Am J Cancer Res 2022;12(4):1784-1823
www.ajcr.us /ISSN:2156-6976/ajcr0141105

Original Article

Investigation of the effects of overexpression of jumping translocation breakpoint (JTB) protein in MCF7 cells for potential use as a biomarker in breast cancer

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Received December 13, 2021; Accepted January 27, 2022; Epub April 15, 2022; Published April 30, 2022

Abstract: Jumping translocation breakpoint (JTB) gene acts as a tumor suppressor or an oncogene in different malignancies, including breast cancer (BC), where it was reported as overexpressed. However, the molecular functions, biological processes and underlying mechanisms through which JTB protein causes increased cell growth, proliferation and invasion is still not fully deciphered. Our goal is to identify the functions of JTB protein by cellular proteomics approaches. MCF7 breast cancer cells were transfected with sense orientation of hJTB cDNA in HA, His and FLAG tagged CMV expression vector to overexpress hJTB and the expression levels were confirmed by Western blotting (WB). Proteins extracted from transfected cells were separated by SDS-PAGE and the in-gel digested peptides were analyzed by nano-liquid chromatography tandem mass spectrometry (nanoLC-MS/MS). By comparing the proteome of cells with upregulated conditions of JTB vs control and identifying the protein dysregulation patterns, we aim to understand the function of this protein and its contribution to tumorigenesis. Gene Set Enrichment Analysis (GSEA) algorithm was performed to investigate the biological processes and pathways that are associated with the JTB protein upregulation. The results demonstrated four significantly enriched gene sets from the following significantly upregulated pathways: mitotic spindle assembly, estrogen response late, epithelial-to-mesenchymal transition (EMT) and estrogen response early. JTB protein itself is involved in mitotic spindle pathway by its role in cell division/cytokinesis, and within estrogen response early and late pathways, contributing to discrimination between luminal and mesenchymal breast cancer. Thus, the overexpressed JTB condition was significantly associated with an increased expression of ACTNs, FLNA, FLNB, EZR, MYOF, COL3A1, COL11A1, HSPA1A, HSP90A, WDR, EPPK1, FASN and FOXA1 proteins related to deregulation of cytoskeletal organization and biogenesis, mitotic spindle organization, ECM remodeling, cellular response to estrogen, proliferation, migration, metastasis, increased lipid biogenesis, endocrine therapy resistance, antiapoptosis and discrimination between different breast cancer subtypes. Other upregulated proteins for overexpressed JTB condition are involved in multiple cellular functions and pathways that become dysregulated, such as tumor microenvironment (TME) acidification, the transmembrane transport pathways, glycolytic flux, iron metabolism and oxidative stress, metabolic reprogramming, nucleocytosolic mRNA transport, transcriptional activation, chromatin remodeling, modulation of cell death pathways, stress responsive pathways, and cancer drug resistance. The downregulated proteins for overexpressed JTB condition are involved in adaptive communication between external and internal environment of cells and maintenance between pro-apoptotic and anti-apoptotic signaling pathways, vesicle trafficking and secretion, DNA lesions repair and suppression of genes involved in tumor progression, proteostasis, redox state regulation, biosynthesis of macromolecules, lipolytic pathway, carbohydrate metabolism, dysregulation of ubiquitin-mediated degradation system, cancer cell immune escape, cell-to-cell and cell-to-ECM interactions, and cytoskeletal behaviour. There were no significantly enriched downregulated pathways.

Keywords: Breast cancer, jumping translocation breakpoint (JTB) protein, JTB overexpressed condition, proteomics

Introduction

Around the world, breast cancer is the most common cancer in women [1, 2]. About 1 in 8 women in America are diagnosed with breast cancer in their lifetime [3]. Jumping translocation breakpoint (JTB) gene is located on the human chromosome 1 at q21, which is involved

in an unbalanced translocation in various types of cancers [4, 5]. The JTB protein, later rediscovered as the prostate androgen-regulated (PAR) protein [6], belongs to an ubiquitous transmembrane family of proteins [5] expressed in various tissues and cells, from kidney cortical collecting duct cells [7], lung, stomach and colon [5] to cultured neonatal mouse myocytes [8], breast [9] and prostate [10] cancer cell lines. It is highly conserved among divergent eukaryotic species [4], from freshwater cnidarian polyp *Hydra vulgaris* [11], nematodes and flies to humans [12]. JTBs are located in the cell membrane, mitochondria [4, 5], and microtubule cytoskeleton [13], being identified during mitosis with a dynamic localization in centrosome, spindle and cytoplasm [14]. Human JTB (hJTB) protein is an orphan receptor [12], consisting of 146 amino acid polypeptide [6] that has a total molecular weight of about 16.4 kDa [9], with a 30-amino acid signal sequence that could be processed and removed, and a 116 amino acid sequence consisting of a 75-amino acid extracellular domain that is rich in cysteine [12], a 21-amino acid helical and highly hydrophobic trans-membrane domain, and a 20-amino acid short intracellular/cytoplasmic domain, all these three domains counting a molecular mass of 13.2 kDa [4].

This protein that is ubiquitously present in normal cells has an suppressed expression in many cancers [5] but it is overexpressed in breast cancer cells, prostate and liver cancers [4, 15]. Hence, it could be a tumor biomarker for different types of malignancies and a potential target for their treatment. However, the molecular functions and biological processes or pathways through which this protein causes increased cell growth and proliferation is not entirely clear. In MCF7 and T47D breast cancer cell lines, as well as in all primary breast tumors compared to their normal tissue samples counterparts, the PAR expression was reported to be higher; PAR gene expression was 4.5 and 5 fold higher in human breast cancer cell lines compared to the human normal breast total RNA, while in malignant specimens in breast, this difference was 3 fold higher compared to normal tissues [6]. According to the public datasets of cbioportal.org, JTB gene was amplified in 4.6% [16]-22.1% [17] of breast cancer patients with primary breast tumors/breast invasive carcinoma, including invasive lobular carcinoma (ILC), with 12.6%. In metastatic breast cancer, the frequency of amplification is 10.2% [18] or 13.9%, cited for FFPE primary and/or metastatic breast cancer samples, according to Metastatic Breast Cancer Project.

Hence, our goal is to identify the function of JTB protein by using cellular proteomics. MCF7 cells here were transfected with sense orientation of hJTB cDNA in HA, His and FLAG tagged CMV expression vector to overexpress hJTB and the expression levels were confirmed by western blotting (WB). Proteins extracted from transfected cells were separated by SDS-PAGE and the in-gel digested peptides were analyzed by nano liquid chromatography tandem mass spectrometry (nanoLC-MS/MS). By comparing the proteome of cells with upregulated conditions of JTB vs control and identifying the protein dysregulation patterns, we aim to understand the function of this protein and its contribution to breast tumorigenesis. GSEA algorithm was performed to investigate the biological processes and pathways that are associated with the hJTB protein upregulation in MCF7 cells. The results demonstrated four significantly enriched gene sets from the following pathways that were significantly up-regulated: mitotic spindle assembly, estrogen response late, epithelial-to-mesenchymal transition and estrogen response early. There were no significantly enriched downregulated pathways.

Materials and methods

Cell culture

The MCF7 cell line were purchased from American Type Culture Collection (HTB-22 ATCC) and grown in RPMI-1640 medium supplemented with 10% FBS, 1% Penicillin-Streptomycin, 0.2% Gentamycin and 0.2% of Amphotericin (growth media) at 37°C and in 5% CO_2. The cells were grown until they reached ~70% confluency and transfected with JTB cDNA plasmid for overexpression.

Plasmids

Plasmids were custom made by Genscript®. One plasmid with the hJTB gene containing the full coding region of cDNA, ggtaccGCCACCATGCATCATCATCATCATCATCTTGCGGGTGCCGGGAGGCCTGGCCTCCCCCAGGGCCGCCACCTCTGCTGGTTGCTCTGTGCTTTCACCTTAAAGCTCTG-

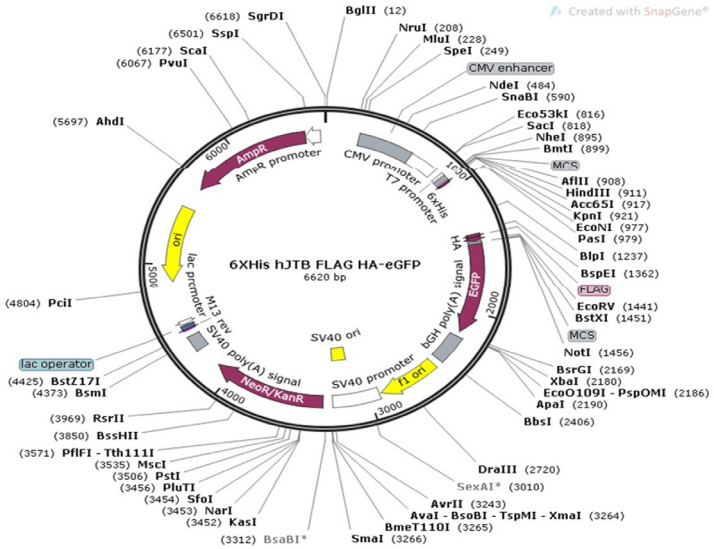

Figure 1. hJTB plasmid with 6X His tag at the N-terminus and FLAG, HA and eGFP tag at its C-terminus for the overexpression with Neomycin and Ampicillin resistance genes customized by Genscript®.

CCAAGCAGAGGCTCCCGTGCAGGAAGAGAAG-CTGTCAGCAAGCACCTCAAATTTGCCATGCT-GGCTGGTGGAAGAGTTTGTGGTAGCAGAAGC-TCTCCATGCTCTAATTTCCGGGCTAAAACTAC-CCCTGAGTGTGGTCCCACAGGATATGTAGAGA-AACACATGCAGCTCATCTAAGAGAAATGAGT-TCAAAAGCTGCCGCTCAGCTTTGATGGAACAACG-CTTATTTTGGAAGTTCGAAGGGGCTGTCGTGT-GTGTGGCCCTGATCTTCGCTTGTCTTGTCATC-ATTCGTCAGCGACAATTGGACAGAAAGGCTCT-GGAAAAGGTCCGGAAGCAAATCGAGTCCATA-GACTACAAAGACGATGACGACAAGTACCCATA-CGATGTTCCAGATTACGCTgatatc corresponding to 146 amino acids of the protein was used. The hJTB cDNA in sense orientation was inserted into a CMV promoter based plasmid for JTB overexpression. The plasmid was further customized to have three tags His, HA and FLAG tags (**Figure 1**). It also had an eGFP tag to enable confirmation of transfection in MCF7 cells. The second plasmid was an empty vector with an eGFP tag to serve as control. The cellular proteomic workflow used in this experiment is presented in **Figure 2**.

Transfection into MCF7 cells

Lipofectamine™ 3000/DNA and DNA/Plasmid (10 µg/µl) complexes were prepared in Opti-MEM Reduced Serum Media (Invitrogen) for each condition and added directly to the cells in culture medium. 2 mg/mL of Neomycin was added after 48 hours and incubated at 37°C. Cells that survived were allowed to reach 80% confluency by replacing the growth media every 48 h with new media containing 2 mg/mL antibiotic. Transfection efficiency was confirmed by visualizing the green fluorescence emitted by the eGFP using a confocal microscope (**Figure 3**).

Western blot analysis

Cell lysates from each condition were collected using a lysis buffer containing 20 mM Tris HCl, 150 mM Nacl, 0.2 mM EDTA, 1.1% Triton-X and protease/phosphatase inhibitors. The lysates were then incubated for 30 minutes on ice and centrifuged at 14000 rpm for 20 minutes at 4°C. The supernatants were collected and protein concentration was determined using BioRad assay with bovine serum albumin standards. Lysates containing 20 µg of proteins were run in a 14% SDS-polyacrylamide gels and transferred to nitrocellulose membranes. The blots were incubated with blocking buffer containing 5% milk and 0.1% tween-20 overnight at 4°C with shaking. Primary antibody (JTB Polyclonal Antibody-PA5-52307, Invitrogen) diluted to 1:1000 was added and incubated at 4°C for 1 h with constant shaking. Secondary antibody (mouse anti-rabbit IgG-HRP sc-2357, Santa Cruz Biotechnlogy, Inc.) diluted to 1:2000 ratio was added and incubated for 1 h at room temperature with constant shaking. After each incubation, the blots were washed thrice with TBS-T (1X TBS buffer, containing 0.05% tween-20) for 10 minutes each with constant shaking. Finally, the enhanced chemi-luminescence substrate (Pierce™ ECL Western Blotting Substrate-32106, ThermoFisher) was added to the blot and the blot was analyzed using a CCD Imager. For normalization, the blots were treated with Mouse GAPDH monoclonal antibody (51332, cell-signaling technology) and incubated for 1 h, followed by 1 h incubation of goat anti-mouse IgG-HRP (sc-2005, Santa Cruz Biotechnology) and the addition of ECL substrate. Detection and comparison of the intensity of the bands were done using ImageJ software (**Figure 4**).

