Assessing genomic instability and global methylation in sporadic and hereditary triple-negative breast tumors

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Abstract:

Considerable variation in terms of genomic instability, aggressiveness and drug sensitivity is observed between or within breast tumors from different or same patients. This heterogeneity represents a big challenge for clinical treatment. Breast cancers are routinely classified according to expression of hormone receptors as well as amplification/overexpression of the gene HER2 (also known as ERBB2). Triple-negative breast cancers (TNBCs) is a subtype defined by lack of estrogen and progesterone receptors and absence of ERBB2 gene amplification/overexpression. It is associated with rapid growth, early metastasis and a poorer prognosis than other breast cancer subtypes. The presence of germline mutation in genes associated to breast cancer predisposition, such as BRCA1 and BRCA2, defines a group known as hereditary breast cancer while absence of pathogenic mutations in both genes defines mainly the group of sporadic tumors. Among the hereditary breast cancer with BRCA1 germline mutation, the TNBC subtype accounts for around 80% of cases. In a clinical aspect, TNBCs breast cancer clearly does not behave as a single entity in response to current therapies. For instance, only a subset of TNBCs shows sensitivity to the DNA double-strand break inducing drug Cisplatin or to a new drug class, the PARP inhibitors. This could be, in part, accounted to inactivation of BRCA1 by loss of function mutations or by expression silencing mediated by epigenetic mechanisms. While TNBC does show higher genomic instability and global hypermethylation relative to other breast tumor subtypes, genomic instability and methylation differences between hereditary and sporadic TNBCs is still an open question. In the present study we investigate differences in genomic instability between BRCA1-mutant TNBC, BRCA1-Wild-type TNBC and normal breast tissue, used as reference group. The genomic instability was investigated by aCHG array to identify differences in structural variations (CNVs). Additionally, a high-density array was used to assess global methylation profile in these sample groups. Our preliminary results show a tendency of hypermethylation in gene promoters and high number of CNV in BRCA1-Wild-type TNBC relative to BRCA1-mutant TNBC. Regarding intra-group heterogeneity - assessed by the ranges of CNVs and methylation measures - we show that BRCA1-Wild-type TNBC is a more heterogeneous subtype than BRCA1-mutant TNBC , while normal breast shows the highest homogeneity. Our results suggests (i) detectable signatures of clonal sweep in hereditary TNBCs and (ii) that further molecular subtyping of sporadic breast TNBC may reveal new targets to the breast cancer treatment as it remains as a heterogeneous entity in clinical and molecular aspects.