Low TCEAL3 expression distinguishes basal-like human breast cancer.

Shahan Mamoor, MS¹

¹shahanmamoor@gmail.com

East Islip, NY 11730

Patients diagnosed with basal-like breast cancer face a more aggressive disease course and more dismal prognosis than patients diagnosed with luminal A and luminal B breast cancer molecular subtypes (1-4). We mined published microarray data (5, 6) to understand in an unbiased fashion the most distinguishing transcriptional features of tumors from patients with basal or basal-like subtype breast cancer. We observed transcriptome-wide differential expression of transcription elongation factor A-like 3, TCEAL3, when comparing tumors of patients with basal-like breast cancer with that of other PAM50 molecular subtypes. TCEAL3 mRNA was present at significantly lower quantities in the tumors of patients with basal-like breast cancer. Low TCEAL3 expression appears to distinguish basal-like human breast cancer from the other molecular subtypes.

Keywords: basal subtype, basal-like breast cancer, TCEAL3, systems biology of breast cancer, targeted therapeutics in breast cancer, molecular subtype

Classification of disease types and disease subtypes enables development of enhanced diagnostic capabilities, acquisition of prognostic information, as well as an understanding of human disease that can support superior medical, surgical and radiological treatment of complex diseases such as cancer. Molecular subtypes in human breast cancer include luminal A, luminal B, basal or basal-like, and HER2+. Systems-level analyses, such as comparative tumor transcriptome analyses, can inform such approaches. We mined published microarray data (5, 6) to identify the most significant transcriptional differences when comparing human breast cancer molecular subtypes. Integrative microarray dataset analysis has provided data illuminating genes whose expression define basal-like subtype breast cancers, and we present evidence here.

Methods

We utilized datasets GSE74667 (5) and GSE87049 (6) for this global differential gene expression analysis of basal subtype human breast cancer in conjunction with GEO2R. GSE74667 was generated using Agilent-014850 Whole Human Genome Microarray 4x44K G4112F technology with $n=23$ basal-like breast tumors and $n=72$ breast tumors of other molecular subtypes (luminal A, luminal B, HER2-enriched, and normal-like); analysis was performed using platform GPL6480. GSE87049 was generated using Affymetrix Human Gene 1.0 ST Array [transcript (gene) version] technology with $n=14$ basal-like breast tumors and $n=109$ breast tumors of other molecular subtypes (luminal A, luminal B, HER2-enriched, and normal-like); analysis was performed using platform GPL6244. The Benjamini and Hochberg method of p -value adjustment was used for ranking of differential expression but raw p -values were used to assess statistical significance of global differential expression. Log-transformation of data was auto-detected, and the NCBI generated category of platform annotation was used. A statistical test was performed to evaluate whether TCEAL3 gene expression was significantly different between the tumors of patients with basal and non-basal molecular subtype breast cancer using a two-tailed t-test with Welch's correction (PRISM 9.1.1 (225)).

Results

TCEAL3 is among the genes whose expression is most different when comparing basal-like breast cancers with breast cancers of other molecular subtypes.

We used published microarray data (5) to compare the whole tumor transcriptomes of 23 patients with basal subtype breast cancer and 72 patients with breast cancer of other molecular subtypes (luminal A, luminal B, HER2+ and normal-like) to identify genes whose expression marked the basal-like molecular subtype. We observed transcriptome-wide differential expression of transcription elongation factor A-like 3, TCEAL3, when comparing the tumors of patients with basal-like cancer with that of patients with luminal A, luminal B and HER2+ cancers (Table 1). When sorting each of the transcripts whose expression was measured globally, TCEAL3 expression ranked 198 out of 31157 total transcripts, equating to 99.4% differential expression; this was statistically significant (p -value: $3.27E-09$).

Analysis of a second published microarray dataset, comparing tumor transcriptome data from a separate cohort of patients (14 patients with basal-like breast cancer and 109 patients with breast cancer of other molecular subtype (luminal A, luminal B, HER2+ and normal-like) (5) revealed transcriptome-wide differential expression of TCEAL3 in patients with basal subtype human breast cancer (Table 2). When sorting each of the transcripts whose expression was measured globally, TCEAL3 expression ranked 3659 out of 33297 total transcripts, equating to 89.0% differential expression; this was statistically significant (p -value: $4.94E-04$). Thus, the data suggested differential expression of TCEAL3 was a fundamental feature of basal-like breast cancer in humans rather than an artifact of a single microarray dataset or research group, or a finding derived from cell culture or an animal model that was not relevant to human

breast cancer.

TCEAL3 expression is significantly lower in basal-like breast cancers.

We obtained exact TCEAL3 mRNA expression data for basal-like breast tumors and tumors from other molecular subtypes (luminal A, luminal B, HER2+ and normal-like) to determine magnitude and direction of TCEAL3 gene expression change in basal-like breast cancer. TCEAL3 was expressed at lower levels in the tumors of patients with basal-like breast cancer as compared to the tumors of patients from other PAM50 molecular subtypes, and this difference was statistically significant (Figure 1; $p < 0.0001$). TCEAL3 was expressed at 0.234 ± 0.893 arbitrary units (A.U.) in basal-like breast cancer and 1.532 ± 0.826 A.U. in all other molecular subtypes (Figure 1).

Discussion

We find here that TCEAL3 is among the genes whose expression is most different when comparing basal-like breast cancers (BLBC) to cancers of other molecular subtypes, with significantly more TCEAL3 mRNA in BLBC. TCEAL3 may be one factor that specifies or reflects tumor subtype identity in basal-like breast cancer.

References

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Rank: 198
probe ID: A_23_P434442
p-value: 3.27E-09
t: -6.5
B: 10.79909
Gene: TCEAL3
Gene name: transcription elongation factor A-like 3

Table 1: TCEAL3 is among the genes whose expression is most different, across the transcriptome, when comparing basal-like breast cancers with luminal A, luminal B, and HER2+ and normal-like breast cancers.

The rank of global differential expression, probe ID, the *p*-value with respect to differential expression transcriptome-wide, *t*, a moderated *t*-statistic, and *B*, the log-odds of differential expression between the groups compared are listed in this chart.

Rank: 3659
probe ID: 8169044
 p -value: 4.94E-04
 t : -3.5779337
 B : -0.66973
Gene: TCEAL3
Gene name: transcription elongation factor A-like 3

Table 2: In a separate cohort of patients with basal subtype breast cancer, TCEAL3 is again among the genes most differentially expressed transcriptome-wide when compared to the tumors of patients with breast cancer of other molecular subtypes: luminal A, luminal B, and HER2+ and normal-like.

The rank of global differential expression, probe/transcript ID, the p -value with respect to differential expression transcriptome-wide, t , a moderated t -statistic, B , the log-odds of differential expression between the groups compared, the gene and gene name are listed in this chart.

Figure 1: TCEAL3 expression is significantly lower in basal-like breast cancers.

Depicted is mRNA expression of TCEAL3 in tumors from patients with basal-like breast cancer (left) and from patients with cancer of all other molecular subtypes (luminal A, luminal B, HER2+ and normal-like) (right). The horizontal bar corresponds to the mean value, and the result of a statistical test evaluating the significance of difference in expression between the two groups compared, a *p*-value, is listed above.