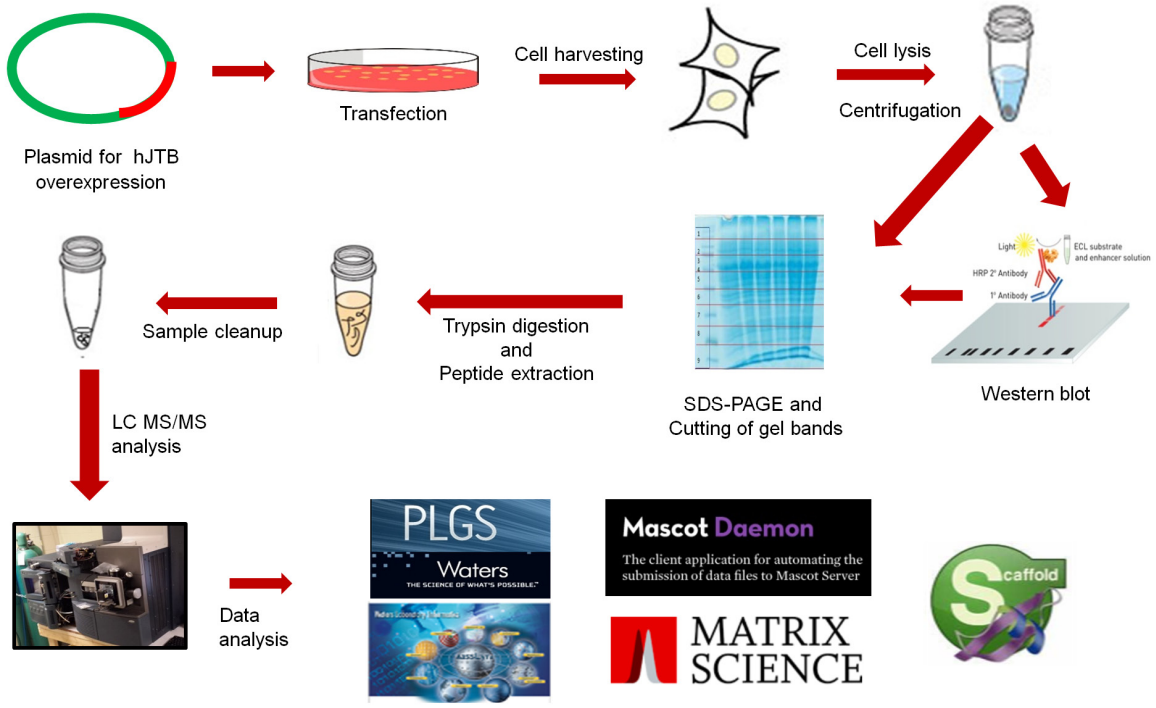

Figure 2. Workflow for cellular proteomics from 1D-SDS PAGE and in gel-trypsin digestion.

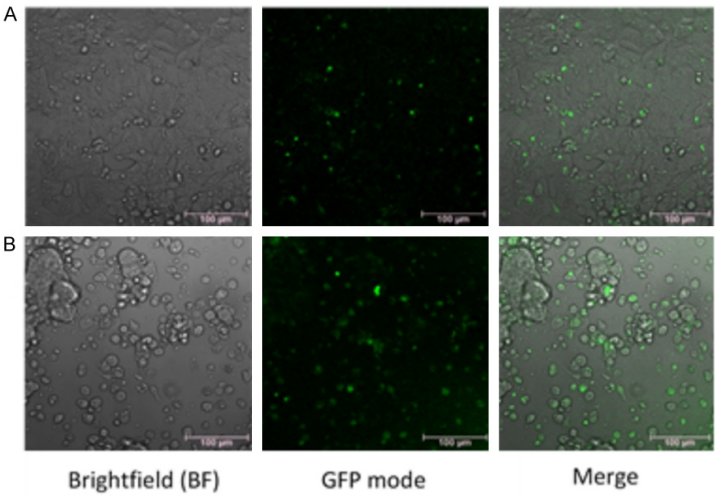

Figure 3. Confocal microscope images showing confirmation of stable transfection for control (A) and overexpressed (B) JTB condition. Left panel is the BF mode, middle panel is the GFP mode and the right panel is a merge between the BF and GFP modes.

from each sample was loaded on to the gel for three biological replicates. Once they were run, they were stained by Coomassie brilliant blue stain and distained with 10% acetic acid. The six gel lanes for control and upregulated JTB sample from the three biological replicates were divided into individual gel pieces and subjected to trypsin in-gel digestion [20, 21]. The peptides were then extracted using 50:50 Ammonium bicarbonate and Acetonitrile (ACN) with 5% formic acid (FA) solution twice and with 100% (v/v) ACN with 5% (v/v) FA solution. The tubes were then dried in a Speedvac and cleaned with a C18 Ziptip and solubilized in 2% (v/v) ACN/0.1% (v/v) FA in HPLC water [21].

Proteomic analysis

The proteins were subjected to fractionation by one-dimensional polyacrylamide gel electrophoresis (1D-PAGE) on a large format using a homemade 12% SDS-PAGE [19] {Channaveerappa, 2017 #48} (**Figure 5**). 200 µg of proteins

NanoAcquity liquid chromatography (LC) and MS (LC-MS/MS) was used to analyze the peptide mixture in NanoAcquity UPLC (Waters) coupled to a QTOF Xevo G2 MS (Waters) according to the procedures mentioned in [22-24]. The peptides were loaded onto a 100 µm × 10 mm NanoAcquity UPLC column BEH130 C18 1.7

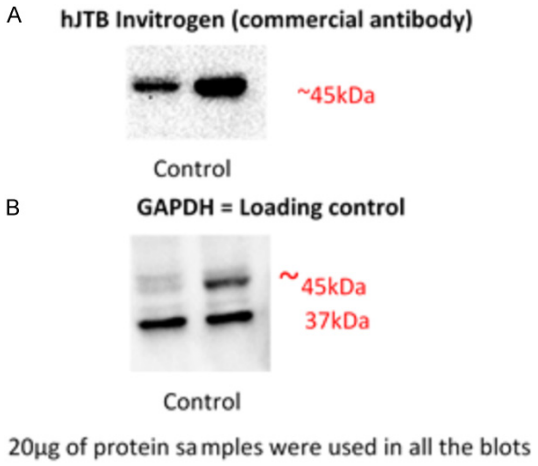

Figure 4. Overexpression confirmation of hJTB compared to control samples with (A) showing the overexpression at ~45 kDa in upregulated MCF7 cell lysate compared to control using the commercially available full length hJTB antibody from Invitrogen. (B) shows GAPDH used as the loading control at 37 kDa.

µM (Waters) and eluted over a 120 minute gradient at a flow rate of 400 nL/min. The aqueous solvent A was 0.1% FA in HPLC water and organic solvent B used was ACN containing 0.1% FA. The 120-min gradient was run as follows: 1% B (1 min), 8% B (1-5 min), 50% B (5-80 min), 85% B (80-105 min) and 1% B (105-120 min). A Picotip Emitter Silicatip nano-electrospray needle (New Objective, MA, USA) was coupled to the column. MS data acquisition involved MS scans (m/z range 350-1800) and survey of 0.2 sec. and direct dependent analysis of the top ten ions with the highest intensity, with the charge of 2+ to 6+. The MS/MS recorded over m/z 50-2000 was triggered when the intensity of the MS signal exceeded 500 counts/sec. The ten most intense peaks were selected in survey MS scans, for collision induced dissociation (CID) and fragmented until the count of MS/MS ions reached up to 6000 to 0.48 sec. each [23]. 1 pmol GluFib (Glu1-Fibrinopeptide B) standard peptide with the sequence EGVNDNEEGFFSAR and the doubly charged monoisotopic peak with m/z of 785.84 was used for calibration of both precursor and product ions [21].

Data processing and protein identification

The raw data were converted into peak list (pkl) files using ProteinLynx Global Server (PLGS, version 2.4) software as described in [21, 23]. The following parameters were used: polynomial order five-background subtraction with a threshold of 30%, two smoothing with a window of three channels in Savitzy-Golay mode and centroid calculation of top 80% of peaks based on a minimum peak width of four channels at half height [21]. The pkl files were submitted to the in-house Mascot server (www.matrixscience.com. Matrix science, London, UK, version 2.5.1) for data database search using the following parameters: human databases from NCBI, 0.5 parent mass error of Da, 0.8 product ion error of Da, enzyme used: trypsin with three missed cleavages and carbamidomethyl cysteine, methionine oxidized and propionamide cysteine as variable modifications. A list of proteins for each gel band was obtained from Mascot searches. These data files were then uploaded into Scaffold version 4.2.1 software (Proteome software, Inc., Portland, OR, USA) for quantitative analysis [21, 23].

Data sharing

Raw data from Masslynx, HTML files from Mascot and Scaffold files will be provided upon request, according to Clarkson University Material Transfer Agreement.

Statistical analysis

Data are presented as mean ± S.E.M. Statistical comparisons of three means were made using paired Student's t-test where appropriate. *P* values <0.05 was considered statistically significant.

Gene set enrichment analysis

Gene Set Enrichment Analysis (GSEA, https://www.gsea-msigdb.org/) was conducted to study hJTB related pathways and biological processes associated with the protein based on the protein dysregulations in control and upregulated JTB conditions in MCF7 cells. The corresponding genes for the dysregulated proteins and their fold change was used for the Hallmark enrichment (h.all.v.7.4.symbols.gmt) with 1000 number of permutations and with 500 maximum size to exclude larger sets and 3 minimum size to exclude smaller sets. This analysis was performed to look at the gene set summary that indicates whether the biological pathways are upregulated or downregulated. A false discovery rate (FDR) of <0.25 (25%) was

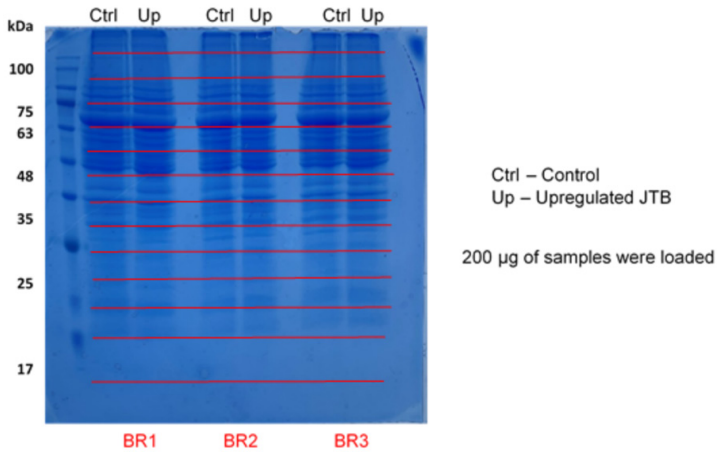

Figure 5. 12% SDS-PAGE gel with 200 µg protein from Control and Up (overexpressed hJTB) from MCF7 cell lysates cut into individual gel bands from each lane.

considered statistically significant according to GSEA threshold.

Results

Upregulated proteins for overexpressed JTB condition

GSEA algorithm was performed to investigate the main pathways that are associated with the JTB protein upregulation. The gene signatures corresponding to the dysregulated proteins and their respective fold change in control vs upregulated JTB sample was used for the Hallmark enrichment analysis. 47 genes were run through the GSEA Hallmark dataset. The result demonstrated four significantly enriched gene sets, from the following significantly upregulated pathways, with a FDR <0.25 (**Table 1**): HALLMARK_ESTROGEN_RESPONSE_EARLY, with an NES score of 1.43, HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION, with an NES score of 1.57, HALLMARK_ESTROGEN_RESPONSE_LATE, with an NES score of 1.62, and HALLMARK_MITOTIC_SPINDLE, with an NES score of 1.63. There were no significantly enriched downregulated pathways.

