# TRANSCRIPTOMIC FEATURES OF FAP+ CELLS ACROSS MOLECULAR SUBTYPES OF BREAST CANCER

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Understanding subtype-specific variability of functional programs in FAP+ tumor-associated fibroblasts (TAFs) is fundamental for developing effective therapeutic strategies targeting stromal components. The aim of this study was to identify subtype-specific signaling pathways, markers, and molecular features of FAP+ TAFs. Using spatial transcriptomic analysis, we demonstrated that FAP+ TAFs in luminal breast cancer exhibit a phenotype characterized by extracellular matrix organization (GO:0030198, FDR q-value = 0.0307) and expression of genes associated with metastasis (*COL10A1*, *MMP13*, *CXCL14*, *TSPAN8*). In contrast, FAP+ TAFs in triple-negative breast cancer display a pronounced immunomodulatory phenotype with overexpression of immunosuppressive genes (*CD36*, *PLA2G2A*, *CHI3L1*) and enrichment of immune response-related pathways (immune response (GO:0006955, FDR q-value = 7.85e-17), inflammatory response (GO:0006954, FDR q-value = 2.79e-11), regulation of cytokine production (GO:0001817, FDR q-value = 3.39e-10)). We also identified subtype-specific gene signatures related to radioresistance: luminal A and B subtypes showed activation of DNA repair pathways (*IGF1R*, *ERBB3*, *CRIP1*), while triple-negative tumors demonstrated enrichment of epithelial-mesenchymal transition and stemness markers (*ZEB2*, *NOTCH4*, *FOXM1*). These findings emphasize that FAP+ fibroblasts are not a homogeneous population but functionally specialize depending on tumor subtype — acting as stromal architects in luminal breast cancer and as regulators of immune response in triple-negative breast cancer.

**Keywords:** breast cancer, tumor microenvironment, fibroblasts, spatial transcriptomics

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# ОСОБЕННОСТИ ТРАНСКРИПТОМНОГО ПРОФИЛЯ FAP+-КЛЕТОК В ОПУХОЛЯХ МОЛОЧНОЙ ЖЕЛЕЗЫ РАЗЛИЧНЫХ МОЛЕКУЛЯРНО-БИОЛОГИЧЕСКИХ ПОДТИПОВ

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Понимание подтип-специфичной вариабельности функциональных программ FAP+ опухоль-ассоциированных фибробластов (ОАФ) является фундаментальным для разработки эффективных терапевтических стратегий, нацеленных на стромальные мишени. Целью работы было идентифицировать подтип-специфичные сигнальные пути, маркеры и молекулярные особенности FAP+ ОАФ. Исследовали образцы тканей, полученные от 15 пациенток с раком молочной железы (РМЖ). С помощью пространственного транскриптомного анализа продемонстрировано, что FAP+ ОАФ при люминальном РМЖ проявляют фенотип, характеризующийся организацией внеклеточного матрикса (GO:0030198, FDR q-value = 0,0307) и экспрессией генов, ассоциированных с метастазированием (*COL10A1*, *MMP13*, *CXCL14*, *TSPAN8*). В отличие от этого, FAP+ ОАФ при тройном негативном раке демонстрируют выраженный иммуномодуляторный фенотип со сверхэкспрессией генов иммуносупрессии (*CD36, PLA2G2A*, *CHI3L1*) и обогащением сигнальных путей иммунного ответа (иммунный ответ (GO:0006955, FDR q-value = 7,85e-17), ответ на воспаление (GO:0006954, FDR q-value = 2,79e-11), регуляция продукции цитокинов (GO:0001817, FDR q-value = 3,39e-10)). Идентифицированы также подтип-специфичные сигнатуры генов радиорезистентности: люминальные А- и Б-подтипы, показана активация путей репарации ДНК (*IGF1R*, *ERBB3*, *CRIP1*), в то время как тройные негативные опухоли демонстрируют обогащение маркеров эпителиально-мезенхимального перехода и стволовости (*ZEB2*, *NOTCH4*, *FOXM1*). Эти данные подчеркивают, что FAP+-фибробласты не являются однородной популяцией, а функционально специализируются в зависимости от подтипа опухоли, выступая в качестве архитекторов стромы при люминальном раке и регуляторов иммунного ответа при тройном негативном РМЖ.

