OR6C76 expression associates with survival in triple negative breast cancer.

Shahan Mamoor, MS¹

¹shahanmamoor@gmail.com

East Islip, NY USA

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 olfactory receptor, family 6, subfamily C, member 76, encoded by OR6C76 when comparing the primary tumors of triple negative breast cancer patients dead or alive. OR6C76 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, OR6C76, olfactory receptor, family 6, subfamily C, member 76.

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 OR6C76 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.

OR6C76 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 olfactory receptor, family 6, subfamily C, member 76, *OR6C76*, 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, *OR6C76* ranked 15 out of 53617 total transcripts, equivalent to 99.97% differential expression (Chart 1). *OR6C76* differential expression in the tumors of patients based on survival outcomes was statistically significant (Figure 1; $p=0.00028098$).

OR6C76 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 *OR6C76* from breast tumors of TNBC patients dead and alive to understand the magnitude and direction of *OR6C76* expression change based on survival outcomes. *OR6C76* was expressed at lower levels in tumors of TNBC patients alive as compared to that of TNBC patients dead (Figure 1). Decreased expression of *OR6C76* in primary breast tumors was

1 statistically significant (Figure 1: $p=0.0007$). OR6C76 was expressed at 0.28 ± 1.18 arbitrary units (AU)
2 in the primary tumors of TNBC patients dead, while it was expressed at -0.22 ± 0.82 AU in the primary
3 tumors of TNBC patients alive.

4 Thus, we found through unbiased comparative transcriptome analysis that OR6C76 was among the
5 genes whose expression was most significantly different in the primary tumors of triple negative breast
6 cancer patients alive when compared to that of TNBC patients dead, and that OR6C76 was expressed at
significantly lower levels in the primary tumors of TNBC patients alive as compared to TNBC patients
dead.

7 **Discussion**

8 It is not understood why women of African descent (black women) are diagnosed with triple
9 negative breast cancer more frequently than white women, and why this disease is more aggressive in
10 black women. OR6C76 may be of relevance as a biomarker in identifying patients who are more likely to
11 survive, perhaps as part of a panel of genes used for prognostic stratification, and the molecule itself may
12 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

1. Purrington, K.S., Knight III, J., Dyson, G., Ali-Fehmi, R., Schwartz, A.G., Boerner, J.L. and Bandyopadhyay, S., 2020. CLCA2 expression is associated with survival among African American women with triple negative breast cancer. *PloS one*, 15(4), p.e0231712.
2. Foulkes, W.D., Smith, I.E. and Reis-Filho, J.S., 2010. Triple-negative breast cancer. *New England journal of medicine*, 363(20), pp.1938-1948.
3. Dietze, E.C., Sistrunk, C., Miranda-Carboni, G., O'regan, R. and Seewaldt, V.L., 2015. Triple-negative breast cancer in African-American women: disparities versus biology. *Nature Reviews Cancer*, 15(4), pp.248-254.

Rank: 15
Probe ID: 16752172
p-value: 0.00028098
t: 3.6322353
B: -2.56
Gene: OR6C76
Gene name: olfactory receptor, family 6, subfamily C, member 76

Chart 1: OR6C76 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: OR6C76 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 OR6C76 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 OR6C76 expression between the primary tumors of TNBC patients dead and alive, a p -value, listed here: $p=0.0007$.