Mitotic spindle assembly pathway

As a hallmark of cancer, the limitless cell division is sustained by deregulation of the cell cycle [25]. Proper formation of the mitotic spindle is a key to genetic stability [26], alterations of the mitotic spindle checkpoint genes and their protein products contributing to common abnormalities in breast carcinoma [27]. The overexpressed JTB condition was accompanied by several upregulated proteins included in the mitotic spindle pathway, such as ACTNs, FLNA, FLNB, EZR, HSPA1A, HSP90A and WDR1 (**Table 1**). JTB is also involved in cell division/cytokinesis, as an important biological process in mitotic spindle pathway. Alpha-actinins (ACTNs) are cytoskeletal proteins that protect cells from mechanical stress and control cell motility [28], cross-linking actin filaments [29]. Alpha-actinins participate along with actin and myosin in the movement of membrane associated with cytokinesis [30]. α-actinin-1 (ACTN-1) is frequently increased in human breast cancer [31]. When overexpressed in mammary epithelial cells, ACTN-1 destabilizes E-cadherin-based adhesions associated with actin cytoskeleton, and promotes cell migration, leading to a poor prognosis in basal-like breast cancer cell lines and patients; the upregulation of α-actinin-4 (ACTN-4) expression was associated with breast carcinogenesis [28], and with a poor prognosis in breast cancer patients [31]. Also, ACTN-4 was highly expressed in several best studied breast cancer cell lines [32], interacting with signaling mediators, chromatin remodeling factors, and transcription factors [28]. Filamins (FLNs) have significant expression in breast cancer cell lines [32]. They are large actin-binding proteins that anchor the actin network onto the plasma membrane, regulate cell motility and the dynamic changes of the actin cytoskeleton in response to extracellular stimuli, interacting with signaling molecules, transcription factors, ion channels and transmembrane receptors [33]. Filamin is required for mitotic spindle function [34]. Depending on its subcellular localization and binding partner proteins, filamin A (FLNA) was initially known as a cancer-promoting protein [33, 35], but recent findings emphasize the contrary for its nuclear isoform [36]. However, the most evidences suggest that FLNA protein emphasizes an enforced expression in breast cancer tissues compared with benign breast tissues, in association with

Table 1. GSEA upregulated hallmarks pathways and gene ontology

Upregulated hallmark pathways	GSEA		Gene symbol for upregulated proteins	Gene description	GO (gene ontology): molecular function, cellular component, biological & tumor processes	
	NES	FDR q-val			GSEA https://www.gsea-msigdb.org/gsea/msigdb/genesets.jsp	other references
Mitotic spindle assembly	1.63	0.1	ACTNs (ACTN-1 [31] and ACTN-4 [28]) *both overexpressed in BC	actinins alpha	cytoskeletal and perinuclear part, cell projection, actin binding, actin filament based process, regulation of actin filament lenght, regulation of anatomical structure and morphogenesis, mitotic spindle assembly	destabilization of E-cadherin-based adhesion, cell migration, poor prognosis in BL-BC cell lines and patients [28, 31]
			FLNA *overexpressed in BC [37, 38]	filamin A	cortical and perinuclear cytoskeletal part, actin cytoskeleton organization and biogenesis, actin binding, microtubule based process, cell projection, mitotic spindle and organelle, including non-membrane bound, organization, anatomical structure and morphogenesis	FLNs are cancer-promoting protein [33], advanced stage, lymph node metastasis, invasion [37, 38], cytoplasmic FLNA promotes invasive cancer [35]
			FLNB *regulator of tumorigenesis [40]	filamin B	actin cytoskeleton organization and biogenesis, actin binding, non-membrane bound organelle, mitotic spindle organization	in human BC, an alternative splicing switch in FLNB promotes EMT, dissociation and migration of cancer cells [43]
			EZR/VIL2 *overexpressed in BC [47]	ezrin/cytovillin 2	cortical and perinuclear cytoskeletal part, cell projection/ruffle, actin cytoskeleton organization and biogenesis, actin filament based process, actin binding, microtubule based process, regulation of organelle organization, including non-membrane bound ones, anatomical structure, morphogenesis, and cell shape, regulation of cellular component size	EMT, metastasis [46] positive lymph node status, angiogenesis, lymphangiogenesis, poor outcome [47]
			HSPA1A *overexpressed in a large variety of tumors [57], including BC [61]	heat shock protein family A (Hsp70) member	mitotic spindle organization, regulation of organelle organization	*the intracellular isoform induces tumor growth and cell survival [58], drug resistance and suppression of anticancer immune responses [59], refolding damaged proteins or inhibiting apoptosis [60]; *the extracellular isoform induces anticancer immune responses or suppresses immune cell activity, inducing tumor growth [60]
			HSP90A *overexpressed in BC [63]	heat shock protein 90 alpha family	regulation of cellular component size	tumor progression, metastatic spread [67], stimulates immune memory, carcinogenesis, activates oncogenic proteins, stimulates cell survival, proliferation, growth, invasiveness, EMT, metastasis [63]
			WDR1 *overexpressed in IDC [69]	WD repeat-containing protein 1/WD repeat domain 1	actin/actin filament binding/actin filament based process, actin polymerization and depolymerization	increased migration [69], cytokinesis, invasion, proliferation [332]
			JTB/PAR/hJTB *overexpressed in many tumors [14]	jumping translocation breackpoint	cell division/cytokinesis	involved in cell cycle [14], required for normal cytokinesis and cell proliferation (www.nexprot.org)

Estrogen response late/ genes defining late response to estrogen	1.62	0.057	FLNB	filamin B	Massarweh response to estradiol, Doane response to androgen up	
			MYOF/FER1L3 *overexpressed in BC [73]	myoferlin	Dutertre estradiol response 6 hr up (gene up-regulated in MCF7 BC cells at 6 hr of estradiol treatment)	oncogenic protein [72] involved in proliferation, migration, adhesion [77], mobility, invasion in TNBC [78], MMPs activation [333], EMT, angiogenesis, metastasis [72], worse clinical outcome [74]
			FOXA1/HNF-3A *overexpressed in ER+ endocrine-resistant metastatic BC [86]; downregulated in TNBC [89]	forkhead box A1/ hepatocyte nuclear factor 3-alpha	Lim mammary luminal mature up (gene consistently up-regulated in mature mammary luminal cells both in human and mouse species but down-regulated in mammary stem cells)	promotes aggressive cancer cell phenotype, activates prometastatic transcriptional programs [86], mediates endocrine-therapy resistance [88]; increases malignancy, cancer stemness, decreases apoptosis in TNBC cells
			EPPK1	epiplakin	Aigner ZEB1 targets (gene up-regulated in MDA-MB-231 BC cell line after knockdown of ZEB1 transcription factor by RNAi)	
			FASN *overexpressed in BC [92]	fatty acyd synthase	Doane BC classes up, Doane response to androgen up	cancer malignant progression [94], tumor cell migration, metastasis [96]
			JTB/PAR/hJTB	jumping translocation breackpoint	Charafe BC luminal vs mesenchymal up	
EMT	1.57	0.068	FLNA	filamin A	cell cortex/cytoskeletal part, actin cytoskeleton organization and biogenesis, microtubule based process, cell projection	
			COL3A1 *overexpressed in BC [107, 108], GC [103], bladder cancer (BLCA) [104]	collagen type III alpha 1 chain	ECM part, Kegg ECM-receptor interaction, reactome integrin cell surface interactions, up-regulated in the early tumor vs normal samples, Anastassiou multicancer invasiveness signature resulting from cancer cell-TME interaction, Turashvili breast ductal carcinoma vs ductal normal up, Turashvili breast ductal carcinoma vs lobular normal up, Turashvili breast lobular carcinoma vs ductal normal up	migration, invasion, local recurrence, advanced tumor stage, metastasis, worse prognosis [104]
			COL11A1 *early-onset BC patients [114], overexpressed in chondroid MBC [112]	collagen type XI alpha 1 chain	ECM part, Kegg ECM-receptor interaction, up-regulated in the early tumor vs normal samples, Anastassiou multicancer invasiveness signature resulting from cancer cell-TME interaction, Turashvili breast ductal carcinoma vs ductal normal up, Turashvili breast ductal carcinoma vs lobular normal up, Turashvili breast lobular carcinoma vs ductal normal up	ECM-receptor interaction, focal adhesion [114]
Estrogen response early/genes defining early response to estrogen	1.43	0.115	MYOF	myoferlin	Creighton endocrine therapy resistance 1 in BC expressing ESR1 and ERBB2, Massarweh response to estradiol (gene rapidly up-regulated in BC cell cultures by estradiol)	
			FASN	fatty acid synthase	Doane BC classes up, Doane response to androgen up, Farmer BC apocrine vs basal, Smid BC ERBB2 up	
			EPPK1	epiplakin	Aigner ZEB1 targets (gene up-regulated in MDA-MB-231 BC cell line after knockdown of ZEB1 transcription factor by RNAi)	
			FLNB	filamin B	BHAT ESR1 targets not via AKT1 up (gene bound by ESR1 and up-regulated by estradiol in MCF7 BC cells) and via AKT1 up	
			FOXA1/HNF-3A	forkhead box A1/ hepatocyte nuclear factor 3-alpha	Vantveer BC ESR1 up (up-regulated genes from optimal discriminating ER+ vs ER- breast tumors)	
			JTB/PAR/hJTB	jumping translocation breackpoint	Charafe BC luminal vs mesenchymal up	

*ERBB2, receptor tyrosine-protein kinase erbB-2; ESR1, estrogen receptor 1; ZEB1, Zinc finger E-box binding homeobox 1.

advanced stage, lymph node metastasis, invasion, menstruation state and other risk factors, contributing to breast cancer tumorigenesis and progression [37, 38]. Also, FLNA was expressed at high levels in different breast cancer cell lines [32]. High levels of cytoplasmic FLNA and the vascular endothelial growth factor are involved in R-Ras (small GTP binding and hydrolyzing proteins) regulators of signal transduction that mediate cell growth, division, differentiation, death and integrin-mediated cell adhesion [39], promoting invasive cancers [35]. Filamin B (FLNB) is a protein isoform that acts as a regulator of tumorigenesis [40], has a key role in endothelial cell motility and migration related to angiogenesis [41]. Within cells, increasing the filamin concentrations during tumoral progression could modify the actin filament organization and cell behaviour [42]. In human breast cancer, an alternative splicing switch in FLNB promotes the mesenchymal cell state that encourages the dissociation and migration of cancer cells from primary site to distant sites [43]. Cytovillin 2 (VIL2)/ezrin (EZR) is a highly related actin filament binding protein that links transmembrane proteins with the actin cytoskeleton [44]. In normal cells, EZR contributes in epithelial morphogenesis and maintenance of the normal shape and polarity of epithelial cells, adhesion and migration [44]. As a member of ezrin-radixin-moesin (ERM) family, EZR is commonly upregulated in aggressive cancers and it is implicated in cell signaling and cytoskeletal dynamics at plasma membrane level [32]. EZR overexpression sustains the survival of cancer cells and disrupts cell-to-cell contacts, facilitating migration and invasion of cancer cells [45]. EZR is involved in EMT, metastasis [46], and regulation of tumor-induced angiogenesis and lymphangiogenesis promoted by Src, a non-receptor tyrosine kinase; its overexpression and abnormal localization were associated with positive lymph node status, metastasis, and poor outcome in breast cancer patients [47]. Also, EZR interacts with protein kinase B (AKT), promoting its kinase activity and regulation of the AKT signaling pathway in breast cancer [46]. EZR also interacts with FES kinase, which promotes cell migration, decreases β-catenin levels, and increases cell survival *via* activation of PI3K [45]. EZR is significantly phosphorylated, upregulated and activated in cancer cells, increasing their invasive proprieties [44]. It is upregulated by oncogenic transcription factors and downregulated by tumor suppressor factors.