**Ключевые слова:** рак молочной железы, опухолевое микроокружение, фибробласты, пространственная транскриптомика

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The heterogeneity of breast cancer (BC) is determined not only by the diversity of tumor cells, but also by the complex cellular composition of the tumor microenvironment [1]. One of the key cell types in the tumor microenvironment are cancer-associated fibroblasts (CAFs), which actively contribute to oncogenesis through multiple mechanisms: extracellular matrix remodeling [2], immunosuppression mediated via physical barrier formation against immunocompetent cells [3], and secretion of proinflammatory cytokines and growth factors that directly promote tumor cell proliferation and angiogenesis [4, 5].

Among the various subpopulations of CAFs, fibroblasts expressing fibroblast activation protein alpha (FAP) are of particular interest due to their critical role in carcinogenesis. In certain carcinomas, elevated FAP expression serves as a universal marker of aggressive tumor stroma and is consistently associated with poor clinical prognosis [6]. However, in breast cancer its significance is controversial. As is well established, the molecular subtype of breast cancer holds significant prognostic value, due in part to the distinct tumor microenvironment characteristics associated with each subtype. Studies utilizing FAP inhibitor conjugated with Technetium-99m ([99mTc]Tc-iFAP) single-photon emission computed tomography (SPECT) have demonstrated that FAP expression significantly correlates with specific molecular subtypes. For instance, Vallejo-Armenta et al. reported a strong positive correlation between radiotracer accumulation in the primary tumor and molecular subtypes. Notably, the authors demonstrated that HER2-enriched and luminal B HER2-positive subtypes exhibited the highest radiotracer uptake ratios, suggesting a more pronounced FAP expression within the stroma of these particularly aggressive breast cancer phenotypes [7]. The association of FAP expression with clinical parameters is further supported by the work of Tchou et al., who confirmed its localization within the tumor stroma and documented heterogeneity depending on various tumor characteristics. However, in their study, differences in the proportion of FAP-expressing cells across molecular subtypes did not reach statistical significance [8]. Another study suggests that certain subsets of CAFs enriched in FAP expression are associated with a subtype of triple-negative breast cancer [9]. Subsequent studies confirmed that fibroblasts in breast cancer represent a heterogeneous population. Croizer H. et al. demonstrated that the luminal A subtype is characterized by numerous clusters containing CAFs that secrete cytokines, including TGFβ, as well as CAFs associated with the extracellular matrix. In contrast, the luminal B, HER2-enriched, and triple-negative subtypes exhibited clusters enriched with CAFs linked to wound healing processes [10]. The study by Kashyap et al. showed that in luminal breast cancer, higher levels of FAP were associated with distant recurrence [11]. Nevertheless, to date, there are no direct data comparing the transcriptomic profiles of FAP$^+$ cells across breast cancer subtypes. At the same time, a key question remains open regarding the extent to which the transcriptomic landscape — and consequently, the functional program — of FAP$^+$ cells varies among the main molecular subtypes of breast cancer. Understanding these subtype-specific differences is critically important for the development of new therapeutic strategies.

Currently, therapy targeting FAP represents one of the most promising directions in oncology. The high and specific expression of FAP on stromal cells within tumors, combined with its almost complete absence in healthy tissues, makes this protein an ideal target for the development of highly selective agents. Various therapeutic modalities targeting FAP are actively being developed and are undergoing clinical trials, including Chimeric Antigen Receptor T-cells (CAR-T cells), bispecific antibodies, antibody-drug conjugates (ADCs), and radiopharmaceuticals delivering cytotoxic agents directly to the tumor stroma [6]. The success of these innovative approaches directly depends on a deep understanding of the target biology. The heterogeneity of FAP$^+$ cells among breast cancer subtypes may lead to variable drug efficacy, highlighting the need for their stratification. In this study, we conducted a comparative analysis of the transcriptomic profiles of FAP$^+$ cells associated with luminal and triple-negative breast cancer subtypes. Our goal was to identify subtype-specific signaling pathways, markers, and molecular characteristics of this cell population. The obtained data not only deepen the understanding of stromal biology in breast cancer but also have direct translational relevance, providing a rationale for the development and optimization of subtype-specific targeted therapies directed at FAP$^+$ cells.

