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Molecular features of the basal-like breast cancer subtype based on BRCA1 mutation status

Aleix Prat · Cristina Cruz · Katherine A. Hoadley · Orland Diez · Charles M. Perou · Judith Balmaña

Abstract BRCA1-mutated breast cancer is associated with basal-like disease; however, it is currently unclear if the presence of a BRCA1 mutation depicts a different entity within this subgroup. In this study, we compared the molecular features among basal-like tumors with and without BRCA1 mutations. Fourteen patients with BRCA1-mutated (nine germline and five somatic) tumors and basal-like disease, and 79 patients with BRCA1 non-mutated tumors and basal-like disease, were identified from the cancer genome atlas dataset. The following molecular data types were evaluated: global gene expression, selected protein and phospho-protein expression, global miRNA expression, global DNA methylation, total number of somatic mutations, TP53 and PIK3CA somatic mutations, and global DNA copy-number aberrations. For intrinsic subtype identification, we used the PAM50 subtype predictor. Within the basal-like disease, we observed minor molecular differences in terms of gene, protein, and miRNA expression, and DNA methylation variation, according to BRCA1 status (either germline or somatic). However, there were significant differences according to average number of mutations and DNA copy-number aberrations, and four amplified regions (2q32.2, 3q29, 6p22.3, and 22q12.2), which are characteristic in high-grade serous ovarian carcinomas, were observed in both germline and somatic BRCA1-mutated breast tumors. These results suggest that minor, but potentially relevant, baseline molecular features exist among basal-like tumors according to BRCA1 status. Additional studies are needed to better clarify if BRCA1 genetic status is an independent prognostic feature, and more importantly, if BRCA1 mutation status is a predictive biomarker of benefit from DNA-damaging agents among basal-like disease.

Keywords Basal-like · BRCA1 · Intrinsic subtype · Breast cancer

Abbreviations

TN Triple-negative
BRCA1 Breast cancer 1 early onset

Aleix Prat and Cristina Cruz have contributed equally to this work.

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**ID4** Inhibitor of DNA binding 4, dominant negative helix-loop-helix protein  
**PIK3CA** Phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit alpha

**Introduction**

Studies based on gene expression data have identified and characterized four main intrinsic subtypes of breast cancer (luminal A, luminal B, HER2-enriched, and basal-like) [1, 2]. Among them, the basal-like subtype is associated with young age, *BRCA1* germline and somatic mutations [1, 3, 4] and an overall poor prognosis despite that a subgroup of patients with these tumors has an excellent outcome when treated with chemotherapy [5]. In the clinical setting, basal-like tumors are usually identified by the lack of expression of hormone receptors by immunohistochemistry (IHC) and lack of overexpression of HER2 by IHC and/or FISH (the so called triple-negative [TN] status) [1, 2, 6]. Although the TN definition enriches for basal-like disease, considerable discordance exists [2, 6].

*BRCA1* mutations and other associated molecular traits might confer sensitivity to specific therapeutic agents [7–10]. Nevertheless, it is unclear how different, from a biological perspective, *BRCA1*-mutated basal-like tumors are from *BRCA1* non-mutated basal-like tumors, and whether *BRCA1* mutation is an independent prognostic and/or predictive biomarker when the intrinsic subtype is taken into account [11–15]. This line of thought directed us to formulate the question of how much the biology of basal-like tumors with *BRCA1* mutations differs from the biology of basal-like tumors without *BRCA1* mutations. To address this question, we interrogated The Cancer Genome Atlas (TCGA) breast cancer project which provides various types of molecular data coming from DNA, RNAs, and proteins [1].

**Methods**

The Cancer Genome Atlas dataset

In this study, we evaluated TCGA breast cancer dataset and all data were obtained from the TCGA breast cancer online portal (https://tcga-data.nci.nih.gov/docs/publications/brcabcrca_2012/). The following files were used. For microarray gene expression data: “BRCA.exp.547.med.txt.” For reverse-phase protein array (RPPA) expression data: “rppaData-403Samp-171Ab-Trimmed.txt.” For sequencing miRNA expression: “BRCA.780.mimat.txt.” For microarray DNA methylation variation: “BRCA.methylation.27 k.450 k.txt.” For microarray DNA copy-number aberration data: “brca_scna_all_thresholded.by_genes.txt.” For intrinsic subtype identification, we used the PAM50 subtype calls as provided in the TCGA portal.