HSPA1/HSP72 [48] are cancer-relevant anti-apoptotic chaperones that inhibit stress-inducing signals, prevents the permeabilization of mitochondrial membrane, and suppresses caspase activation or DNA fragmentation [49]. HSP70 proteins are overexpressed in human breast tumors and breast cancer cell lines [50], promoting cancer cell growth [51], cancer cell viability and protein damage repair [52], in correlation with metastasis and chemotherapy resistance [48]. As such, majority of human cancers overexpress HSP70 family members as biomarkers for poor prognosis [53], HSPs representing promising therapeutic targets [54]. In MCF7 breast cancer cell lines acquiring thermotolerance, the HSPA1 chaperone and its co-factors were upregulated [55]. The unmethylated HSPA1 is a prognostic biomarker in high-grade serous carcinoma, the trimethylated isoform being found as prevalent in metastatic breast carcinoma (MBC) [56]. Heat shock 70 kDa protein 1 (HSPA1A) is involved in protection of proteome against oncogenic stress, being the major stress-induced member of the HSP70 family [53], which is detectable in cytoplasm, nucleus, plasma membrane and extracellular exosomes [52]. The intracellular HSPA-1A is highly expressed in a large variety of tumors [57], where promotes tumor cell growth and survival [58], drug resistance, modulation of cell death pathways and supresses anticancer immune responses [59], refolding damaged proteins or inhibiting apoptosis [60], inclusive in breast cancer [61]. Heat shock proteins 90 (HSP90) is an essential family of molecular chaperones also involved in breast cancer that was correlated with increased cancer cell survival and poor prognosis, cell proliferation, differentiation, apoptosis, invasion, neoangiogenesis, metastasis, protease-dependent matrix remodelling and integrin-mediated cell adhesion [62, 63], adaptation to stress, cell motility and signal transduction [64]. Its inhibitors are tested as a breast cancer treatment [65]. HSP90 facilitates malignant transformation of mammary cells, by stabilizing the mutated and upregulated oncoproteins in breast tumors, and contributing to the activation of several cell pathways, such as growth stimulatory and transforming, in absence of growth factors [66]. Heat shock protein-90α (HSP90A/

HSP90AA1) is the inducible isoform of HSP90, mainly involved in cell responses to external stressors and predominantly secreted by cancer cells, HSP90α levels being positively correlated with tumor progression and metastatic spread and functioning as diagnostic and prognostic biomarker [67]. It can be secreted into the ECM and can also enter the nucleus to stimulate the formation of immune memory and participate in carcinogenesis, DNA damage regulation, cell cycle regulation, and activates many oncogenic proteins, stimulating cell survival, proliferation, growth, invasiveness, metastasis, EMT, and could be a potential target for cancer treatments [63]. The overexpression of HSP90AA1 was related with diverse tumor types, including breast cancer; HSP90AA1 might serve as a putative biomarker for breast cancer, its plasma level of predicting the risk of breast cancer onset and distant metastasis [63]. WD repeat domain 1 (WDR1) protein is a cofactor of the actin depolymerizing factor (ADF)/cofilin, accelerating ADF/cofilin-mediated actin disassembly [68]. It is overexpressed in invasive ductal carcinoma (IDC), in association with an increased migration and a shorter distant metastasis-free survival [69].

Estrogen response late pathway

A meta-analysis of estrogen response in MCF7 breast cancer cells revealed a set of early target genes involved in early response pathways, related especially to cell signaling and proliferation, and later target genes involved in late response pathways, related to breast cancer cell division, DNA repair and recombination [70]. FLNB, overexpressed in this experiment, was included among the 36 genes involved in tamoxifen response prognostic signature as targets of estrogen signaling [71], being involved in mitotic spindle assembly and in early estrogen response pathway. Included in both early and late estrogen response pathways (**Table 1**), myoferlin (MYOF) is a mammalian protein belonging to ferlin family expressed in different membranes, where it participates in membrane repair and trafficking processes [72]. MYOF is overexpressed in several cancers, including breast carcinoma [73], related to a worse clinical outcome [74], as well as in several invasive cancer cell lines, its depletion reducing migration and invasion by reversion of cancer cells to an epithelial phenotype [75], suggesting a mesenchymal-to-epithelial transition (MET) [76]. As an oncogenic protein [72], it contributes to proliferation and migration, depletion of cell-to-cell and cell-to-ECM adhesion [77], inducing invasion of cancer cells in TNBC [78], enhancing breast cancer cells mobility [77], EMT, angiogenesis and metastasis [72], energy reprogramming and exosomal modulation [77]. MYOF has an important role in degradation of the epidermal growth factor receptor (EGFR), consequently to its activation and internalization in breast carcinoma cells [79], also targeting MMPs [76] and transforming growth factor beta (TGF-β) [77]. MYOF increases the disintegrin and metalloproteinase domain-containing protein ADAM12 expression level that is highly upregulated in human breast cancer [80], decreasing tumor cell apoptosis and increasing stromal cell apoptosis that leads to tumor progression [81]. MYOF targeting by therapeutic drugs may impair breast cancer metastasis [73], its depletion blocking cell migration and EMT [79]. Thus, MYOF was identified as a promising biomarker in breast cancer [77]. Hepatocyte nuclear factor-3 alpha (HNF3α)/forkhead transcription factor A1 (FOXA1) is important for growth and differentiation of breast epithelium [82]. It belongs to the forkhead box (FOX) transcription factor family of proteins that are significantly involved in cancer [83], the overexpression of HNF3α being emphasized in esophageal and lung adenocarcinomas [84]. FOX deregulation was correlated with the onset, progression and drug resistance of human various malignancies [85]. FOXA1 overexpression leads to aggressive phenotypes of estrogen receptor-positive (ER^+) metastatic breast cancer by activating prometastatic transcriptional programs [86], promotes tumor progression and dedifferentiation [87], as well as mediating endocrine-therapy resistance [88]. FOXA1 downregulation can lead to increased malignancy and cancer stemness, and decreases apoptosis in TNBC cells by transcriptionally suppressing the expression of SOD2 and IL6 [89]. Metabolic reprogramming is a hallmark of carcinogenesis and progression [90], increased lipid biogenesis being critical for rapid proliferation of cancer cells [91]. Fatty acid synthase (FASN), a key enzyme for endogenous synthesis of long chain fatty acids (FAs), is overexpressed in lipogenic tumors, including breast carcinomas [92], such as HER-2/*neu*-positive breast tumors [93]. Endo-

genous FAs biogenesis, which occurs at a high rate in tumor tissues [91], constitutes oncogenic stimuli that drives cancer malignant progression [94]. FASN was found to be highly upregulated in various breast cancer cell lines, including the hormone-dependent MCF7 cell line; its levels increased with tumor stage, while the inhibition of fatty acid synthesis induced apoptosis and cytotoxicity [95]. In invasive ductal carcinoma (IDC) and breast cancer cell lines, the FASN expression affects the content of fatty acids and these FASN-mediated changes in specific fatty acids promote tumor cells migration and metastasis [96]. Inhibition of FASN and lipid synthesis could be beneficial for tumor treatment resistance [94].

Epithelial-to-mesenchymal transition pathway

The epithelial-to-mesenchymal transition (**Table 1**) is linked to alteration of the intracellular cytoskeleton and the ECM remodeling to facilitate local invasion in cancer [97]. Apart its role in mitotic spindle function, the actin-binding FLNA protein forms a complex with refilinB that controls formation of a new perinuclear actin network that accompanies nuclear shape changes during EMT [98]. ECM remodeling is an essential event that promotes cancer invasion and metastasis [99]. Fibrillar collagens, such as type III and XI collagen [100], are involved in attachment of cells to ECM molecules, either directly or via extracellular collagen-binding proteins, all of them being involved in cell adhesion and migration [101]. An extensive deposition of fibrillary collagen network in the TME promotes cancer progression and metastasis, followed by low survival rates for patients [100]. Collagen type III alpha-1 chain (COL3A1), an important component of the ECM, functions in cell adhesion, migration, proliferation and differentiation by its interations with collagen-binding integrins, which are transmembrane receptors that mediate cell adhesion [102], and are also involved in breast cancer development [99]. COL3A1 is known to be significantly overexpressed in many cancers, i.e., gastric cancer (GC) [103] or bladder cancer [104], its upregulation being positively related to a worse prognosis, advanced tumor stage, local recurence and invasion [104], tumor-infiltrating immune cells (TIICs) recruitment, ECM-receptor interaction, regulation of actin cytoskeleton and adhesion pathways [105]. A considerable degradation of ECM components, including collagen molecules, is required for cell locomotion [106]. COL3A1 was overexpressed in lymph nodes affected by metastatic ductal breast carcinoma cells [107], and also in ductal carcinoma *in situ* (DCIS) myoepithelial cells compared with normal mammary myoepithelium [108]. COL3A1 overexpression was cited in relation with breast cancer distant metastasis and death after surgery and systemic treatment [109]. COL3A1 might affect cancer cell migration and invasion through mitogen-activated protein kinase (MAPK) signaling pathway [104] involved in the regulation of cell proliferation, differenciation, apoptosis [110], stress responses, tumor ECM degradation and angiogenesis. The hyperactivation of ERK/MAPK signaling pathway plays a key role in cancer development and progression [111]. According to GSEA, COL3A1, as well as COL11A2, is a ECM part involved in Kegg ECM-receptor interaction, reactome integrin cell surface interactions, it is upregulated in the early tumor vs normal samples, Anastassiou multicancer invasiveness signature resulting from cancer cell-TME interaction, Turashvili breast ductal carcinoma vs ductal normal (as a gene upregulated in ductal carcinoma vs normal ductal breast cells), Turashvili breast ductal carcinoma vs lobular normal, Turashvili breast lobular carcinoma vs ductal normal. Collagen type XI alpha-2 (COL11A2) expression was upregulated in chondroid metaplastic breast cancer (MBC), a rare type of TNBC, compared with squamous MBC or with MBC with spindle cell differentiation [112]. COL11A2, a small collagen fiber involved in the construction of ECM [113], was detected in early-onset breast cancer patients, being involved in ECM-receptor interaction and focal adhesion [114].

Estrogen response early pathway

The estrogen response early score generated by GSEA was previously published as significantly associated with immune cell infiltration, patient survival, and endocrine therapy in both primary and metastatic ER-positive breast cancer, having potential as both prognostic and predictive biomarker for endocrine therapy [115]. In this experiment (**Table 1**), JTB overexpression induced an increased expression of MYOF, FASN, EPPK1, FLNB, FOXA1, all of them described in the previously discussed pathways.

*Other upregulated proteins (**Table 2**)*

The breast cancer landscape is characterized by oxidative stress (OS) associated with tumorigenesis and cancer progression [116], hypoxia [117], and extracellular acidosis that promote tumor malignant and aggressive phenotype [118] and compromise the protein folding [119]. The epithelial cells exposed to OS acquire invasiveness, emphasizing the direct role of reactive oxygen species (ROS) in the carcinogenetic metamorphosis of epithelial cells, by dissolution of cell-to-cell contacts, redistribution of E-cadherin in the cytoplasm, up-regulation of integrins and matrix metalloproteinases (MMPs) [120]. H^+/K^+-ATPase subunit alpha/gastric proton pump subunit alpha (H^+/K^+-ATPase/H^+-ATPase/ATP4A or HKA) is a transmembrane protein with an essential role in cellular functions [121] that was upregulated for these JTB overexpressed condition. The overexpression of gastric proton pump could be correlated with a chronically hypoxic and acidic microenvironment that leads to an aggressive cancer cell phenotype [122]. By their specific metabolism, especially by the Warburg effect [123], cancer cells chronically acidify their tumor microenvironment (TME) [124], leading to an aggressive cancer cell phenotype characterized by a normal or alkaline pH inside the tumor cells [122]. Proliferation, viability, invasion and metastasis of cancer cells can be promoted by an acidic TME [124], *in vitro* tumor cell proliferation rate being highest at pH 6.8 compared with pH 7.3 necessary for the proliferation of normal cells [122]. HKA is a heterodimeric proton pump composed of α- and β-subunits that generates and maintains the electro-chemical gradients across cell membranes, transporting cations, heavy metals and lipids [125]. The catalytic α-subunit forms the pores through plasma membrane, or mitochondria and other organelles [126] that allow the ion transport [126], bind the proton pump inhibitors and potassium acid blockers and is composed of 10 transmembrane helices [127]. The overexpression and activation of membrane-bound pH-regulating systems allow to cell to survive into an acidic TME and avoid the acidification inside cancer cells [128]. The expression of both α- and β-subunits of HKA was significantly higher in laryngeal carcinoma tissues than in normal laryngeal or paracarcinoma tissues [127], while it was downregulated in esophageal carcinoma (ESCA) tissues [129] and stomach adenocarcinoma (STAD) relative to its high expression in healthy gastric cells, correlated with a good prognosis [130]. A recent review shows that the HKA subunits expressed in normal and cancer cell lines, including breast invasive carcinoma, have no significant alterations, with the exception of gastric and esophageal cancer cells; consequently, these subunits might be explored as biomarkers or putative target for cancer treatment [121]. The suppression of growth in MDA-MB-468 TNBC cells, reduction of cell migration in MDA-MB-231 or the anti-proliferative behaviour by apoptosis in MCF7 breast cancer cell lines [131] have been possible by inhibiting tumor cell ability to remove acid accumulated during its metabolism using proton pump inhibitors (PPIs) that could reduce the breast cancer risk [132], potentiate the chemotherapy efficiency and suppress breast cancer metastasis [131]. In breast carcinoma compared with normal breast tissue samples, ABC transporter variant T2 (ABCA2), also identified in this experiment, as well as ABC3/7/12/13, ABCB2/3/8/9/10, ABCC1/4/5/10/11/12, ABCD1/3, ABCE1, ABCF1/2/3 and ABCG1 were significantly upregulated, while ABCA5/6/8/9/10, ABCB1/5/11, ABCC6/9, ABCD2/4, ABCG5, and ABCG8 were downregulated [133]. Upregulated ABCA2 plays a role in the trafficking of LDL-derived free cholesterol, its dysregulation inducing cancer pathogenesis [134]. It is possible that ABCA2, also present in lysosomes and exosomes that could mediate tumor progression, to contribute to the lipid composition control in the plasma membrane and lipid transport activity [135].