## METHODS

### Patients

The study included samples from 15 female patients diagnosed with luminal A/B ($n$ = 7) and triple-negative ($n$ = 8) breast cancer. Inclusion criteria: morphologically confirmed luminal A/B ($n$ = 7) and triple negative ($n$ = 8) breast cancer. The exclusion criterion was HER2-positive subtypes. Spatial transcriptomic analysis was performed on formalin-fixed, paraffin-embedded (FFPE) tissue sections obtained during trypan-biopsy or surgical intervention before treatment. Detailed descriptions of histological sample preparation, library construction, and sequencing using the 10X Visium platform can be found in the original articles [12, 13]. The sequencing data of breast cancer tissue sections used in this publication are available under GEO series accession number GSE242311.

### Bioinformatic Data Analysis

The initial processing of raw data in FASTQ format was performed using Space Ranger v1.3 software (10x Genomics, Pleasanton, CA, USA) with default parameters. Alignment of FASTQ files was carried out against the human reference genome (GRCh38). Aggregation of tissue sections for manual annotation was conducted using the "spaceranger aggr" function. Manual annotation of the sections was performed using Loupe Browser v8.1.2 software (10x Genomics, Pleasanton, CA, USA) and involved identification of spots with FAP expression levels greater than 3, analyzed separately for luminal and triple-negative patients (Fig. 1).

Each selected spot was evaluated by a pathologist to confirm the presence of fibroblasts. Spots lacking fibroblasts were manually excluded from the cluster. Differential gene expression analysis between annotated clusters was conducted using the built-in tools of Loupe Browser v8.1.2 (10x Genomics, Pleasanton, CA, USA). Genes with $|\log \text{fold change (LFC)}| > 0.58$ and adjusted p-values (FDR) $< 0.05$ were considered differentially expressed. To visualize the annotated cell clusters in reduced-dimensional space, the t-SNE (t-Distributed Stochastic Neighbor Embedding) method was applied using Loupe Browser's built-in tools. Functional pathway enrichment analysis was performed using the STRING online resource [14], based on the Gene Ontology database [15], employing lists of differentially expressed genes ranked by expression level and corrected p-values (FDR q-value) obtained from the differential expression analysis. Biological processes with FDR q-value $< 0.05$ were considered significant. Further analysis was carried out

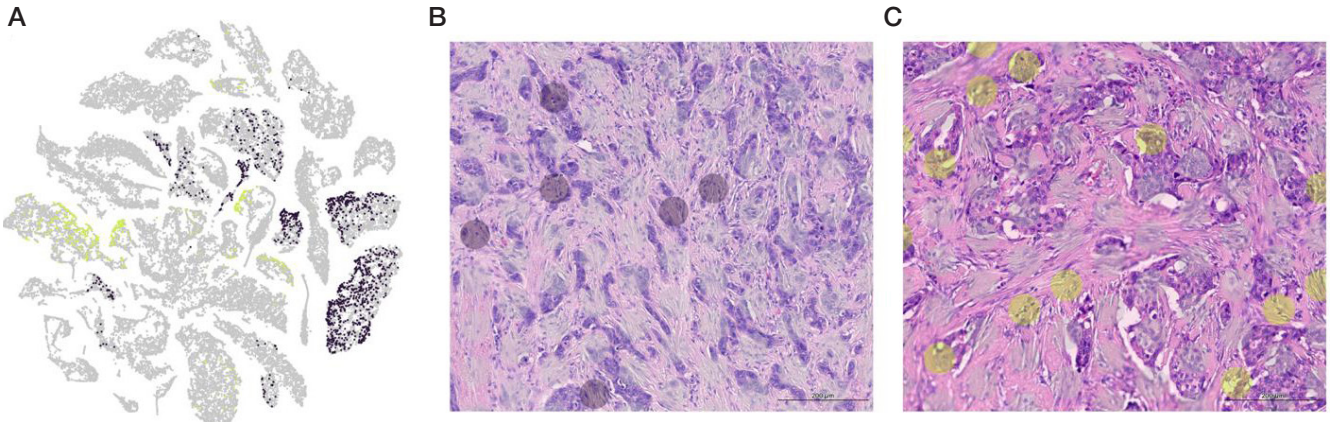


**Fig. 1. A**. Clusters of FAP+ cells in luminal (*blue*) and triple-negative (*yellow*) breast cancer patients obtained by combining data in Space Ranger v1.3 software. **B**. Tissue section of a luminal breast tumor with identified FAP+ spots. **C**. Tissue section of a triple-negative breast tumor with identified FAP+ spots