**Independent dataset**

We evaluated an independent and publicly available microarray-based gene expression dataset (GSE40115) that includes breast tumors from 32 patients with basal-like disease (20 with *BRCA1* germline mutations and 12 with sporadic tumors [i.e. unknown *BRCA1* status]). The file “GSE40115-GPL15931_series_matrix.txt” with the normalized log2 ratios (Cy5 sample/Cy3 control) of probes was used. Probes mapping to the same gene (Entrez ID as defined by the manufacturer) were averaged to generate independent expression estimates.

**Seven-TN subtype classification**

To identify the 7-TN subtypes described by Lehmann et al. [16], (i.e., basal one, basal two, immunomodulatory, luminal androgen receptor, mesenchymal, mesenchymal stem cell, and unstable), we submitted the raw gene expression data of each individual dataset of basal-like disease to the TNBC type online predictor (http://cbc.mc.vanderbilt.edu/tnbc/) [17].

**Statistical analysis**

All multiple-testing comparisons were done using an unpaired two-class significance analysis of microarrays (SAM, http://www-stat.stanford.edu/~tibs/SAM/). The mutation rates of *TP53* and *PIK3CA* genes between two groups, the 7-TN subtype distribution between *BRCA1*-mutated and non-mutated basal-like tumors, and the amplification rates of *ID4* between two groups, were compared using the Chi square and Fisher’s exact tests. The total number of somatic mutations between two groups was compared using a Student’s t test. All statistical computations were performed in R v.2.15.1 (http://cran.r-project.org).

**Results and discussion**

From TCGA breast cancer dataset, we identified 12 tumor samples with *BRCA1* germline mutations (all classified as deleterious), seven tumor samples with somatic *BRCA1* mutations, and one tumor sample with both *BRCA1* germline and somatic mutations (Supplemental Material). As expected, 70 % of *BRCA1* mutated tumors where of the basal-like intrinsic subtype (nine germline and five
somatic), but luminal A (two germline, one germline/somatic, and one somatic), luminal B (one germline), and HER2-enriched (one somatic) tumors were also identified (Fig. 1). Similarly, 66.7% of BRCA1 mutated tumors were TN.

Within basal-like disease, we observed minor molecular differences (0–1.1%) in terms of gene expression, protein expression, miRNA expression, and DNA methylation variation according to BRCA1 status (Table 1 and Supplementary Material). Indeed, no genes among 17,876 genes were found differentially expressed between basal-like BRCA1-mutated tumors versus basal-like BRCA1 non-mutated tumors (Table 1), including the BRCA1 mRNA transcript (Fig. 2). Similar results were observed when only the tumors with BRCA1 germline mutations were taken into consideration (Supplemental Material). Concordant with this result, analysis of microarray gene expression data of an independent dataset of 32 tumors with basal-like disease (20 with a BRCA1 germline mutation and 12 with sporadic tumors) revealed only 0.03% differentially expressed genes (6 of 21,848, false discovery rate

**Table 1** Significant molecular differences between basal-like BRCA1-mutated tumors \((n = 14)\) and basal-like BRCA1 non-mutated tumors \((n = 79)\)

| Total biomarkers evaluated | Type of evaluation | Comparison (more expressed or amplified) | Significant biomarkers identified (FDR = 0%) | Percentage of altered biomarkers (%) |
|---------------------------|--------------------|------------------------------------------|---------------------------------------------|-------------------------------------|
| 17,786 (unique genes)     | Expression         | BRCA1MUT                                 | 0                                           | 0                                   |
|                           |                    | BRCA1WT                                  | 0                                           |                                     |
| 171 (unique proteins or phospho-proteins by RPPA) | Expression | BRCA1MUT                                 | 0                                           | 0.6                                 |
|                           |                    | BRCA1WT                                  | 1                                           |                                     |
| 1,222 (mature/star miRNA strands) | Expression | BRCA1MUT                                 | 3                                           | 0.2                                 |
|                           |                    | BRCA1WT                                  | 0                                           |                                     |
| 530 (unique genes)        | Methylation        | BRCA1MUT                                 | 0                                           | 1.1                                 |
|                           |                    | BRCA1WT                                  | 6                                           |                                     |
| 19,613 (unique genes)     | DNA amplification  | BRCA1MUT                                 | 250                                         | 1.3                                 |
|                           |                    | BRCA1WT                                  | 0                                           |                                     |