Iron metabolism and homeostasis are essential for cellular, tissular and systemic health [136]. Numerous iron metabolism-related proteins and signaling-related pathways are frequently dysregulated in breast cancer [137]. As an essential dietary nutrient, iron is also a key cofactor for cancer growth, enhancing breast tumor initiation, progression, metastasis [137], OS and control of enzymes activity involved in lipid peroxidation, protein modification, and DNA damage by ROS [138]. Hemochromatosis (HFE/high iron FE/homeostatic iron regulator) protein was highly upregulated for JTB overexpressed condition. HFE is a transmembrane glycoprotein [139] that binds to transferrin receptor-1 (TRF1) and transferrin receptor-2

Table 2. Other upregulated proteins for JTB overexpressed condition

Proteins	Symbol	BC/other malignancies		neoplastic effect
Membrane proteins and membrane-associated proteins				
H^+/K^+-ATPase subunit alpha/gastric proton pump subunit alpha	H^+/K^+-ATPase/ H^+-ATPase/ ATP4A/HKA	no significant alterations reported in BC [121]; $^+$overexpressed in laryngeal carcinoma [127]; downregulated in ESCA [129] and STAD [130]	$^+$TME acidification and hypoxia [124], aggressive cancer cell phenotype [122], cell survival in acidic TME and maintenance of normal pH inside cancer cells [128]	protumorigenic
ATP-binding cassette (ABC) transporter variant T2	ABCA2	overexpressed in BC [133]	chemoresistance [334] and MDR [335], possible tumor progression [135], trafficking of LDL-derived free cholesterol related to cancer pathogenesis [134]	protumorigenic
Hemochromatosis protein	HFE	overexpressed in BC [137]	breast tumor initiation, cancer cell growth, metastases [137]	protumorigenic
Receptor expression-enhancing protein 2/receptor accessory protein 2 (also in interaction with microtubules [149])	REEP2	mRNAs expressed in BC [336] and CRC [337]	enhances cell surface expression of some GPCRs, promotes DNA damage-induces apoptosis [150]	favorable prognosis in BC patients (according to HPA)
Tumor protein p63 regulated 1 like/family with sequence similarity 79 member A/ Mover	FAM79A/ TPRG1L	activated expression by p63/p73 transcription factors [155]	repression of Wnt responsive genes [155]	inhibition of the Wnt signaling pathway, putative antioncogenic [157]
Polycystic kidney disease protein 1-like 2/polycystin 1-like 2	PKD1L2	mRNA overexpressed in BC [160], deleterious mutations of *PKD1L2* gene identified in BC [161]	component and regulator of cationic channels [338], cell adhesion [339], GPRCs-like action [159]	improved prognosis in BC patients [160]
ER proteins				
Ubiquitin-specific-processing protease 19/ubiquitin carboxyl-terminal hydrolase 19 (possible present also in cytoplasm [164])	USP19	overexpressed in metastatic BC [164]	cell proliferation, modulation of DNA damage repair, inhibition of apoptosis [163], distant metastasis, cancer cell migration and invasion [164]	prooncogenic
Chromatin remodeling and transcription/translation regulators				
Chromatin-remodeling ATP-ase INO80	INO80	overexpressed in BC [168, 169]	oncogenic transcription, tumor growth in NSCLC [165] cell proliferation, tumorigenesis [172]	protumorigenic
Specificity protein 1 transcription factor	Sp1	overexpressed in BC [174]	proliferation, invasion, metastasis, chemoresistance, oncogene upregulation [173], poor prognosis [174]	protumorigenic
Programmed cell death 11 transcription factor	PDCD11	-	induces activation of NF-κB [176], cell proliferation, survival, differentiation [179], carcinogenesis [180]	protumorigenic
Transcriptional coactivator ALY	ALY	overexpressed in BC [183] and other malignancies [182]	lymph node metastasis, invasiveness and migration [182]	protumorigenic
Trinucleotide repeat-containing adaptor 6C protein	TNRC6C	downregulated in PTC [190]	carcinogenesis and tumor progression [191]	tumor suppressor, inhibition of proliferation, migration, invasion, promotion of apoptosis [190], mediates the apoptosis of circRNAs involved in carcinogenesis and tumor progression [191]
Eukaryotic translation elongation factor-1 alpha 2	EEF1A2	overexpressed in BC [192]	good prognosis in BC [193]	good prognosis
Intermediary metabolism related proteins				

Human transketolase in covalent complex with donor ketose D-fructose-6-phosphate chain A	TKT	overexpressed in BC [90]	cancer cell rapid proliferation [195], growth [197], lymph node metastasis [90], decreases OS and ROS [196]	protumorigenic
Stress-responsive proteome				
Heat shock 70 kDa protein 9/mortalin	HSPA9/ GRP75	overexpressed in BC [202]	cell stemness [201], proliferation [203], carcino-genesis [204], lymph node metastasis in IDC [202]	protumorigenic
Serum proteome				
Serum albumin	ALB	low/high levels in patients with BC [213]	poor prognosis/increased OS [213]	increased OS
Hormones				
Human chorionic gonadotropin	hCG	overexpressed as β-hCG in BRCA mutated cancer cells [215]	migration and invasion [215]	protumorigenic

*CRC, colorectal cancer; ESCA, esophageal carcinoma; IDC, invasive ductal carcinoma; OS, oxidative stress; PTC, papillary thyroid carcinoma; ROS, reactive oxygen species; STAD, stomach adenocarcinoma.

(TFR2) [139] in competition with transferrin (TF) and its expression may lead to iron accumulation in cancer cells that exhibit a high dependence on iron for their growth and proliferation [140], called iron addiction [141], and in cancer-associated cells, such as macrophages, which potentially deliver iron to cancer cells [140], and to other cells of TME, where HFE is strongly expressed, raising intracellular iron levels by inhibiting iron release and upregulating of iron import [142]. HFE stimulates breast tumor growth, proliferation, DNA synthesis, and the stemness wingless signaling pathway (Wnt) [139]. Chronic exposure to excess iron induces EMT, loss of p53, suppression of p53 transcriptional activity and decreased expression of p53 target genes, such as p21, cyclin D1, Bax, and solute carrier family 7, member 11 (SLC7A11) [143]. The SLC7A11 downregulation, a ferroptosis-related gene [144], induces drug resistance in MCF7 breast cancer cells [145]. As a non-apoptotic regulated cell death (RCD) type, ferroptosis is a form of iron-dependent cell death involving the ROS production [141] and accumulation of lipid peroxides [146] that is impaired in cancer [147]. HFE was identified as potentially novel prognostic biomarker that promotes tumor progression in some malignancies, such as head and neck squamous cell carcinoma (HNSCC) [139]. Receptor expression-enhancing protein 2/receptor accessory protein 2 (REEP2) is an integral membrane protein usually expressed in gustatory cells [148]. In interaction with microtubules or localized in ER membranes [149], REEPs enhance cell surface expression of plasma membrane G protein-coupled receptors (GPCRs) and some REEP subtypes affect ER structure and ER cargo capacity of specific GPCRs and their surface expression, regulating the ER-Golgi processing [150]. As an ER-shaping protein, REEP2 could act in promoting DNA damage-induces apoptosis, its promoters being significantly activated by p53 overexpression [151] that prevents neoplastic development [152]. According to the Human Protein Atlas, the REEP2 high expression is favourable in breast cancer. Tumor protein p63 regulated 1-like (TPRG1L)/family with sequence similarity 79 member A (FAM79A)/mover is one of the members of the FAM protein family [153] that have a controversial role in cancer [154]. TPRG1L gene expression is activated by p63/p73 transcription factors [155], that represses the *Wnt* responsive genes [155], which are normally involved in breast cancer proliferation, metastasis, immune landscape regulation, stemness maintenance, drug resistance, and morpho-physiological shaping [156]. Inhibition of Wnt signaling reduced the capacity of tumor cells to self-renew and disseminate, while it induced a reexpression of breast epithelial differentiation markers and repression of several EMT factors in basal-like breast cancers [157]. Polycystic kidney disease protein 1-like 2/polycystin 1-like 2 (PKD1L2) is a transmembrane signalling protein, which mediates fluid flow, taste, and pH in different tissues [158], but also in mammary gland [159]. The mRNA overexpression of PKD1L2 indicated an improved prognosis for breast cancer patients [160]. It is possible that *PKD1L2* to be a candidate gene for breast cancer [159] as long as deleterious mutations have been identified in *PKD1L2* gene in breast cancer [161]. Ubiquitin-specific-processing protease 19/ubiquitin carboxyl-terminal hydrolase 19 (USP19) is a deubiquitinating enzyme (DUB), a tail-anchored ubiquitin-specific protease localized to the ER that controls the degradation of proteins, being overexpressed during the unfolded protein response (UPR) [162]. Among DUBs, the ubiquitin-specific protease (USP) family has a key role in EMT induction and behaviour of mammary epithelial stem cells [163]. USP19 is involved in maintenance of cell proliferation, modulation of DNA damage repair, and inhibition of apoptosis [163]. In gastric cancer, USP19 promoted tumor progression by inducing MMP2/MMP9 expression and related enzyme activity [163]. USP19 overexpression is associated with distant metastasis in patients with early breast cancer, due to its implications in increasing cancer cell migration and invasive potential, both *in vitro* and *in vivo* [164]. Chromatin-remodeling ATPase INO80 (INO80/KIAA1259 protein) is required for oncogenic transcription and tumor growth [165], DNA replication and chromosome segregation [166], DNA damage repair, such as in the case of UV-damaged DNA [167], and recombination [168], also being associated with spindle microtubule during mitosis [166]. It is overexpressed in breast cancer [168, 169], cervical cancer cell lines and tumor tissues, where promotes cell proliferation and tumorigenesis by activation of the pluripotency homeobox domain transcription factor NANOG [170], that possesses protumorigenic abilities [171] and that it is over-

expressed in breast cancer cells, promoting migration and invasion [172]. Specificity protein 1 (Sp1) is a multifunctional transcription factor involved in cell differentiation and growth, apoptosis, immune response, DNA damage response, chromatin remodeling [173], senescence and angiogenesis [174]. It is overexpressed in many cancers, being associated with poor prognosis [174], such as in breast, lung, pancreatic, glioma, thyroid [174], and ovarian cancer [175], where enhance proliferation, invasion, metastasis and chemoresistance, upregulating the oncogenes involved in these processes [173]. Programmed cell death 11 (PDCD11)/NF-κB-binding protein (NFKB)/KIAA0185/ALG-4 [176]/RRP5 homolog is a nucleolar transcription factor binding protein that induces activation of the proinflammatory nuclear transcription factor kappa-light-chain-enhancer of activated B cells (NF-κB) family of DNA-binding proteins [176]. The aberrant activation of NF-κB is commonly observed in breast cancer, facilitating the development of invasive tumor phenotype [177], directly regulating the transcription of EMT-transcription factors (TFs) genes in breast cancer cells [178] and sustaining cell proliferation, survival, differentiation [179], and carcinogenesis [180]. The high expression of circPDCD11 that acts as an oncogene in TNBC tissues and cells was significantly correlated with a poor prognosis of TNBC patients, circPDCD11 promoting proliferation and aerobic glycolysis of TNBC cells, by acceleration of glucose uptake, lactate production, ATP generation, and the ECM acidification [181]. The transcriptional coactivator ALY is an essential mRNA export factor that is upregulated in different malignancies, such as human oral squamous cell carcinoma (OSCC), where it was related to lymph node metastasis by regulating cellular invasiveness and migration [182]. The immunohistochemical analysis indicated an overexpression of ALY protein in breast carcinoma [183]. Depletion of ALY results in cell growth suppression and mRNA export decreasing [184], the inappropriate RNAs transport causing a dysregulation of a wide range of cellular processes, which can contribute to cancer [185]. Formerly described as a transcriptional coactivator, ALY influences the expression of more than 400 genes; i.e., it represses the transcriptional regulatory activity of E2F2, a member of E2F family of transcription factors that control cell cycle progression [186], mediate the expression of genes involved in tumor neoangiogenesis, TME remodelling, cell survival, interaction with endothelial cells to facilitate metastasis in mouse models and human metastatic breast cancer [187]. Trinucleotide repeat-containing adaptor 6C protein (TNRC6C), also known as GW182C, is a member of GW182 protein family that restricts the selective export of used microRNA in mammalian cancer cells by its retention in RNA processing bodies (GW/P-bodies), preventing thus the extracellular vesicle/exosome (EV)-mediated export of miRNAs, increasing cellular miRNA levels in cancer cells to induce senescence [188]. The tumor cell transformation alters the pathways through which microRNAs are exported from cells [189]. The overexpression of TNRC6C significantly inhibited proliferation, migration and invasion and promoted apoptosis of thyroid cancer cell lines, demonstrating that TNRC6C functions as a tumor suppressor and it is frequently downregulated in papillary thyroid carcinoma (PTC) [190]. Overexpression of TNRC6C can reduce the abundance of related circRNAs that can encode proteins or peptides involved in carcinogenesis and tumor progression and that are important in tumorigenesis, proliferation, metastasis, invasion, and drug resistance [191]. The elongation factors are proteins that function at ribosomal level. The eukaryotic translation elongation factor-1 alpha 2 (EEF1A2) is a member of eukaryotic translation elongation factor family involved in onset and progression of different cancers, EEF1A2 showing a higher expression in most of cancer types, including breast cancer, being a significant predictor of outcome [192]. It emphasized a predicted poor prognosis in pancreatic, ovarian and gastric cancers [192], while its overexpression was associated with good prognosis in breast cancer [193]. Human transketolase (TKT) in covalent complex with donor ketose D-fructose-6-phosphate chain A is a metabolic enzyme that links the pentose phosphate pathway (PPP) to glycolysis, the TKT pathway being involved in cancer progression and metastasis [194], by promotion of the rapid proliferation of tumor cells [195]. The TKT overexpression was correlated with lymph node metastasis in breast cancer [90] and decreased overall survival (OS) and relapse-free survival (RFS) among breast cancer patient [196]. TKT provides tumor cells with materials for biosynthesis [195], and regulates the meta-

bolic switch to control breast cancer cell metastasis through the α-ketoglutarate signalling pathway [90]. Also, the TKT is required for cell cancer growth due to its ability to affect the antioxidant NADPH production to counteract the oxidative stress and to drive cancer development [197]. In human breast cancer cell line MCF7, silencing of TKT reduced the glycolytic flux [196].

