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ARTICLE

Differential Transcriptomic Analysis Reveals Molecular Mechanisms and Key Gene Clusters in Breast Cancer Brain Metastasis

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Abstract: Breast cancer (BC) is the most common malignancy among women worldwide. Despite therapeutic advances, 30–40% of cases progress to metastasis, which is the leading cause of BC-related mortality. To explore the molecular mechanisms underlying metastasis, two gene expression datasets (GSE42568 and GSE43837) were retrieved from the GEO database. GSE42568 included 104 BC and 17 normal breast tissue samples, while GSE43837 comprised 19 HER2-positive brain metastases and 19 HER2-positive nonmetastatic breast cancers. Differentially expressed genes common to BC and metastatic brain cancer were integrated, and protein–protein interaction (PPI) networks were constructed. Two significant gene clusters were identified. The first cluster included EEF1A1, RPL8, RPS3A, RPN2, PSMD2, RPL18, RPL7, and RPS3, associated mainly with ribosomal and translational processes. The second cluster comprised ASPN, COL6A3, COL3A1, LUM, VCAM1, FASLG, GBP1, CXCL9, DAXX, H3F3A, H3F3B, and KMT2D, linked to extracellular matrix organization and chromatin remodeling. KEGG pathway analysis indicated enrichment in pericentric and telomeric heterochromatin assembly, as well as collagen type III trimer formation. These findings suggest that extracellular matrix remodeling and epigenetic regulation play key roles in breast cancer metastasis, particularly to the brain, offering potential molecular targets for future therapeutic interventions.

Keywords: Molecular mechanisms, Transcriptomics, Differential gene expression.

1 Introduction

Breast Cancer [BC] is the most frequently occurring cancer [1] and is the second-most common cause of cancer death in women [2]. BC initiates because of abnormal alterations of cell growth leading to tumor development. The prevalence of BC accounts for approximately 25% of that of all cancers. In 2018, recent estimations have reported approximately 2.1 million cancer patients all over the world. Among Saudi women, BC accounts for approximately 21.8% of all cancers. BC is considered the ninth-most common cause of death among Saudi women [3] and has been reported as the most second-most frequently occurring cancer [4]. The number of BC estimations will increase proportionally to community growth and age in Saudi Arabia over the coming years [5]. Several studies have concentrated on inferring molecular mechanisms of the BC [6]. Multiple genetic alterations have been recognized as causative factor of functional defects in BC cells. Many receptors and the associated signaling pathways are considered as prominent elements that impact BC development [7]. In addition, numerous oncogenes and anti-oncogenes are implicated [8]. Although recently developed therapies improve the quality of life of patients with BC, 30-40% of cases progress to metastasis. BC cells can relocate to various tissues and organs such as the bones, lungs, and brain [9].

Gene expression alteration can be effectively investigated by microarray data analysis, which is a highly sensitive and high throughput approach. Consequently, the expansion of microarray analysis will enhance the understanding of BC diagnosis and treatment [10]. Approximately 5-10% of BC are caused by inherited mutations. The most frequent causative genes are BRCA1 and BRCA2 [11], which increase the probability of hereditary breast cancer [12]. The possibility of BC progression escalates up to 55-65% in women carrying a mutated BRCA1. Moreover, the BC risk increases to 45% if BRCA2 is mutated [13]. Mutations in some genes such as ATM, TP53, CHEK2, PTEN, CDH1, STK11, and PALB2, are associated with the development of BC [14]. Non-genetic risk factors may initiate BC development, including family history, race/ethnicity, breast lesion, radiation exposure, hormones, overweight/obesity, and lack of physical activity [15]. Brain metastases [BM] are one of the most frequently occurring adult brain tumors [16],

