

The metastatic profile of breast cancer stem cells and circulating tumor cells

Das metastatische Profil von Brustkrebs Stammzellen und zirkulierende Tumorzellen

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Introduction: Breast cancer is the most frequent type of cancer in women. Even though great progress has been made in treatment, resistance to chemotherapy and metastasis are still major problems. The study of cancer stem cells (CSCs) and circulating tumor cells (CTCs) could help to understand the above mechanisms, as both cells are implicated on the above. The present study aims to identify the gene expression of genes correlated with metastasis in specific organs in breast CSCs and CTCs.

Materials & Methods: Human established breast cancer stems cells (provided by CelProgen), as well as breast CSCs and CTCs derived from six different patients suffered from breast cancer have been used. RNA was extracted from each cell line and whole genome gene expression microarrays have been performed. The data were normalized according to a normal (non-cancerous) sample. The array data were then evaluated with qPCR by using specific primers. The relative quantification was performed according to Livak method, by using 18SrRNA as housekeeping gene

Results: There was observed an over-expression in all breast CSCs for integrins, while the TGFb-R2 was over-expressed in all CTCs. On the other hand, an under-expression was noticed for all genes correlated with brain metastasis in CSCs, but CX3CR1 and STAT3 were over-expressed in CTCs. The gene expression of HGFR was higher for all CSCs and was under-expressed in the majority of CTCs. All the data are presented in table 1.

Metastasis location	Marker	Breast CSCs	Patient-1 CSCs	Patient-2 CSCs	Patient-1 CTCs	Patient-2 CTCs	Patient-3 CTCs	Patient-4 CTCs
General	TGF-β R2	↓	↓	↓	↑	↑	↑	↑
	ITGB-4 R	↑	↑	↑	N/E	N/E	↓	↓
	ITGB-5 R	↑	↑	↑	↑	↓	↓	↓
	ITGB-6 R	↑	↑	↑	N/E	N/E	N/E	N/E
Pleura	CCR6	N/E	↑	↑	↓	↓	N/E	↓
	MSLN	↑	↓	↑	N/E	N/E	N/E	N/E
Skin	CCR7	↓	↓	↑	↓	↓	↓	↓
Lung	IGF-R2	↑	↓	-	↓	N/E	↓	↓
	ERK1	↑	↑	↑	↑	N/E	↑	↑
	ERK2	↓	↓	↓	↑	↑	↑	-
Bone	BMPR1A	-	↑	↑	N/E	N/E	N/E	N/E
	BMPR1B	↑	↓	↑	N/E	N/E	N/E	N/E
	BMPR2	↑	↓	↓	N/E	N/E	N/E	N/E
	CXCR4	↑	↓	↓	↓	↓	-	-
	RANK	↓	↓	↑	↓	N/E	↓	↓
Liver	BST-2	↑	↑	↑	↑	↓	↑	-
	CXCR4	↑	↓	↓	↓	↓	-	-
	TRAIL-R2	↓	↓	↓	↓	↑	↓	↓
	FAS R	↓	↓	↓	N/E	N/E	N/E	N/E
Brain	HGFR	↑	↑	↑	↓	↑	↓	↓
	STAT-3	↓	↓	↓	↓	↑	↑	↓
	CX3CR1	↓	↓	↓	↑	↑	↑	↑
	DSC-2	↓	↓	↓	↓	↓	↓	↓

Table 1: Gene expression analysis.