Heat shock proteins (HSPs) are essentially involved in cellular proteostasis [198] and are permanently secreted by cancer cells as extracellular HSPs (eHSPs), in stress conditions, within the ECM, where they regulate extracellular protein activity, send autocrine and paracrine signals, and increase cancer cell growth and malignancy, being involved in ECM remodelling, resistance to apoptosis, promotion of cell migration and invasion, stimulate the EMT, neoangiogenesis and activation of the cancer-associated stromal cells and metastatic dissemination [67]. HSPs protect proteins from degradation, their expression increasing in oxidative stress condition, hypoxia and anoxia, ischemia and hyperthermia [199], nutrient deprivation and acidosis [67], infection, inflammation and exposure to toxic compounds or other environmental stressors [198]. HSP isoforms can be upregulated in malignant cells, including mammary carcinoma cells [66], contributing to cancer cell survival [200] and malignant progression [54], being associated with poor clinical outcomes [49]. Overexpressed in many cancers [201], including breast cancer [202], the heat shock 70 kDa protein 9 (HSPA9)/mortalin/GRP75 is an ubiquitous mitochondrial chaperone [202], also emphasizing other subcellular localizations, such as ER and plasma membrane [203]. It is also used as a biomarker and a prognostic factor in breast cancer [204]. It is involved in membrane trafficking, energy generation, stress response and maintenance of mitochondria and ER, apoptosis [203], cell senescence [66], and activation of EMT signalling [201] through Wnt/β-catenin signalling pathway [204], control of cell proliferation [203], progress of carcinogenesis and breast cancer malignancy [204] by inactivation of tumor suppressor p53 protein [205], thereby reducing breast cancer patients disease free and OS [202, 204]. The overexpression of mortalin contributes to cancer cell stemness [201]. Overexpression of mortalin in invasive ductal carcinoma (IDC) of breast has been correlated with histological grade, clinical stage, lymph node metastasis [202]. The heat shock 70 kDa protein 2 (HSPA2/HSP70.2) is important for cancer cell biology [206]. HSPA2 might be involved in protecting nucleoli and centrosomes integrity in cancer heated-stressed cells [207]. It is overexpressed in various tumors [208], being also highly expressed in most breast cancer patients [209]. In breast cancer cell lines, HSPA2 silencing reduces proliferation and induces cell senescence [206], as well as in lung adenocarcinoma, where the downregulation of HSPA2 inhibits proliferation through ERK1/2 pathway and ER stress [210]. Also, HSPA2 is overexpressed in breast cancer patients and in different breast cancer cells lines, like MCF7, being involved in cell growth, migration and invasion of breast cancer and could be a potential candidate for development a novel breast cancer treatment [211].

Usually, serum albumin (ALB) indicates malnutrition and inflammation state [212]. The preoperative low serum albumin (ALB) levels are associated with poor prognosis in patients with breast cancer [213], as well as in endometrial cancer patients [214], while elevated levels of ALB are significantly associated with increased overall survival in breast cancer patients. However, the albumin level are not indicated for predicting disease aggressiveness or recurrence in breast cancer [212]. Human chorionic gonadotropin (hCG), a placental protein hormone detected in blood and urine, has a controversial effect in breast cancer development [215]. It was cited to have tumor-suppressive effects against MCF7 breast cancer cell lines, inhibiting cell growth through p53-mediated mitochondrial apoptotic pathway and ovarian steroid secretion that overexpresses the estrogen [216]. However, β-hCG is overexpressed in BRCA1 mutated breast cancer cells, promoting migration and invasion [215].

Downregulated proteins for overexpressed JTB condition

GSEA results demonstrated that there were no significantly enriched downregulated pathways. However, many proteins have been downregulated in JTB overexpressed condition (**Table 3**).

Membrane proteins and membrane-associated proteins

As the largest, the most diverse and ubiquitous superfamily of cell-surface signaling proteins

Table 3. Downregulated proteins for overexpressed JTB condition

Proteins	Symbol	BC/other malignancies		neoplastic effects
Membrane proteins and membrane-associated proteins				
Seven-transmembrane-helix receptor/G protein-coupled receptor	7TM/GPCRs	overexpressed in many cancers, including BC [223]	cell motility, growth, proliferation, differentiation [224], invasion, migration [223], immune mediate functions, angiogenesis, survival at metastatic secondary sites [225], poor prognosis [340]	downregulated, also in leukemia [231] and CRC [232], inhibits proliferation, pro-apoptotic effect [231]
Dipeptidyl aminopeptidase-like protein 6	DPP6	overexpressed in BC [235] and CC [237]; downregulated in ccRCC [237]	good prognosis [235] nodal metastasis, tumor grade [237]	poor prognosis
Calcium-dependent secretion activator 2	CAPS2/CADPS2	no available data for BC; CAPS1 overexpressed in CRC [243]	secretion, transport, exocytosis of LDCVs [240]; metastasis, EMT, cell migration, invasion, decreasing of epithelial markers, increasing of mesenchymal biomarkers in CRC cells [243]	inhibition of exosome secretion is helpful for treatment of patients with metastatic CRC [244]
Beta tubulin	TUBB	overexpressed in axillary lymph node metastasis in BC [311]; overexpressed TUBB3 in BC [246], especially in lobular BC [341]	cell survival, growth, tumor progression, metastasis [311]; aggressive tumor features and reduced patients survival [341]; EMT, migration, invasiveness [342], poor outcome in solid malignancies [247], BC metastases to the brain [251]	TUBB3 knockdown reduces invasive/metastatic abilities in breast cancer cell lines [251]; *TUBB3 absence could be a sign of dedifferentiation and more aggressive disease [247]
Spectrin domain with coiled-coils 1	SPECC1	overexpressed in cancer cells [254]	neoplastic activity, tumor progression, metastasis [254, 255]	decreases cell proliferation and migration [254]
ER proteome/enzymome				
Protein disulfide isomerase	PDI	overexpressed in many cancers, including BC [259]	proliferation, cell survival, metastasis [259], PDIA1 has pro-apoptotic effects in ERα+ MCF cells and pro-survival effects in TNBC MDA-MB-231 cells [258]	cancer cell cytoxicity, apoptosis, ER stress, accumulation of unfolded and misfolded proteins, downregulation of DNA repair and DNA damage response genes [260]
Nuclear proteome				
LEM domain-containing protein 2/ nuclear envelope/transmembrane protein	LEMD2/NET25	depletion in MCF7 BC cell line [267] and TNBC [268]	ERK signaling pathway activation [268]	cell growth, abnormal proliferation, EMT, angiogenesis, differentiation, malignant transformation [266], survival, migration, metastasis, higher recurrence rate, shorter survival [268]
High mobility group nucleosome binding domain 1	HMGN1	overexpressed in stem and epithelial cells [343]; downregulated in metastatic BC [272]	antitumor responses [270], DNA repair, regulation of genes involved in tumor progression, supresses cancer development [344]	metastatic cancer and altered immune functions [271]
Mitochondrial proteome				
ATP synthase mitochondrial F1 complex assembly factor 1	ATPAF1	overexpressed in PC [276]	cell proliferation, migration [274]	impair growth and proliferation under androgen-deficient condition [276]
Mitochondrial NAD kinase 2	mNADK/NADK2	deficiencient in T47D BC cell line and other cancer cell lines [283]	reduces cell viability, growth and proliferation, stopping the proline synthesis and maintenance [283]	suppression of cancer growth [278]
Lysosomal proteome				
α-L-iduronidase	IDUA	downregulated in BC patients with visceral metastasis [285]	proliferation, cell growth, invasion, metastasis, angiogenesis, preservation of cancer cell stemness [287] by abnormal accumulation of GAGs [286]	protumorigenic

Lipid metabolism-related proteome				
Phosphatidic acid/phosphatidate phosphatase, i.e., lipin-1	PAP, i.e., LPIN1	overexpressed in basal-like TNBC [91], and LUAD [291]	poor prognosis in TNBC patients [91]	the knockdown increases apoptosis, inhibits tumor growth [91], decreases cancer cell viability and proliferation [291], silencing increases autophagy, ER stress, and represses prostate and BC proliferation and migration [293]
Patatin-like phospholipase domain-containing protein 2/adipose triglyceride lipase	PNPLA2/ATGL	overexpressed in CRC [298], and BC cells co-cultivated with mature adipocytes [301], obese patients with BC [300]	CRC growth and proliferation [298], cancer aggressive features [297] migration and invasion in co-cultivation with adipocytes in BC	inhibits proliferation, promotes apoptosis [298] and malignancy attenuation [301]
Very-long-chain (3R)-3-hydroxyacyl-CoA dehydratase 2	HACD2	downregulated after transfection with ACLS4 ferroptosis-related gene of MCF7 BC cell line [302]	ferroptosis [302]	reduction of FAs elongation [303], possible apoptotic effect (antitumorigenic)
Glucose metabolism-related proteome				
Triosephosphate isomerase	TPI	overexpressed in many cancers, including IDC [307] and HER-2/*neu*-positive BC cell lines [93]	cell growth, proliferation, migration, invasion, shorter survival [308]	decreased invasion and mobility [312]
Ubiquitin-mediated degradation system				
Ubiquitin-activating enzyme E1-domain containing 1	UBE1DC1/UBA5	overexpressed in ERα-positive BC [315]/invasive BC [317]	activates estrogen-induced ASC1 UFMylation for promotion of transcriptional activation of ERα [315]	reduces proliferation in BC [315]
Immunosomics				
Mannose/mannan-binding lectin/ mannan-binding protein	MBL/MBP	deficiency reported in malignant diseases [345]	defective apoptotic cell clearance [320], chronic inflammation, tumor progression [321]	worse prognosis in paediatric patients, defective apoptotic cell clearance [320], chronic inflammation, tumor progression [321]
Galectin-3 (membrane, cytoplasm [323], nucleus, ECM, serum [325])	Gal-3	overexpressed serum levels in BC with and without metastasis [325], overexpressed in TNBC [322]	tumor cell survival, metastatic dissemination [324], cell growth [326], differentiation, inflammation [327], angiogenesis [346]; cytosolic Gal-3 is anti-apoptotic, nuclear isoform is associated with gene expression and extracellular Gal-3 mediates cell migration and adhesion [346]	ECM remodelling, metastasis, increases cancer cell motility [326], growth, poor prognosis [327], drug resistance and reduced OS in node positive BC [328]
T-cell receptor beta chain	TCRβ/TCRB	overexpressed in early stage of BC compared with nontumor tissue [329], higher diversity in axillary lymph nodes in BC [330]	immune surveillance [330]	perturbation of immune surveillance, cancer cells immune escape

*LUAD, lung squamous cell carcinoma.