**Fig. 1** Intrinsic profile of BRCA1-mutated breast tumors. Hierarchical clustering of 509 breast samples of the cancer genome atlas (TCGA) project using the ~1,900 intrinsic gene list [30]. PAM50 intrinsic subtype calls [30] and BRCA1 mutation status is shown below the array tree

**Fig. 2** Relative BRCA1 gene expression in basal-like disease based on BRCA1 mutational status. Data have been obtained from the TCGA breast cancer project. The BRCA1 gene expression has been median centered across all breast cancer samples with DNA-seq data (i.e., basal-like and not basal-like). The p-value was calculated by comparing gene expression means across the three groups. In red color, breast samples with ≥2-fold decrease in BRCA1 expression compared to its median expression in breast cancer are shown.
[FDR] = 0 % between the two groups [18] (Supplemental Material). In addition, we did not identify significant differences in the proportion of the recently reported 7-TN subtype classification proposed by Lehmann and colleagues [16], between basal-like tumors with and without BRCA1 mutations (Supplemental Material). Interestingly, two clear groups within the basal-like BRCA1 wild-type disease were identified based on BRCA1 mRNA expression-only (i.e., high and low) (Fig. 2).

In terms of DNA copy-number aberrations, we identified 250 genes (representing 14 different DNA regions and 1.3 % of all genes evaluated) showing higher amplification rates in basal-like BRCA1-mutated tumors compared to basal-like BRCA1 wild-type tumors (Table 2).
them, we identified four regions (2q32.2, 3q29, 6p22.3, and 22q11.2) that have been previously shown to be amplified and characteristic of high-grade serous ovarian carcinomas [19]. Interestingly, region 6p22.3 contains ID4, a gene long known to be a marker of basal-like breast cancers [20], and known to code for a DNA-binding protein that negatively regulates BRCA1 expression in breast and ovarian cancers [21]. This gene was found amplified (i.e. low or high gains) in 78.6 % (11/14) of basal-like BRCA1 mutated tumors versus 35.1 % (26/74) of basal-like BRCA1 wild-type tumors ($p = 0.008$, Fisher’s exact test). Similar results were observed when the BRCA1 somatic mutations were excluded (Supplemental Material). The biological role of ID4 amplification in BRCA1 mutated breast cancer is currently unknown, and we could hypothesize that ID4 might inhibit residual function of mutant BRCA1.

In terms of somatic gene mutations, basal-like BRCA1 mutated tumors showed higher average number of mutations than basal-like BRCA1 wild-type tumors (122.6 vs. 80.3, $p = 0.004$, Student’s t test). Regarding the distribution of TP53 and PIK3CA somatic mutations according to BRCA1 status, TP53 mutations were found in 100 % (14/14) of basal-like BRCA1 mutated tumors versus 75.9 % (60/79) of basal-like BRCA1 wild-type tumors ($p = 0.065$, Fisher’s exact test). Finally, PIK3CA mutations were found in 0 % (0/14) of basal-like BRCA1 mutated tumors versus 10.1 % (8/79) of basal-like BRCA1 wild-type tumors ($p = 0.602$).