in the R environment (https://www.R-project.org/) using the Seurat package (v5.0.0) [16]. Each of the 15 samples was converted into a Seurat object via the "Load10X_spatial" command and subsequently merged into a single object using the "merge" function. Preprocessing included filtering spots with parameters "nCount_Spatial" > 500 and "nFeature_Spatial" > 200. Manual annotation results exported from Loupe Browser v8.1.2 as tables were incorporated into the metadata section of each respective sample.

To generate averaged transcriptomic profiles from the annotated FAP-positive spots for each sample, the "AggregateExpression" function from the Seurat package (v5.0.0) was used with parameters slot = "counts", normalization.method = "LogNormalize", and scale.factor = 10,000. As a result, 15 transcriptomic profiles were obtained, each representing the averaged expression levels across all spots of the corresponding sample. These profiles were normalized using a scaling factor of 10,000 and subjected to logarithmic transformation. For visualization of fibroblast and radioresistance gene signature expression in the studied samples, heatmaps were created in the R environment (https://www.R-project.org/) using the packages pheatmap (v1.0.13) [17], RColorBrewer (v1.1-3) [18], and dplyr (vX.X.X) [19]. The heatmap visualization included a step of Z-score standardization of the target gene expression matrix by rows (genes). Spatial transcriptomic analysis was conducted on formalin-fixed, paraffin-embedded (FFPE) tissue sections obtained during surgery.

## RESULTS

### Biological processes enriched in FAP+ regions of luminal and triple-negative breast cancer

To understand the differences in biological processes between the two clusters of luminal and triple-negative tumors, we performed pathway enrichment analysis to identify enriched molecular processes in the transcriptomic data. The most significant pathways were identified from Gene Ontology datasets (Fig. 2).

The conducted study identified key biological processes activated in FAP+ regions of patients with luminal and triple-negative breast cancer. FAP+ spots in luminal breast cancer patients were characterized by activation of morphogenesis (GO:0009887, FDR q-value = 0,00058), tissue development (GO:0009888, FDR q-value = 0,0013), and extracellular matrix organization processes (GO:0030198, FDR q-value = 0,0307), whereas in triple-negative breast cancer patients, immune signaling pathways predominated, including immune response (GO:0006955, FDR q-value = $7{,}85e^{-17}$), inflammatory response (GO:0006954, FDR q-value = $2{,}79e^{-11}$), cytokine production regulation (GO:0001817, FDR q-value = $3{,}39e^{-10}$), as well as angiogenesis (GO:0001525, FDR q-value = $7{,}83e^{-08}$).

### Fibroblast- specific markers in FAP+ tumor regions

Next, we selected fibroblast-specific, highly expressed, and significantly enriched genes in the two groups of breast cancer patients. These genes were annotated as functionally important in cancer development (Fig. 3).

In luminal breast tumors, the list of DEGs included *ASPN, COL10A1*, *COL2A1*, *OMD*, *DCN*, *MMP13*, *SERPINA1/SERPINA3*, *PLAT, LRRC15*, *CXCL14*, and *TSPAN8*, whereas in triple-negative tumors, the genes comprised *MMP7*, *COL4A1*, *COL4A2*, *COL15A1*, *ENG*, *TGM2*, *SLC11A1*, *CHI3L1*, *PLA2G2A*, *FDCSP*, and *CD36*.

### Gene signatures associated with resistance to radiotherapy

An important question regarding the characteristics of FAP+ cells is their radiosensitivity or resistance, as FAP represents a promising target for radionuclide therapy. In this regard, we selected among the overexpressed genes those that are pathogenetically associated with radioresistance according to the literature data, in two groups of breast cancer patients (Fig. 4).

In luminal breast cancer, the expression of genes *IGF1R, ERBB3*, *GREB1*, *XBP1*, *SERPINA1/SERPINA3*, *TIMP3*, *FASN, IL6ST*, *BCAM*, and *CRIP1* was observed. Meanwhile, in triple-negative tumors, the overexpressed genes included *CD36, CX3CL1*, *A2M*, *MYBL2*, *NOTCH4*, *S100A8/S100A9*, *TGM2*, *UBE2C*, *FOXM1*, and *ZEB2*.