that function as plasma membrane embedded receptors [217] that include seven membrane-spanning α-helical segments (TM) in their core [218], G protein (heterotrimeric guanine nucleotide-binding protein)-coupled receptors (GPCRs), also named seven-transmembrane-helix receptors (7TMRs), are the most potential target for anticancer drug discovery [219]. GPCRs combine actions of G proteins, GPCR kinases, and arrestins [220], and mediate cellular response to various external stimuli [221], and regulate many biological and cellular processes, such as cell growth, differentiation, migration, apoptosis, chemotaxis and exocytosis [222], serving as "*eyes and ears of the cell*" [218] to assure an adequate adaptive communication between external and internal environment of cells [221]. GPCRs are involved in many physiological functions, but also contribute to development and progression of many cancers, including breast cancer [223], regulating cell motility, growth, proliferation and cell differentiation [224], immune-cell mediated functions, angiogenesis and cancer cell survival at secondary metastatic sites [225]. The GPCRs downregulation or desensitization occurs in diverse ways, that could dysregulate signaling cascades mediated by G protein subunits downstream of GPCRs [226] and cross-talk pathways, including the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinases (ERK) [227], c-Jun N-terminal kinase (JNK) [228], and PI13K/AKT [229] that are well known for their predominant pro-oncogenic role related to cell growth, metabolism reprogramming, enhanced proliferation and inhibited apoptosis [229], highlighting the putative role of G-protein-regulated MAPK pathways in genesis and progression of different cancers, including breast cancer [228]. Arrestins, as scaffold proteins in GPCRs, are able to affect the balance between activation of pro-apoptotic MAPK and the anti-apoptotic AKT signaling pathways [230]. In conclusion, the overexpression of GPCRs in many types of cancer was associated with tumorigenesis, while the downregulation of GPCRs, e.g., through lentivirus-mediated silenced system, could inhibit proliferation and promotes apoptosis in tumor cells, as noted in leukemia cells [231]. Also, the absence of G-protein-coupled receptor ($P2Y_6R$) expression reduces number and volume of tumors in a mouse model of CRC, by inhibition of the X-linked inhibitor of apoptosis (XIAP) through a PI3K/AKT-dependent mechanism, inducing pro-apoptotic processes [232]. As a single integral membrane glycoprotein with a large extracellular domain, dipeptidyl aminopeptidase-like protein 6 (DPP6/DPPX) belongs to the dipeptidyl peptidase-like protein (DPLP) family/dipeptidyl peptidase IV family of proteins [233]. DPP6 gene was associated with cancer [234], sustaining cell differentiation, proliferation and carcinogenesis [233]. The overexpressed DPP6 was associated with good prognoses in breast cancer patients [235], due to its ability to bind to the ECM components [236]. DPP6 was significantly downregulated in in clear cell renal cell carcinoma (ccRCC) in association with nodal metastasis and tumor grade [237], acute myeloid leukemia (AML) and melanoma but overexpressed in colon cancer (CC) [237]. DPP6 is also studied as an auxiliary subunit of voltage-gated potassium channels of the Kv4 family [236]. As a second member of the calcium-dependent activator for secretion (CAPS/CADPS) protein family, the calcium-dependent secretion activator 2 (CAPS2/CADPS2) is a calcium-binding protein ubiquitously expressed in cytoplasmic vesicle membranes or on cytoplasmic side of peripheral membrane, which acts as a calcium sensor in constitutive vesicle trafficking and secretion [238], being involved in calcium-binding and regulation of protein exocytosis, related to hyperactive behavior and autism [239], facilitating secretion, transport and exocytosis of large dense-core vesicles (LDCVs) [240], a process also necessary for cancer cell communication [241]. CAPS1 overexpression inhibits hepatoma cancer cell proliferation and migration by changing the exocytosis-associated TME *in vitro* and inhibits xenograft tumor growth *in vivo* [242], while its overexpression in CRC tissues induces metastasis via PI3K/Akt/GSK3β/Snail signaling pathway-mediated EMT process and poor prognosis, promoting CRC cell migration and invasion *in vitro*, liver metastasis *in vivo*, decreasing of E-cadherin and ZO-1 as epithelial biomarkers expression and increasing the expression of mesenchymal markers, such as N-cadherin and Snail [243]. Inhibiting the secretion of exosomes by CAPS1 downregulation could be helpful for treatment or patients with metastatic CRC [244].

Cancer cells use their cytoskeleton to adapt and survive in hostile environments to success-

fully move and metastasize [245]. As cytoskeleton components involved in cell shape maintenance, organelles distribution, mitosis and meiosis, cell motility, and intracellular transport [246], microtubules (MTs) are highly dynamic, hollow-tube filamentous polymers, mostly composed of tubulin, a family of globular proteins that mainly contains α- (TUBAs) and β-tubulin (TUBBs) subunits, at least seven isotypes of β-tubulin being identified in human cells [247]. TUBB3 is the most investigated tubulin isotype and it is known as biomarker of poor outcome in solid malignancies [247], being cited as target for breast cancer chemotherapy [248, 249]. *TUBB3* is absent in normal mammary epithelia, but showed a great elevated expression in most tumors, while maximal *TUBB6* expression occurred in breast and is largely decreased in most tumors [250]. *TUBB3* knockdown approaches in breast cancer models revealed significant reduction in their invasive/metastatic abilities [251]. Spectrin domain with coiled-coils 1 (SPECC1) was also downregulated in JTB overexpressed condition. Spectrins link the actin cytoskeleton to the cell membrane, being located at the internal side of the plasma membrane [29]. They are essential for structural stability and maintenance of the plasma membrane, as well as for preservation of the cell shape [252] and formation of lamellipodia and filopodia [253]. Spectrins contribute to cell polarity, cell adhesion and apoptosis [254], cell motility and proliferation [255], cell spreading and cell cycle [252]. The spectrin-integrin complex is important to balance adequate forces, in order to preserve a monolayered epithelium [256]. Significant spectrin downregulation was correlated to decreasing cell proliferation and migration [254]. In high-grade breast cancer, spectrin could serve as a biomarker [255].

ER proteome/enzymome

The oxidoreductase protein disulfide isomerase (PDI) family includes multifunctional ER enzymes that play a key role in proteostasis and ER stress [257], UPR, ER-mitochondria communication and balance between pro-survival and pro-death signals [258] essential for tumor proliferation and cancer cell survival [91]. PDI mediates formation of S-S bonds and assists correct folding of the polypeptide chains in the ER lumen, but their function could be divergent in different tissues [257]. PDI enzymes catalyze the cysteine-based redox reaction and assist the quality control of proteins, functioning as molecular chaperones [259]. PDIA1 family members, present in ER, mitochondria, nucleus, cytoplasm and ECM [258], play a differential role in redox state regulation in the ERα-positive MCF7 cells compared to TNBC MDA-MB-271 breast cancer cell lines; PDIA1 is a pro-apoptotic factor in MCF7 breast cancer cell line and a pro-survival factor in TNBC cell line [258]. The most evidences suggest that PDI is involved in proliferation, cancer cell survival, and metastasis, being upregulated in a variety of cancer types, including breast cancer, emerging as a therapeutic target for cancer therapy [259]. PDI is involved in the UPR pathway [257] and it is upregulated by the UPR as a cancer cell survival mechanism [260], the chronic activation of UPR in tumor cells being a mechanism of tumor progression [261] in malignant cell phenotypes [262]. PDI knockdown-induced cytotoxicity and cell death is cell-line-dependent and involves caspase-dependent apoptosis in MCF7 cells [263], accumulation of unfolded and misfolded proteins and ER stress [260].

Nuclear proteome

Tumor development and progression depends on components of the nuclear envelope environment associated to many signaling molecules [264]. Depletion of LEM domain-containing protein 2 (LEMD2)/nuclear envelope/transmembrane protein (NET25) in cancer cells caused elevated levels of phosphorylation of ERK1 following EGF exposure [264] and hyperactivation of the EGF pathway [265]. ERK1 is a serine-threonine protein kinase belonging to the mitogen-activated protein kinase (MAPK) family, which participates in intracellular signal transduction [266]. In MCF7 breast cancer cell line [267] and in TNBC cells [268], activation of ERK signaling pathway or high ERK protein expression levels affect the regulation of several transcription and translation factors and promotes cell growth and abnormal proliferation, EMT, angiogenesis, cell differentiation and malignant transformation, cell cycle regulation [266], cell survival, and facilitates cell migration, metastasis to lymph nodes, higher recurrence rate and shorter survival [268]. Contrariwise, depending on its activity in specific subcellular compartments, presence of

ROS, cell and stimulus type, ERK signaling pathway mediates several antiproliferative processes, such as apoptosis, autophagy and senescence [269]. High mobility group (HMG) nucleosome binding domain 1 (HMGN1) is a nucleosome binding protein that dinamically regulates the structure of chromatin fiber in response to DNA lesions, the level of histone PTMs, gene expression, and contributes to the induction of innate and adaptive immunity, acting as an alarmin that promotes antitumor responses [270]. The loss of HMGNs can lead to cancer and altered immune functions [271]. A reduced expression of HMGN1 was identified in metastatic breast cancer compared with low metastatic cells [272].

Mitochondrial proteome

ATP synthase mitochondrial F1 complex assembly factor 1 (ATPAF1) is an intra-mitochondrial-transporting protein [273]. The mitochondrial ATP synthase functions are associated with cell proliferation, migration, metastasis and mitochondria dependent cell death in cancer models [274]. ATPAF1 has a key role for ATP synthase assembly and mitochondrial oxidative phosphorylation [275]. ATPAF1 was overexpressed in prostate cancer tissue, but knockdown of this gene should significantly impair growth and proliferation under androgen-deficient condition [276]. Mitochondrial NAD kinase 2 (mNADK/NADK2) catalyzes the phosphorylation of nicotinamide adenine dinucleotide (NAD^+) to form *de novo* nicotinamide adenine dinucleotide phosphate ($NADP^+$) that is then reduced to the antioxidant NADPH required for biosynthesis of macromolecules, protection from OS and survival or rapid growth of cancer cells [277], known to preserve high levels of NADPH [278]. NADK2/mNADK is responsible for the maintenance of the mitochondrial NADPH pool [279], attenuates OS in mitochondria [278], playing a key role in controlling the ROS level locally generated and expressed in tumor cells [280]. The overproduction of ROS initially can induce uncontrolled cancer cell proliferation, DNA damage/genomic instability that supports a metastatic phenotype [281], but high levels of ROS leads to cell apoptosis [278]. NADH, NADPH and high levels of $NADP^+$ inhibit NADK2 [282], whose silencing impairs the NADPH pool and suppress cancer cell growth [278]. NADK2 deficiency reduced cell growth and proliferation in many cancer cell lines, including T47D breast cancer cell line, NADK2 activity being required for de novo proline biosynthesis and for maintenance of proline levels [283]. Disruption of proline synthesis in cancer cells inhibits protein production, decreasing tumor cells viability and tumor growth [284]. Inhibitors of NADK might be promising anticancer agents [279].

Lisosomal proteome

α-L-iduronidase (IDUA) is a lysosomal hydrolase that was significanly downregulated in breast cancer patients with visceral metastasis compared with those without visceral metastasis [285]. The deficiency in IDUA results in abnormal lysosomal accumulation of glycosaminoglycans (GAG), like heparan and dermatan sulfates (DS) [286], GAGs and proteoglycans being involved in all stages of tumorigenesis and cancer progression, such as cancer cell proliferation and growth, invasion and metastasis, angiogenesis, and preservation of cancer cell stemness [287]. Cancer epithelia, including breast cancer with epithelial origin, emphasizes overexpressed sulfated proteogycans and DS, which could enhance the invasion of cancer cells [288], the accumulation of DS in cancer epithelia remodeling the collagen around cancer cells, resulting in changes in cell shape and invasiveness through fibrillar ECM that surround them [288].