In our analysis, most of the unique molecular features of basal-like BRCA1 mutated tumors were found at the DNA level (i.e. amplifications and mutation rates). Indeed, basal-like BRCA1 mutated tumors showed higher amplification rates at 14 different chromosomal regions and higher number of somatic mutations, including TP53, compared to basal-like BRCA1 wild-type tumors. However, no significant differences in protein expression were found when comparing basal-like BRCA1 mutated and BRCA1 wild-type tumors. These results suggest that the genomic instability induced by BRCA1 loss [22] does not translate into a recognizable phenotype at the RNA and protein level. The potential explanation of these findings is currently unknown. Nonetheless, the fact that 4 out of 14 (28.5 %) amplified DNA regions were found to be characteristic regions of high-grade serous ovarian carcinomas suggests that, among basal-like breast tumors, those with a BRCA1 mutation are more similar to ovarian carcinoma at the genetic level.

In our analysis, the absence of recognizable prominent differences in molecular alterations based on BRCA1 mutation status would be in line with previous clinical data suggesting that BRCA1 status per se might not play a major role in conferring a distinct prognosis within basal-like disease. Results from three retrospective studies that have evaluated the prognostic role of BRCA1/2 mutations (mostly BRCA1) in TN breast cancer support this hypothesis [13–15]. In Bayraktar et al. [13], BRCA1/2 status was not found to be prognostic in 227 women with early TN breast cancer referred to genetic counseling. Similar results were observed in a cohort of 195 patients with metastatic breast cancer, where the independent prognostic value of BRCA1 in univariate analyses was lost when TN status and other clinical-pathological variables were taken into account [14]. More recently, Huzarski et al. [15] evaluated the association of germline BRCA1 mutation status with 10 year overall survival in 3,350 polish women with a diagnosis of breast cancer. The authors observed that BRCA1 mutation status was significantly associated with worse outcome when standard clinical-pathological variables were taken into account [15]. However, among patients with TN breast cancer, BRCA1 status was not associated with worse outcome [15].

The role of the BRCA1 mutation status as a predictive factor of treatment response among TN breast cancer is also under study. On the one hand, two retrospective studies have evaluated the ability of BRCA1 mutation status to predict response to multi-agent chemotherapy [11, 12]. In the first study, Arun and colleagues showed no significant differences in terms of pathological complete response rates after neoadjuvant chemotherapy (mostly anthracycline/taxane-based) among 75 patients with TN breast cancer in relation to their BRCA1 status [11]. In the second study, Gonzalez-Angulo et al. [12] observed a better outcome in BRCA1/2 mutated TN breast cancer compared to BRCA1/2 non-mutated TN breast cancers after treatment with adjuvant anthracycline/taxane-based chemotherapy. On the other hand, two recent prospective clinical trials (GeparSixto [23] and CALGB40603 [24]) have demonstrated the value of adding carboplatin, a DNA-damaging agent, to standard neoadjuvant anthracycline/taxane-based chemotherapy in 769 patients with newly diagnosed TN breast cancer, regardless of their BRCA1 mutational status.

Previous retrospective studies have suggested that BRCA1 mutated tumors might substantially benefit from platinum [9, 25]. In fact, in the GeparSixto TN trial [23, 26], recent data reported higher pCR rates in BRCA1/2-mutated patients compared to BRCA1/2 non-mutated patients. Nevertheless, data on the intrinsic subtype of the TN wild-type tumors in this clinical trial have not been reported yet and it might be interesting to analyze whether the basal-like benefits the most. Supporting the hypothesis that basal-like BRCA1 non-mutated breast cancers might also benefit to some extent from DNA-damaging agents, several studies have identified BRCA1 mutation-unrelated mechanisms of platinum sensitivity in TN BRCA1 wild-type breast cancer such as the p63/p73 network, telomeric...
allelic imbalance, and homologous recombination deficiency [27–29].

Conclusions

In this study, we compared DNA, RNA, and protein data among basal-like tumors with and without BRCA1 mutations and observed that minor molecular features exist. The clinical relevance of these differences is unknown and further validation in larger and prospective cohorts is warranted. Biomarker analyses are needed to clarify if BRCA1 status is an independent prognostic feature and/or a predictive biomarker of benefit from DNA-damaging agents beyond the basal-like phenotype.

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Conflict of interest

C.M.P. is an equity stock holder, and Board of Director Member, of BioClassifier LLC and University Genomics. C.M.P. is also listed an inventor on a patent application on the PAM50 molecular assay. Uncompensated advisory role of A.P. for Nanostring Technologies.

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