## DISCUSSION

The conducted analysis revealed fundamental differences in the biological functions of FAP+ cells within the microenvironment of luminal and triple-negative breast cancer subtypes. These findings not only highlight the heterogeneity of the tumor stroma but also hold significant implications for the development of personalized therapeutic strategies, particularly for targeted therapy utilizing FAP as a target.

A key finding of our study is the clear distinction in the role of stromal FAP+ cells depending on the molecular subtype of the tumor. In luminal breast cancer, FAP+ cells exhibit pronounced activity in morphogenesis, tissue development, and extracellular matrix organization processes, with no

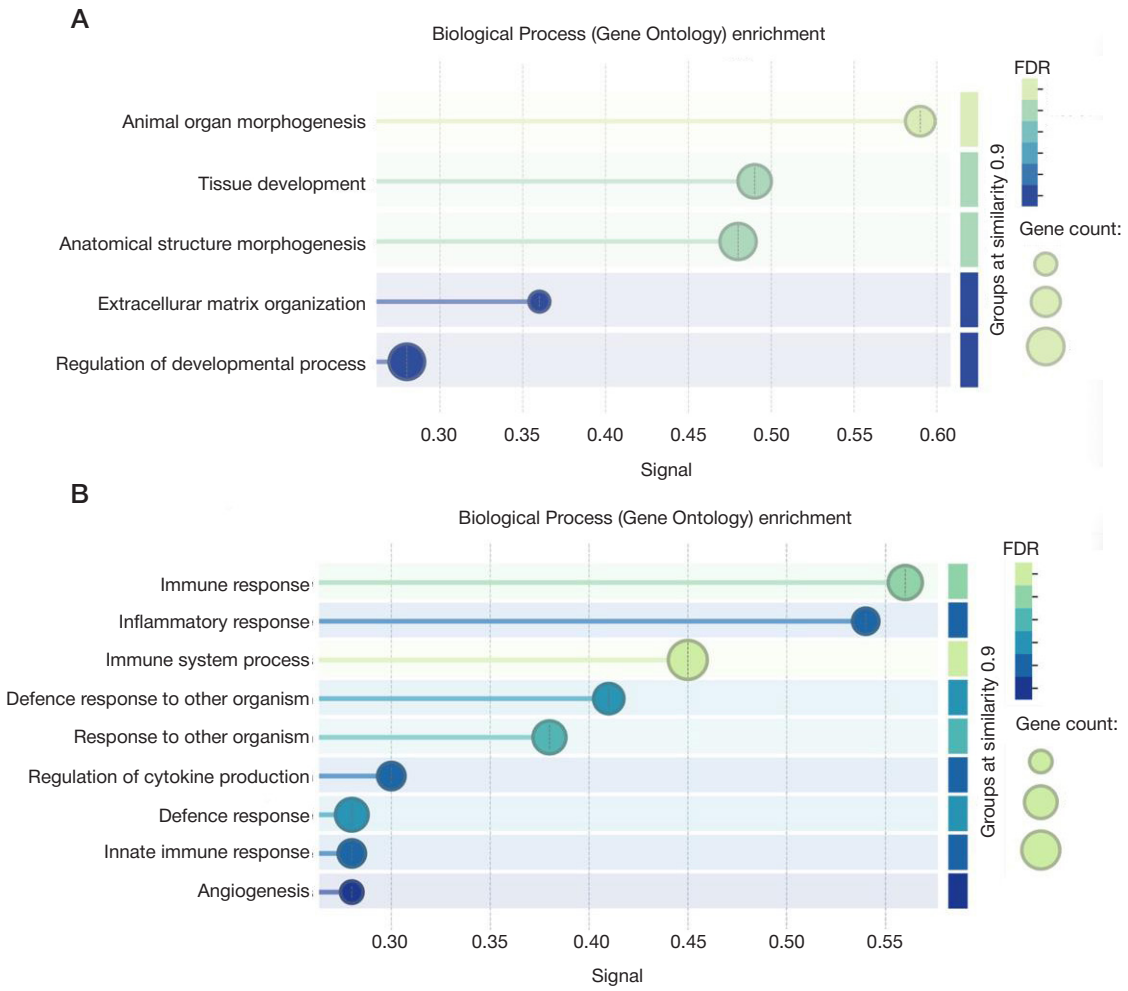


**Fig. 2.** Significant signaling pathways activated in FAP⁺ regions of luminal **(A)** and triple-negative **(B)** breast tumors

