Outcome - DTU Orbit (03/01/2019)

Purpose: High-grade serous cancer (HGSC) is the most common cancer of the ovary and is characterized by chromosomal instability. Defects in homologous recombination repair (HRR) are associated with genomic instability in HGSC, and are exploited by therapy targeting DNA repair. Defective HRR causes uniparental deletions and loss of heterozygosity (LOH). Our purpose is to profile LOH in HGSC and correlate our findings to clinical outcome, and compare HGSC and high-grade breast cancers.

Experimental Design: We examined LOH and copy number changes using single nucleotide polymorphism array data from three HGSC cohorts and compared results to a cohort of high-grade breast cancers. The LOH profiles in HGSC were matched to chemotherapy resistance and progression-free survival (PFS).

Results: LOH-based clustering divided HGSC into two clusters. The major group displayed extensive LOH and was further divided into two subgroups. The second group contained remarkably less LOH. BRCA1 promoter methylation was associated with the major group. LOH clusters were reproducible when validated in two independent HGSC datasets. LOH burden in the major cluster of HGSC was similar to triple-negative, and distinct from other high-grade breast cancers. Our analysis revealed an LOH cluster with lower treatment resistance and a significant correlation between LOH burden and PFS.

Conclusions: Separating HGSC by LOH-based clustering produces remarkably stable subgroups in three different cohorts. Patients in the various LOH clusters differed with respect to chemotherapy resistance, and the extent of LOH correlated with PFS. LOH burden may indicate vulnerability to treatment targeting DNA repair, such as PARP1 inhibitors.

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