ADAM15 expression associates with survival in triple negative breast cancer.

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We mined published microarray data (1) to understand the most significant gene expression differences in the tumors of triple negative breast cancer patients based on survival following treatment: dead or alive. We observed significant transcriptome-wide differential expression of ADAM metalloproteinase domain 15, encoded by ADAM15 when comparing the primary tumors of triple negative breast cancer patients dead or alive. ADAM15 may be of relevance as a biomarker or as a molecule of interest in understanding the etiology or progression of triple negative breast cancer.

Keywords: triple negative breast cancer, TNBC, systems biology of breast cancer, targeted therapeutics in breast cancer, ADAM15, ADAM metalloproteinase domain 15.

Triple negative breast cancer is defined by lack of expression of the receptors for the hormones progesterone and estrogen (PR negative and ER negative), as well as for the human epidermal growth factor receptor 2 (HER2 negative) (2, 3). Though not completely identical, triple negative breast cancer shares significant overlap with the basal or basal-like molecular subtype of human breast cancer (3). TNBC is more frequently diagnosed in women of African descent (black women) for reasons not understood, and their disease course is similarly more aggressive than in white women with triple negative breast cancer (2, 3). To understand the transcriptional biology of triple negative breast cancer in an unbiased fashion and at the systems level, we mined published microarray data paired with patient survival data (1), performing comparative transcriptome analysis based on survival at time of data collection: dead or alive. We present here a finding from the results of this analysis.

Methods

We used dataset GSE142102 (1) for this differential gene expression analysis in conjunction with GEO2R. GSE142102 was generated using Affymetrix Human Gene 2.1 ST Array technology; in this analysis, we used data from $n=87$ tumors from TNBC patients that were dead at time of analysis and $n=123$ tumors from TNBC patients that were alive at time of analysis. 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 ADAM15 expression was significantly different between the primary tumors of TNBC patients that were dead or alive using a two-tailed t-test.

Results

We performed comparative transcriptome analysis using published microarray data (1) to understand in an unbiased fashion the most significant gene expression differences in the primary tumors of patients with triple negative breast cancer based on survival outcomes.

ADAM15 is differentially expressed in triple negative breast cancer and negatively correlates with survival.

When comparing primary tumors of 87 live patients with triple negative breast cancer with that of 123 dead TNBC patients we identified ADAM metalloproteinase domain 15, *ADAM15*, as among the most significant transcriptional differences based on survival in human triple negative breast cancer. When ranking each of the transcripts whose expression was measured by microarray based on significance of difference in expression between the tumors of patients dead and alive, ADAM15 ranked 234 out of 53617 total transcripts, equivalent to 99.6% differential expression (Chart 1). ADAM15 differential expression in the tumors of patients based on survival outcomes was statistically significant (Figure 1; $p=0.0056988$).

ADAM15 is expressed at significantly lower levels in the breast tumors of TNBC patients when comparing based on survival.

We obtained exact mRNA expression levels for ADAM15 from breast tumors of TNBC patients dead and alive to understand the magnitude and direction of ADAM15 expression change based on survival outcomes. ADAM15 was expressed at lower levels in tumors of TNBC patients alive as compared to that of TNBC patients dead (Figure 1). Decreased expression of ADAM15 in primary breast

tumors was statistically significant (Figure 1: $p=0.0069$). ADAM15 was expressed at 0.24 ± 1.05 arbitrary units (AU) in the primary tumors of TNBC patients alive, while it was expressed at -0.14 ± 0.95 AU in the primary tumors of TNBC patients dead.

Thus, we found through unbiased comparative transcriptome analysis that ADAM15 was among the genes whose expression was most significantly different in the primary tumors of triple negative breast cancer patients alive when compared to that of TNBC patients dead, and that ADAM15 was expressed at significantly lower levels in the primary tumors of TNBC patients alive as compared to TNBC patients dead.

Discussion

It is not understood why women of African descent (black women) are diagnosed with triple negative breast cancer more frequently than white women, and why this disease is more aggressive in black women. ADAM15 may be involved in neovascularization in mammals and has been described as over-expressed and associated with aggressive disease in both cancer of the prostate and the breast. ADAM15 may be of relevance as a biomarker in identifying patients who are more likely to survive, perhaps as part of a panel of genes used for prognostic stratification, and the molecule itself may be important to the biology of triple negative breast cancer etiology or more likely its progression. Blind systems-level analyses, like this, can help shed light on the fundamental molecular characteristics of a disease whose racial propensities demand further explanation.

References

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Rank: 234
Probe ID: 16671579
p-value: 0.0056988
t: 2.764627
B: -3.51
Gene: ADAM15
Gene name: ADAM metalloproteinase domain 15

Chart 1: ADAM15 is differentially expressed at the transcriptome-level when comparing the primary tumors of TNBC patients dead and alive.

Rank of differential expression, probe ID, *p*-value of global differential expression, *t*, a moderated *t*-statistic, *B*, the log-odds of differential expression between the groups compared, gene and gene name are listed in this chart.

Figure 1: ADAM15 is expressed at significantly lower levels in the primary tumors of TNBC patients alive as compared to the primary tumors of TNBC patients dead.

The mRNA expression level of ADAM15 in the primary tumors of TNBC patients dead (left) and in primary tumors of TNBC patients alive (right) is graphically depicted with the result of a statistical test evaluating significance of difference in ADAM15 expression between the primary tumors of TNBC patients dead and alive, a p -value, listed here: $p=0.0069$.