Lipid metabolism-related proteome

Inhibition of lipogenesis induces apoptosis and represses cancer cell proliferation [289]. Phosphatidic acid/phosphatidate phosphatase (PAP) catalyzes the dephosphorylation of phosphatidic acid/phosphatidate (PA) to diacylglycerol (DAG), being involved in phospholipid synthesis and signaling [290]. PAP lipins also functions as co-transcriptional regulators [289]. Lipin-1 (LPIN1) is an enzyme that displays PAP activity involved in triacylglycerols (TAGs) and phospholipids (PLs) synthesis pathway and maintenance of ER homeostasis, that was overexpressed in basal-like TNBC cell lines [91], prostate tumor samples and cell lines [289], and lung adenoma cancer cells (LUAD) [291], in correlation with the poor prognosis of these patients. Lipin-1 can be localized in cytosol, ER and the nucleus [292]. The knockdown pf LPIN1 increased apoptosis in TNBC cell lines [91], and decreased cell viability and prolifera-

tion of LUAD cells [291], significantly inhibiting tumor growth *in vivo* [91]. Lipin-1 silencing increased autophagy and ER stress, and significantly represses prostate and breast cancer proliferation and migration [293]. Lipin-1 was upregulated in BC samples compared with adjacent normal tissues and its inhibition reduces the migration of MCF7 breast cancer cells [292]. Proliferating cells exhibits an aberrant FA metabolism [294], the deregulated lipolysis perturbing energy homeostasis and contributing to the different diseases, including breast cancer [295]. Patatin-like phospholipase domain-containing protein 2 (PNPLA2)/ adipose triglyceride lipase (ATGL), an enzyme that belongs to the patalin-like phospholipase domain containing (PNPLA) family [296], mainly catalyzes the first step of intracellular TAGs hydrolysis in lipid droplets (LDs) within adipocytes and non-adipocyte cells [295]. ATGL upregulation in breast cancer was correlated with a high amount of peritumoral adipocytes that losses their lipid content, the free FAs released by adipocytes after lipolysis being transferred and stored in tumor cells as TAGs in LDs, inducing the aggressiveness of high-grade tumors [296, 297]. Also, other studies sustain pro-neoplastic characteristics of ATGL action. ATGL overexpression significantly promotes colorectal cancer (CRC) cell growth and proliferation through enhancing the lipolytic pathway, while its knockdown inhibits the proliferation and promotes the apoptosis of cancer cells *in vitro* [298]. *In vivo*, the ATGL expression was correlated with cancer aggressive features and is upregulated by contact with adipocytes [297]. Thus, a significantly elevated activity of ATGL was detected in overweight patients with pancreatic ductal adenocarcinoma (PDAC) in association with tumor stromal proliferation compared with non-obese patients [299], as well as in obese patients with breast cancer, to whom ATGL was found to be significantly elevated in peritumoral and distant tumor adipose tissue compared with non-obese patients, ATGL promoting a more aggressive cancer phenotype [300]. An increased expression of ATGL in breast cancer cells that were co-cultivated with mature adipocytes significantly enhanced the migration and invasion abilities of cancer cells, while abrogation of ATGL attenuated their malignancy [301]. Very-long-chain (3R)-3-hydroxyacyl-CoA dehydratase 2 (HACD2) regulates long-chain fatty-acyl-CoA biosynthetic process [302] in the ER membrane. The HACD1-4 isozymes catalyze the third step, dehydration, in FAs four-step elongation cycle and disruption of HACD2 reduced FAs elongation toward both saturated and unsaturated FAs [303]. Overexpressed JTB protein was correlated with an elevated level of hemochromatosis protein (HFE) that leads to iron accumulation in cancer cells and cancer-associated cells that stimulates breast tumor growth. Moderate levels of ROS are protumorigenic, while excessive ROS leads to cancer cell death [280]. High iron levels induce lipid peroxidation and iron-dependent accumulation of ROS to lethal levels in cancer cells, also named ferroptosis. Ferroptosis is correlated with a high expression of ferroptosis-related long chain acyl CoA synthetase 4 (ACSL4) gene, also related to better overall survival, associated with significant downregulation of HACD2 protein after interfering ACSL4 transfected into MCF7 and other breast cancer cell lines [302]. It could be possible that JTB overexpression acts in a comparable manner as ACLS4 overexpressed gene to increase apoptosis, as well as ferroptosis, respectively, in transfected MCF7 breast cancer cell line. It is well known that while ACSL4 plays a tumor suppressive role by suppressing tumor survival and invasiveness by promoting ferroptosis [304], JTB overexpression enhances cancer cell apoptosis [305], both antitumorigenic mechanisms of programmed cell death being associated with HACD2 downregulation.

Glucose metabolism-related proteome

The increase in aerobic glycolysis/glycolytic flux is one of the most important hallmarks of cancer [306]. Triosephosphate isomerase (TPI/ TPIS) is one of the key glycolytic enzyme that is essential in carbohydrate metabolism and energy production in all living cells [306], taking part in gluconeogenesis, pentose phosphate pathway (PPP) and FAs biosynthesis [306]. TPI is overexpressed in many cancers, including IDC [307] or HER-2/*neu*-positive breast tumors and cell lines [93], and it is involved in cell growth and maintenance, increased proliferation, migration and invasion of tumor cells, being associated with shorter patients survival [308]. TPI participates in cell cycle activation and is responsible for ATP production by glycolysis [309]. Using a proteomic approach, autoantibodies against TPI have been detected in

sera from breast cancer patients [310]. Up-regulated TPI expression was identified in axillary lymph node metastasis compared to node-negative breast carcinomas [311]. The inhibition or slow-down of TPI activity decreased invasion and mobility in cancer cells [312].

Ubiquitin-mediated degradation system

Cancer may be associated with the loss of the regulator function of the ubiquitin-mediated degradation system [313], that involves ubiquitination as an attachment of a small protein modifier, such as ubiquitin (Ub) and ubiquitin-like proteins (UBLs), to a protein-substrate to regulate its degradation [314]. Various tumorigenic processes, such as DNA repair, cell cycle arrest, cell proliferation, apoptosis, angiogenesis, migration and invasion, metastasis and drug resistance are controlled by the ubiquitin-mediated degradation system, the conjugation of ubiquitin to a target protein for proteolysis being sequentially mediated by three classes of enzymes involved in a three-step enzymatic process: the Ub-activating enzyme E1, Ub-conjugating enzyme E2 and a Ub ligase E3 [314]. Ubiquitin-activating enzyme E1-domain containing 1 (UBE1DC1/UBA5 [315]) is an ubiquitin-activating enzyme [316] that was widely expressed in most of human adult tissues [313], and could activate different ubiquitin-like proteins, such as ubiquitin-fold modifier 1 (UFM1) and small Ub-like modifier (SUMO2), the last one being activated in the nucleus or transferred such as activated-SUMO2 to nucleus after conjugation with UBE1DC1 in cytoplasm [316]. Gene encoding UBA5 was amplified in breast invasive carcinoma [317]. UBA5 is involved in estrogen-induced activating signal co-integrator 1 (ASC1) UFMylation and could be used for development of new drugs against ERα-positive breast cancer as long as this process is associated with PTMs of estrogen receptor-α (ERα) as a steroid hormone-sensitive transcription factor and its co-activators, such as ASC1 target protein, which acts as a transcriptional co-activator of estrogen nuclear receptors, for promotion of transcriptional activation that leads to proliferation of different subtypes of breast tumors [315].

Immunosomics

Mannose/mannan-binding lectin (MBL)/mannan-binding protein (MBP) is a member of collectin (collagen-containing C-type lectins) family of proteins mainly synthetized by hepatocytes [318] and occurs as circulating serum MBP (S-MBP) and intracellular MBP (I-MBP); I-MBP could function as a cargo transport lectin facilitating cytoplasmic ER-to-Golgi vesicle trafficking in glycoprotein control [319]. MBL-deficient mice emphasizes defective apoptotic cell clearance [320] that could lead to chronic inflammation and can contribute to tumor progression [321]. Galectin-3 (Gal-3) is a multifunctional member of the non-integrin β-galactoside-binding lectin family [322], ubiquitously expressed on the cell surface, cytoplasm [323], nucleus, ECM [324] or in circulation, the serum levels of Gal-3 being significantly higher in breast cancer patients with and without metastasis [325]. Gal-3 downregulation during cancer progression, invasion and metastasis is associated with ECM remodeling, which favors the detachment of tumor cells to primary site via glycosaminoglycans regulation [324]. A reduced expression of Gal-3 was correlated with a high histological grade of breast cancer due to a reduction of matrix binding and increased cancer motility [326]. The absence or downregulation of GAL3 was associated with higher *in vivo* growth in murine breast tumors, metastasis, and poor prognosis [327], EMT, lymphovascular invasion and cancer stemness, drug resistance and reduced overall survival in node-positive breast cancer patients [328]. In early-stage breast cancer, immune profiling of the T-cell receptor beta chain (TCRβ/TCRB) repertoire highlighted that the clonal structure of the tumor is significantly different from adjacent nontumor breast tissue, with the tumor containing approximately 2.5-fold greater density of T-cells and increasing clonality compared with normal breast tissue [329], while T-cell repertoire diversity in tumor was lower than in axillary lymph nodes of breast cancer patients [330]. Into a TCRβ-deficient mutant cell line, the expression of the TCRα was greatly diminish, suggesting that the transcript of one gene is required for the optimal expression of another gene [331].

Discussion

In this experiment, JTB overexpressed condition was correlated with overexpression and downregulation of a plethora of proteins involved in neoplastic behavior of MCF7 breast cancer cells. GSEA algorithm was performed to

investigate the biological processes and pathways that are significantly associated with the JTB protein upregulation in MCF7 cells. The results demonstrated four significantly enriched gene sets from the following pathways that were significantly up-regulated: mitotic spindle assembly, estrogen response late, EMT and estrogen response early. Thus, the overexpressed JTB condition was significantly associated with an increased expression of ACTNs, FLNA, FLNB, EZR, MYOF, COL3A1, COL11A1, HSPA1A, HSP90A, WDR, EPPK1, FASN and FOXA1, related to cytoskeletal organization and biogenesis, mitotic spindle organization, ECM remodeling, cellular response to estrogen, proliferation, migration, metastasis, increased lipid biogenesis, estrogen-therapy resistance, and discrimination between different breast cancer subtypes. There were no significantly enriched downregulated pathways.

Other upregulated proteins for overexpressed JTB condition are involved in multiple cellular functions and pathways that become dysregulated, such as TME acidification (H^+/K^+-ATPase), the ion and other molecules transmembrane transport pathways (ABCA2, PKD1L2), glycolytic flux (TKT), iron metabolism and oxidative stress (HFE), metabolic reprogramming, nucleocytosolic mRNA transport pathways (ALY), transcriptional activation (PDCD11), chromatin remodeling (INO80), modulation of cell death pathways (USP19, Sp1), stress responsive pathways (HSPA1A, HSPA2, HSPA9, HSP90A), activation of MMPs (MYOF), cancer drug resistance (ABCA2), and pathways through which microRNAs are exported form cells (TNRC6C). Almost all these effects in breast cancer cells and cancer-associated cells promote cancer cell stemness and aggressiveness, cell cycle progression and rapid proliferation, cancer cell survival, growth, mobility, EMT and migration, invasion and metastasis, cancer cell protection against environmental hostile factors, in association with tumor progression, lymph node metastasis, distant metastasis and invasion, chemoresistance/drug and radiotherapy resistance, and poor clinical outcome of breast cancer patients. Several upregulated proteins could have a controversial role, an antioncogenic function or could improve prognosis in breast cancer patients (TPRG1L, PKD1L2, REEP2, TNRC6C, EEF1A2). Several of these upregulated proteins could be considered as promising biomarkers or putative targets for therapeutic drugs in breast cancer (MYOF, HKA, USP19, HSP90AA1).

The downregulated proteins for overexpressed JTB condition are involved in adaptive communication between external and internal environment of cells and maintenance between pro-apoptotic and anti-apoptotic signaling pathways (7TM/GPCRs, PDI), vesicle trafficking and secretion (CAPS2), DNA lesions repair and suppression of genes involved in tumor progression (HMGN1), proteostasis, ER stress and UPR pathway (PDI), redox state regulation (PDI, NADK2), mitochondrial oxidative phosphorylation (ATPAF1), biosynthesis of macromolecules, such as the antioxidant NADPH or triacylglycerols and phospholipids (PAP/lipin-1), abnormal cellular accumulation of GAGs (IDUA), lipolytic pathway (ATGL), carbohydrate metabolism, including gluconeogenesis, PPP and FAs biosynthesis (TPI), dysregulation of ubiquitin-mediated degradation system (UBA5), cancer cell immune escape (MBL, Gal-3, and TCRβ), cell-to-cell and cell-to-ECM interactions (Gal-3), and cytoskeletal behaviour in breast cancer cells (TUBB, SPECC1). Many proteins that are downregulated in this experiment are usually overexpressed in cancer cells, including breast cancer (GPCRs/7TM, DPP6, PDI, ATPAF1, PAP, ATGL, TPI, UBA5, Gal-3, TUBB, and SPECC1). Their experimental downregulation could inhibit cancer cell growth or proliferation and promotes tumor cell apoptosis, suggesting an anti-neoplastic behavior (GPCRs/7TM, PDI, ATPAF1, NADK2, PAP, ATGL, HACD2, TPI, TUBB, SPECC1, UBA5). Downregulated DPP6, LEMD2, HMGN1, IDUA, MBL, and Gal-3 could develop a proneoplastic behavior. Several of these downregulated proteins could serve as biomarkers and novel therapeutic targets in breast cancer (GPCRs/7-TM, Gal-3, SPECC1).

Acknowledgements

The authors thank the past and current members from The Biochemistry & Proteomics Lab for the pleasant working environment. Research reported in this publication was supported by the National Cancer Institute of the National Institutes of Health under Award Number R15CA260126. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Disclosure of conflict of interest

None.

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