signs of inflammatory response. This is consistent with the identified fibroblast marker genes, such as *COL10A1*, *COL2A1*, *MMP13*, *CXCL14*, and *TSPAN8*. In particular, the high expression of *MMP13* in FAP⁺ cells indicates active matrix remodeling [20]. Among the identified genes, it is important to highlight those associated with chemoresistance in breast cancer. For instance, the expression of *CXCL14* is a distinctive feature of fibroblasts that enhance metastasis and promote chemoresistance [21] according to mechanistic studies, as is TSPAN8, which is expressed by myofibroblasts [22]. Such a stromal niche likely provides structural support to the tumor, promotes its progression and therapy resistance, creating a dense desmoplastic microenvironment.

In triple-negative breast cancer, FAP⁺ cells, on the contrary, display a pronounced immunomodulatory and pro-inflammatory phenotype. Enrichment of signaling pathways related to immune response and cytokine regulation, as well as the overexpression of genes *CHI3L1*, *CD36*, and *PLA2G2A*, indicate active interaction with immune cells in the microenvironment. It is known that CD36⁺ fibroblasts possess a potent immunosuppressive effect [23] by suppressing macrophage activity, whereas PLA2G2A⁺ fibroblasts inhibit the effects of CD8⁺ cytotoxic lymphocytes [24]. It has been shown that fibroblasts can secrete CHI3L1, leading to increased IL8 production and stimulation of angiogenesis [25]. All of this may contribute to the formation of an immunosuppressive microenvironment, tumor evasion from immune surveillance, and the maintenance of chronic inflammation. Thus, the obtained data indicate significant differences in the molecular signatures of tumor-associated fibroblasts of tumors of different molecular biological subtypes.

Understanding the radiosensitivity of FAP⁺ cells is critical for the development of FAP-targeted radionuclide therapies. Our data revealed potential bases for the operation of distinct radioresistance mechanisms in the two subtypes. In the luminal subtype, the identified genes indicate activation of survival and repair pathways. IGF1R and ERBB3 are well-known receptor tyrosine kinases mediating radioresistance in malignancies [26, 27]. It has been shown that the gene *SERPINA1* is associated with radioresistance in lung cancer [28], whereas inhibition of *FASN* improves radiotherapy outcomes in breast cancer [29]. Another gene, *CRIP1*, can interact with BRCA2, enhancing DNA repair during chemotherapy [30]. This suggests that radioresistance in this subtype may be mediated through enhanced DNA repair.

In triple-negative breast cancer, the radioresistance gene signature is broader and is associated with epithelial-mesenchymal transition (EMT) and stemness. ZEB2 and NOTCH4 are key inducers of EMT, which is linked to therapy resistance [31, 32, 33]. *FOXM1* and *UBE2C* regulate the cell cycle and mitosis, contributing to the rapid recovery of the tumor cell population [34, 35]. Moreover, enhanced DNA repair dependent on FoxO3a/FoxM1 may play a key role in the survival of fibroblasts resistant to cell death following irradiation [36]. *TGM2* gene is also associated with radioresistance [37]. This suggests that in triple-negative breast cancer, resistance may be associated with the presence of a population of stem-like tumor cells exhibiting mesenchymal characteristics.

