Genomic structural instability and homologous recombination deficiency in breast and ovarian cancers

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Background: Genomic instability plays an important role in breast and ovarian oncogenesis [1]. Genomic instability could arise from impaired function of a particular genome maintenance pathway or/and due to increased rate of genomic aberrations caused by endogenous or exogenous factors [2]. Identification of various genomic instability patterns and their association to the deregulated genes or metabolic processes is important at a fundamental level and for clinical practice [3]. One source of genomic instability is homologous recombination deficiency (HRD) due to *BRCA1* and *BRCA2* inactivation, which accounts for nearly 50% of cases in serous ovarian carcinoma and triple-negative breast carcinoma [4]. The high rate of chromosomal structural instability was shown to be a hallmark of HRD in triple-negative breast carcinoma and to have a predictive value for overall survival in high-grade serous ovarian carcinomas [5-7]. However, there was no precise correspondence between HRD associated genomic instability and mutational profile established so far. Moreover, other than HRD patterns of genomic instability could be observed in breast and ovarian tumors, they interfere with HRD structural alterations and affect the efficiency of genomic markers of HRD. We aim at (1) clarifying structural and mutational determinants of HRD by in-deep exploration of the cases with positive genomic markers of HRD and lacking *BRCA1/2* inactivation; (2) description of other particular genomic instability patterns, which might interfere with genomic markers of HRD producing false positive calls.

Material and methods: TCGA and in-house data sets of high-grade ovarian carcinoma and ductal breast carcinoma, including SNP-arrays, mutational profiles from exome sequencing,

transcriptomic data (RNAseq and Affymetrix) and Sanger sequencing were used [8-9]. SNP-arrays were processed by the GAP method [10]. As a measure of genomic HRD the number of Large-scale State Transitions was evaluated for each tumor genome [7]. Inactivating mutations were considered only if one allele of a gene in present (genomic loss of heterozygosity). Transcriptomic data was analyzed by PCA and ICA, with and without pathway information. Next generation sequencing data were used to annotate copy number by structural alterations. Publically accessible and in-house sequencing data were analyzed.

Results: Using our genomic signature of HRD we in-deep explored several cohorts of breast and ovarian tumors. Exhaustive case study and sequencing have demonstrated that *BRCA1/2* inactivation explains most of structurally unstable cases in all molecular subtypes of ductal breast carcinoma. On the contrary, one third of structurally unstable genomes in high grade serous ovarian carcinoma lack detected inactivation in *BRCA1/2* genes. Only a small portion of these cases are associated with *RAD51C* methylation, and none with inactivation of Fanconi pathway members. Combining tumor mutational profiles, transcriptomic data and pathway analysis we explored possible origins of HRD in tumors with structurally unstable genomes. We observed that some tumors with genomic HRD and lack of *BRCA1/2* inactivation follow the transcriptomic pattern of *BRCA1/2* inactivated tumors. Which pathway defects lead to genomic and transcriptomic HRD patterns need further functional study.

Some genetically unstable tumors with positive HRD genomic markers were also found to exhibit other recurrent alterations, such as regular small- or middle-scale gains. These tumors were explored for mutations and new gene candidates responsible for these instability patterns are under investigation.

Conclusions: Whereas HRD is consistently associated with *BRCA1/2* inactivation in breast carcinomas, high-grade serous ovarian carcinoma shows more diverse mechanisms leading to structural genomic instability. Starting from the most frequent source of genomic instability in breast and ovarian cancers, namely homologous recombination deficiency we are deciphering tumor genome complexity step by step by connecting patterns of structural alterations and inactivated genes.

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