P-cadherin: A promising prognostic biomarker for homologous repair proficient high grade serous ovarian carcinoma

Introduction/Background North Caucasus hosts several large ethnic groups, which preserved their national identity through the course of history. These populations are likely to have a unique pattern of disease predisposing alleles reflecting the genetic background of their ancestors.

Methodology This study involved ovarian cancer (OC) and breast cancer (BC) patients from Chechnya (n = 147), Kabardino-Balkaria (n = 139), North Ossetia (n = 83), Ingushetia (n = 88) and Dagestan (n = 137). The entire coding sequences of BRCA1, BRCA2 and ATM genes were analyzed by next-generation sequencing (NGS) in 180 OCs and 414 BCs.

Results Consecutive OC series were characterized by high frequency of BRCA1/2 mutations across all analyzed ethnic groups, ranging from 18% to 33%. BC patients, which were enriched by early-onset, family history-positive and receptor triple-negative disease, showed mutation rate varying from 4% to 14%. There were founder pathogenic alleles in Chechens (BRCA1 c.3629_3630delAG; 10 out of 20 BRCA1/2 mutations) and North Ossetians (BRCA2 c.6341delC; 6 out 10

Abstracts

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Ethnicity-specific spectrum of BRCA1, BRCA2 and ATM pathogenic variants in ovarian and breast cancer patients from North Caucasus

1Evgeny Imyantov, 1Elvina Bakaeva, 1AlexandR Romanko, 1Ilya Stepanov, 1Luiza Sul'tarova, 1Zaur Hamgokov, 1Madina Chahkieva, 1Mirza Murachuyev, 1Anna Sokolenko. 2N.N. Petrov Institute of Oncology, St.-Petersburg, Russian Federation; 3Chechen Republican Cancer Center, Grozny, Russian Federation; 4Kabardino-Balkarian Republican Cancer Center, Nalchik, Russian Federation; 5Ingushetian Republican Cancer Center, Nazran, Russian Federation; 6Dagestan Republican Cancer Center, Makhachkala, Russian Federation

Introduction/Background Homologous repair (HR) proficient tumours constitute 2/3 of high grade serous ovarian carcinoma (HGSC), being associated with worse prognosis. Therefore, the identification of clinically relevant biomarkers is an urgent unmet clinical need. Once classic cadherins are transmembrane glycoproteins involved in cell-cell adhesion that are frequently deregulated in cancer, we aimed to: 1) characterize the expression pattern of E-cadherin (CDH1), N-cadherin (CDH2) and P-cadherin (CDH3); 2) evaluate their prognostic impact in terms of overall survival (OS), according to HR status.

Methodology Retrospective study using a convenience sample of archive human tissue (Fallopian tube epithelium (FTE), serous precursor lesions and chemo-naïf HGSC) from a Portuguese cancer centre. In vitro and in silico validation performed using HGSC cell lines (BG1 and OVCAR4 cell lines) and CCLE database, respectively. Protein expression evaluated using immunohistochemistry (H-scoring system) and western blot. Comparisons between groups were made using T-test and X², where appropriate. Survival analyses were estimated using Kaplan-Meier analysis and Log-rank test.

Results We included 321 samples (130 FTE, 53 precursor lesions and 138 HGSC; 41.2% BRCA1/2 or RAD51D mutated) from 221 patients. All HGSC co-expressed the 3 cadherins (28% with high co-expression scores). Expression pattern did not differ according to HR status. P-cadherin was significantly upregulated both in precursor lesions and HGSC, when compared with FTE. CDH3 expression was positively correlated with CDH1, EpCAM and GRHL2 and inversely correlated with VIM, both in silico and in vitro. HGSC with high cadherin co-expression and high P-cadherin expression were significantly associated with shorter OS in the HR proficient subgroup.

Conclusion Our results suggest that P-cadherin upregulation may be an early event in the serous carcinogenesis and a poor prognosis biomarker in HR proficient HGSC. Functional assays are currently ongoing to unravel the biological mechanisms underlying P-cadherin role in this subgroup.