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Specific expression profile of genes associated with extracellular matrix and phenotypic plasticity in triple-negative breast cancer

Mikhail Karpushin (carpushin.misha@yandex.ru) * [1], Nikita Shelepin (kiwi0tails@gmail.com) [2], Elena Komarova (lenakom2904@mail.ru) [1], Irina Balalaeva (irin-b@mail.ru) [1]

1 Department of Biophysics, Institute of Biology and Biomedicine, Lobachevsky University Gagarina Ave. 23, Nizhny Novgorod, 603950 Russian Federation
2 Institute of Biology and Biomedicine, Lobachevsky University Gagarina Ave. 23, Nizhny Novgorod, 603950 Russian Federation

INTRODUCTION & AIM

The tumor extracellular matrix (ECM) promotes the phenotypic plasticity of tumor cells, a key mechanism of metastasis and therapeutic resistance. Therefore, ECM is considered a promising therapeutic target for various cancer subtypes.

The aim of the study was to determine the expression profile of genes associated with ECM and phenotypic plasticity specific to triple-negative breast cancer (TNBC), and to evaluate its prognostic relevance.

Table 1

Characteristics of subtypes of breast cancer (Orrantia-Borunda et al., 2022. Adapted)

	Luminal A	Luminal B	HER2	TNBC
Frequency (%)	50	15	20	15
ER	Yes	Yes	Some cases	No
PR	Yes	Some cases	Some cases	No
HER	No	No	Yes	No
Ki67	Some cases	Some cases	High	High
Prognosis	Good	Middle	Middle/Bad	Bad
Therapy	Hormonal	Hormonal/ Chemo	Hormonal/Chemo/ Herceptin	Chemo/ Experimental

METHOD

To identify differentially expressed genes (DEG), we analyzed datasets (**GSE65194, GSE45827**) from the NCBI GEO. Both datasets have identical composition: 155 samples in total, of which 41 are TNBC samples and 11 are samples of normal breast tissue. The list of genes of interest was compiled based on data from MatrisomeDB and MSigDB. The analysis covered 1,027 genes. DEG analysis (**$|\log_2 FC|>1$, $p>0.001$**) was performed using a software tool, which was developed using Python (pandas, numpy, matpolib) and R. The prognostic significance (**HR≠1, p>0.05**) was assessed by overall survival (**OS**) in basal-like cohorts using the KM-Plotter, comparing the first and fourth quartiles.

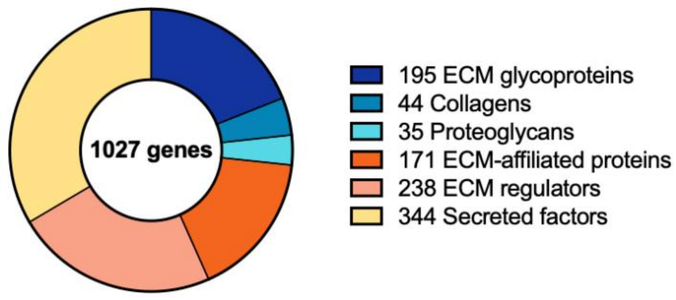

Fig.1. Composition of the list of genes associated with the extracellular matrix from MatrsiomeDB (Naba et al., 2012).