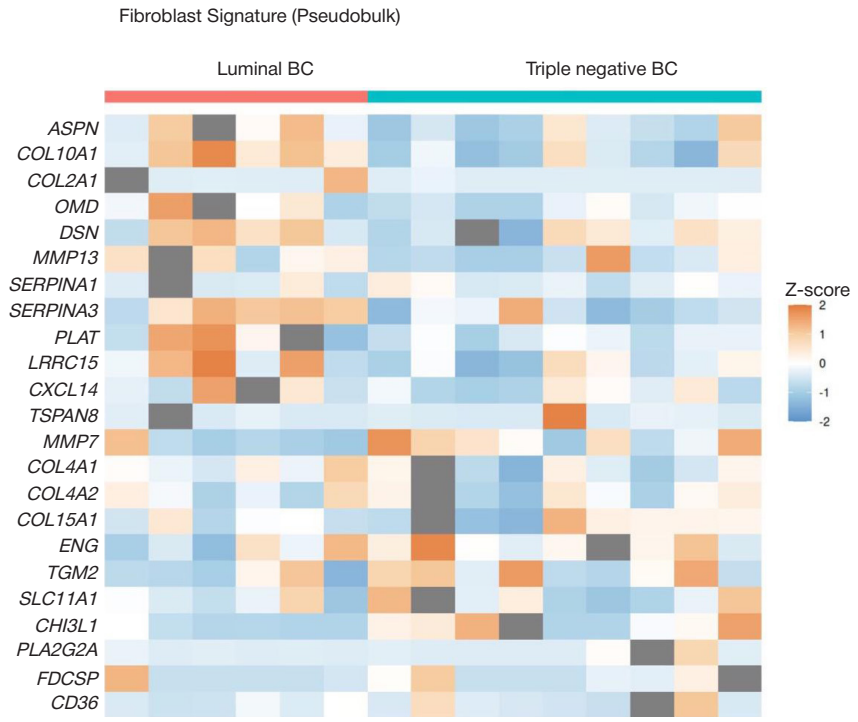


**Fig. 3.** Fibroblast-specific genes in FAP⁺ regions of luminal and triple-negative breast tumors

Our study demonstrates that FAP⁺ fibroblasts are not a homogeneous population but functionally adapt to the molecular subtype specificity. In luminal breast cancer, they act as architects of the stroma, whereas in triple-negative breast cancer, they function as immune regulators and promoters of angiogenesis. The identification of distinct gene sets associated with radioresistance suggests that resistance cases may occur during FAP-targeted radionuclide therapy, warranting the proactive development of strategies to overcome it.

## CONCLUSIONS

The study enabled the identification of highly specific transcriptomic profiles of FAP⁺ stroma of luminal and triple-negative breast tumors, clearly reflecting the biology of molecular subtypes of breast cancer. The obtained data emphasize the necessity of considering the tumor's molecular subtype when developing stroma-targeted therapies and open new avenues for creating personalized combination treatments aimed at specific resistance mechanisms within the tumor microenvironment.

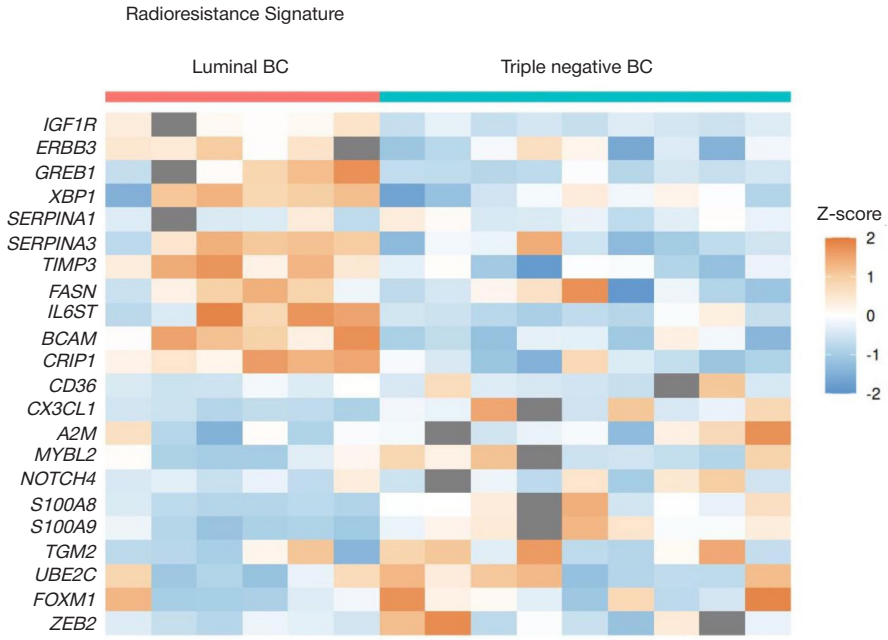


**Fig. 4.** Genes associated with radioresistance in FAP⁺ regions of luminal and triple-negative breast tumors


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