↓: under-expression ; ↑: over-expression;
N/E: Not Expressed; -: No change

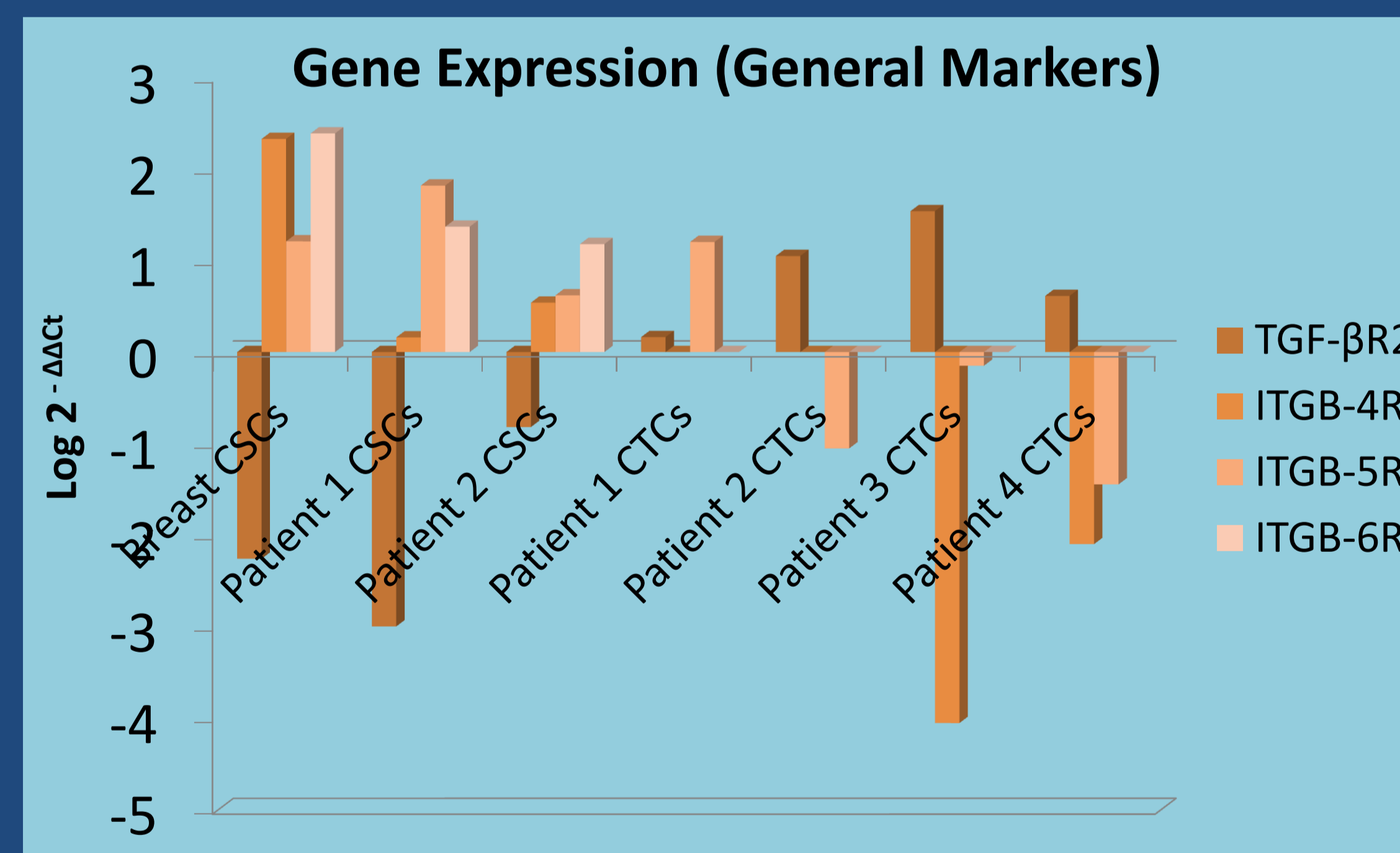


Figure 1: Gene expression of markers correlated with general metastasis

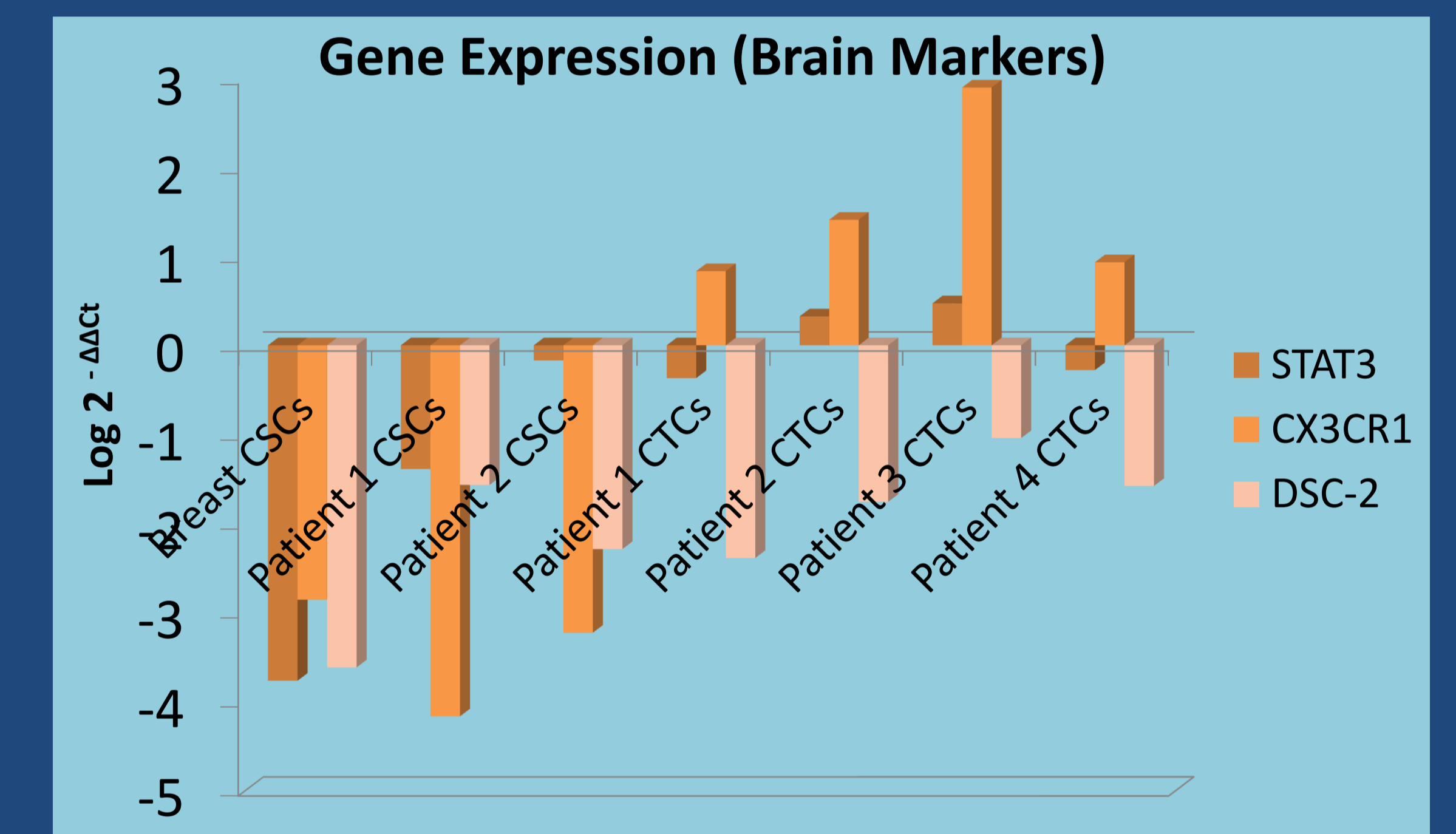


Figure 2: Gene expression of markers correlated with brain metastasis

Conclusion: Taking everything into consideration, it is demonstrated that the gene expression profile of CTCs differs from that of CSCs. The above may explain the response to second or third lines of therapies, which observed in clinical reality. However, the metastases to the brain might be refractory due to CSCs.

Selected References:

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- Baccelli, I., A. Schneeweiss, et al. (2013). "Identification of a population of blood circulating tumor cells from breast cancer patients that initiates metastasis in a xenograft assay." *Nat Biotechnol* 31(6): 539-544.

Disclosure of Potential Conflicts of Interest

None of the authors of the above study has declared any conflict of interest