RESULTS

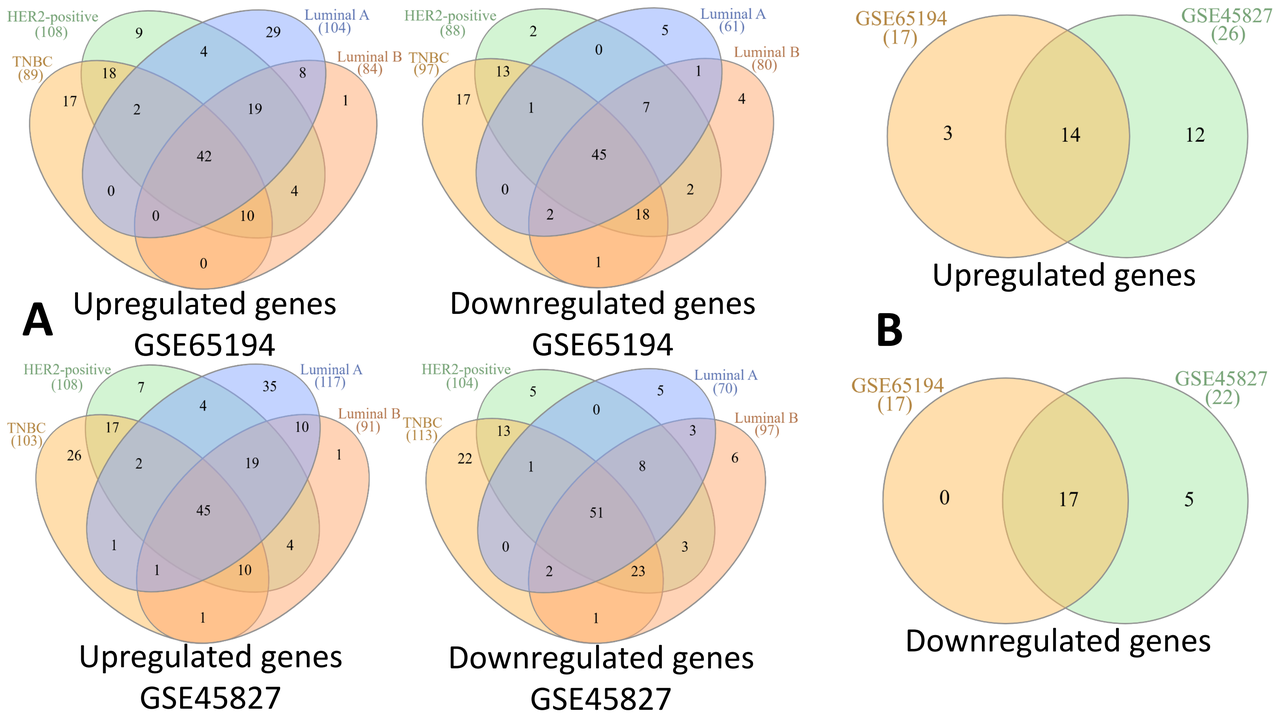

Fig.2. A Identification of DEGs between different BC subtypes and normal tissues. **B** Venn diagram of DEGs obtained from 2 gene expression profiles (GSE65194 and GSE45827).

Venn diagrams were generated showing the number of genes with significantly altered expression (**p<0.001, |log2FC|>1**). Each ellipse in the diagram corresponds to one cancer subtype. Overlapping ellipses correspond to gene changes in two or more cancer subtypes. TNBC is associated with subtype-specific changes in the expression of **31 genes**, including **14 genes that are up-regulated and 17 genes that are down-regulated** relative to normal breast tissue. Subtype-specific changes in the expression of these genes are also observed in other breast cancer subtypes.

A significant relationship was found between the level of gene expression and OS for genes: *CLEC4A, CLEC7A, IFNG, COL22A1, CRLF3, CTSV, HPSE, CXCL12, OMD*, *MUC20, INHBB* and *HTRA1*. High expression of upregulated genes and low expression of downregulated genes were both associated with improved survival. Except for *CXCL12* and *OMD*, which were downregulated, their high expression was associated with improved survival.

Table 2.

Kaplan-Meier survival analysis for patients with TNBC. Reliable results have a “high/low” label and color coding indicating the expression level associated with the best prognosis (orange - increased gene expression, blue - decreased gene expression).

Gene symbol	mRNA gene chip OS ONLY treated (n = 72)	mRNA gene chip OS ALL (n = 296)	mRNA RNA-seq OS ONLY treated (n = 53)	mRNA RNA-seq OS ALL (n = 309)
Up-regulated genes				
CLEC4A	-	high -> positive	-	high -> positive
CLEC5A	-	-	-	-
CLEC7A	-	high -> positive	-	high -> positive
IFNG	-	high -> positive	-	-
MUC16	-	-	-	-
COL9A3	-	-	-	-
COL22A1	-	high -> positive	-	-
PLOD3	-	-	-	-
CRLF3	-	high -> positive	-	-
SDC2	-	-	-	-
NRTN	-	-	-	-
EGLN1	-	-	-	-
CTSV	low -> positive	-	low -> positive	high -> positive
HPSE	-	high -> positive	-	-
Down-regulated genes				
CXCL12	-	-	-	high -> positive
COL4A5	-	-	-	-
DCN	-	-	-	-
DPT	-	-	-	-
LAMB1	-	-	-	-
SPON1	-	-	-	-
OMD	-	-	-	high -> positive
NTN4	-	-	-	-
MUC20	low -> positive	low -> positive	low -> positive	low -> positive
SEMA5A	-	-	-	low -> positive
ANGPTL2	-	-	-	-
INHBB	low -> positive	-	low -> positive	-
PDGFC	-	-	-	-
VWA5A	-	-	-	-
HTRA1	-	-	-	low -> positive
PLAT	-	-	-	-
CST3	-	-	-	-

CONCLUSIONS

Our findings indicate that TNBC exhibits a specific expression profile of genes associated with ECM and phenotypic plasticity. We assume that some of these genes may be promising candidates for therapeutic targeting, as has also been reported by other researchers.

FUTURE WORK/ REFERENCES/ACKNOWLEDGMENT

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