The 17 β -hydroxysteroid dehydrogenase type 4, HSD17B4, is differentially expressed in brain metastatic breast cancer.

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One study reported the incidence of central nervous system metastases in breast cancer patients treated with trastuzumab as 34%¹. We mined published microarray data^{2,3} to discover genes associated with brain metastasis in breast cancer. We identified significant differential expression of the 17 β -hydroxysteroid dehydrogenase type 4, HSD17B4⁴⁻⁶, in patients with breast cancer. HSD17B4 may be relevant to the biology underlying colonization of the brain with metastatic breast cancer clones.

Keyword: breast cancer, metastasis, brain metastasis, central nervous system metastasis, HSD17B4, systems biology of breast cancer, targeted therapeutics in breast cancer.

One study reported a 34% incidence of central nervous system metastases in patients with breast cancer treated with the monoclonal antibody trastuzumab (Herceptin)¹. Treatment options for patients with brain metastatic breast cancer are limited⁸. We mined published microarray datasets²⁻³ to understand in an unbiased and systems-level fashion genes whose expression most significantly distinguished brain metastases from primary tumors of the breast, the cells from which these metastatic clones are presumably derived. We found significant differential expression of HSD17B4 in the brain metastases of patients with brain metastatic breast cancer.

Methods

We utilized microarray datasets GSE43837² and GSE100534³ and for this differential gene expression analysis of brain metastatic breast cancer in conjunction with GEO2R. GSE43837 was generated using Affymetrix Human X3P Array technology with $n=19$ primary breast tumors and $n=19$ brain metastases from patients with breast cancer, analysis performed using platform GPL1352. GSE100534 was generated using Affymetrix Human Gene 1.0 ST Array technology with $n=16$ primary tumors from patients with breast cancer and $n=3$ brain metastases from patients with brain metastatic breast cancer. 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 HSD17B4 gene expression was significantly between primary breast tumors and brain metastases in humans with breast cancer using a two-tailed, unpaired t-test with Welch's correction. We used PRISM for all statistical analyses of differential gene expression in human breast cancer (Version 8.4.0)(455).

Results

We mined published microarray data^{2,3} to discover genes associated with brain metastasis in breast cancer.

HSD17B4 is differentially expressed in brain metastatic breast cancer.

We identified the 17 β -hydroxysteroid dehydrogenase type 4, HSD17B4, as the single most differentially expressed gene transcriptome-wide when comparing brain metastases to primary tumors of the breast in patients with brain metastatic breast cancer² (Table 1). When sorting each of the genes expressed in brain metastases based on significance of change as compared to primary tumors of the breast, HSD17B4 ranked 1 out of 61359 total transcripts (Table 1), equating to 99.998% differential expression. Differential expression of HSD17B4 in brain metastases in brain metastatic breast cancer was statistically significant (Table 1; $p=0.00000327$).

We queried a second microarray dataset³ to validate transcriptome-wide differential expression of HSD17B4 in brain metastatic breast cancer. We again found that HSD17B4 was among the genes whose expression changed most significantly when comparing metastases of the brain to primary tumors of the breast in patients with breast cancer (Table 2). When sorting each of the genes expressed in brain metastases based on significance of change as compared to primary tumors of the breast, HSD17B4 ranked 3075 out of 33297 total transcripts (Table 2), equating to 90.8% differential expression. Differential expression of HSD17B4 in brain metastases in brain metastatic breast cancer was statistically significant (Table 2; $p=4.67E-03$).

HSD17B4 is expressed at significantly lower levels in brain metastases as compared to primary tumors of the breast in brain metastatic breast cancer.

We obtained exact mRNA expression values for HSD17B4 from brain metastases and primary tumors of the breast to evaluate magnitude and direction of change in HSD17B4 expression in brain metastases in patients with breast cancer. HSD17B4 was expressed at lower levels in brain metastases in patients with breast cancer and this difference was statistically significant (Figure 1; $p=0.0136$). We calculated a mean fold change of 0.17 ± 0.17 in HSD17B4 expression when comparing brain metastatic tissues to primary tumors of the breast (Table 1).

Thus, we found that HSD17B4 was among the genes, globally, whose expression was most different when comparing primary tumors of the breast to brain metastases in patients with breast cancer, with significantly decreased expressed of HSD17B4 in the brain metastases of patients with metastatic breast cancer as compared to primary tumors of the breast.

Discussion

An enhanced understanding of brain metastases can facilitate development of novel therapeutic strategies. We identified the 17 β -hydroxysteroid dehydrogenase type 4, HSD17B4, as among the genes most differentially expressed in brain metastases when compared to primary tumors of the breast in patients with breast cancer. As we observed significant reduction in HSD17B4 mRNA levels in the brain metastases of patients with metastatic breast cancer as compared to primary tumors of the breast, future studies can address if and how down-regulation of the metabolic functions of HSD17B4 favor metastasis to the brain in patients with metastatic breast cancer.

References

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Rank	ID	p-value	t	B	FC	Gene	Gene name
1	Hs2.356894.1.S1_3p_at	0.00000327	-5.3459707	3.72582	0.17 ± 0.17	HSD17B4	hydroxysteroid 17-beta dehydrogenase 4

Table 1: HSD17B4 is differentially expressed in brain metastatic breast cancer.

Rank of differential expression, probe ID, *p*-value with respect to differential expression, *t*, a moderated *t*-statistic, *B*, the log-odds of differential expression between the two groups compared, fold change (FC) of HSD17B4 expression between the brain metastases of patients with breast cancer and primary tumors of the breast, gene and gene name are listed in this chart.

Rank	ID	p-value	t	B	Gene	Gene name
3075	8107532	4.67E-03	-3.1822063	-2.293915	HSD17B4	hydroxysteroid 17-beta dehydrogenase 4

Table 2: HSD17B4 is differentially expressed in brain metastatic breast cancer.

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

Figure 1: HSD17B4 is expressed at significantly lower levels in brain metastases as compared to primary tumors of the breast in patients with brain metastatic breast cancer.

The mRNA expression level of HSD17B4 in primary tumors of the breast (left) and in the brain metastases of brain metastatic breast cancer patients (right) is graphically represented here with mean HSD17B4 levels marked and the result of a statistical test evaluating difference in mRNA expression level between brain metastases and primary tumors of the breast, a *p*-value, listed above. The Y-axis is displayed in natural logarithm (ln).