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affecting > 25% of cancer patients. In the later stage of the disease, 10-15% of patients with BC develop BM [17]. The estimation of BM incidence ranges from 7 to 14 per 100,000 [18]. Oncogenes involved in BC to BM cascade can be classified into three types: initiation, progression, and virulence. Initiation genes include CDH2, TWIST, MMPs, and VEGF. CDH2 and TWIST enhance detachment, whereas MMPs cause degeneration of the extracellular matrix. VEGF plays a role in angiogenesis and PTGS2 and MMP-1 are involved in tumor progression. The PTGS2 and MMP-1 are implicated in colonization of metastases by extravasation of tumor cells. The virulence genes include IL6 and TNFα, which support cell survival during circulation and promote growth in the distant microenvironment. KAI-1, BRSM1, and NME1 are suppressor genes that inhibit tumor cell dissemination [19]. Patients with BM have a poor prognosis, with a median survival of about 7.8 months [20]. This study aims to identify common genes in breast/metastatic brain cancer datasets involved in BC metastasis to the brain using microarray analysis. Enrichment analysis is used to determine the annotations for the common and exclusive genes of both datasets. The protein-PPI network analysis is applied to the common genes in both datasets and exclusive genes of metastatic brain cancer. Cluster identification is used to determine the common genes in both datasets and of metastatic brain cancer. Therefore, gene ontology [GO] analysis of the gene clusters is important.

2 Materials and Methods

2.1. Data source

In the present study, two gene expression profiles [GSE42568 and GSE43837] were selected and downloaded from the GEO database. The platform for GSE42568 is the GPL570 Affymetrix Human Genome U133 plus 2.0 Array. GSE42568 was obtained by analysis of 104 breast cancers and 17 normal breast biopsies. The platform for GSE43837 is the GPL1352 Affymetrix Human X3P Array. The profile was obtained by analysis of 19 HER2-positive human BC with brain metastases and 19 HER2-positive nonmetastatic primary human breast cancers.

2.2. Pre-processing of data and analysis of differentially expressed genes

The robust multi-array average algorithm in the R affy package was used for the data analysis. The raw data were converted into expression values, and background correction, quantile normalization, and probe summarization were carried out. Significance of the differentially expressed genes [DEGs] between GSE42568 and GSE43837 datasets was calculated using the paired t-test. The |log2 FC|1.5 was determined as the cutoff value of DEG screening. The common DEGs from the two datasets were obtained using the Venn package of R. The GSE43837 data set that contrasted primary breast cancers with brain metastases found 77 DEGs [51 down and 26 up]. The 10 most highly up and downregulated genes. Genes POSTN, ASPN, and COL6A3 related to the extracellular matrix were upregulated, and ribosomal and cytoskeleton components RPS3 and TUBB2B were the most highly downregulated [Table 1].

2.3. GO enrichment analysis of DEGs

GO analysis and functional enrichment of DEGs were conducted. These analyses included enrichment for biological, cellular, and molecular GO, as well as the KEGG and Reactome pathways and were performed using Clue Go on the Cytoscape software [version 3.7.2]. The analyses were conducted for the common genes between GSE42568 and GSE43837 datasets, unique BM and BC genes, and for the modules of combined common and unique metastases genes.

2.4. Establishment of the PPI network and identification of gene clusters

The STRING database was used to analyze PPI of DEGs identified as common genes. Unique BM genes were separately mapped to the STRING database to estimate the relationships of PPI. The PPI network of combined common and unique metastases genes was also obtained. PPIs were extracted with the interaction score of > 0.4. The PPI network clusters of combined common and unique metastases genes were identified by conducting plug-in MCODE using the Cytoscape software [version 3.7.2]. The steps undertaken have been summarized in figure 1.

3 Results

3.1. Data source

Comparison between normal breast tissue and breast cancer tissue based on the GSE42568 dataset revealed 1,262 DEGs, of which 486 were upregulated and 776 were downregulated. The top 10 most significantly upregulated and downregulated genes, respectively, based on log fold-change values, with interesting candidates such as KRT19, EPCAM, and ESRP1 among the upregulated genes, and FABP4, LEP, and RBP4 among the downregulated genes.

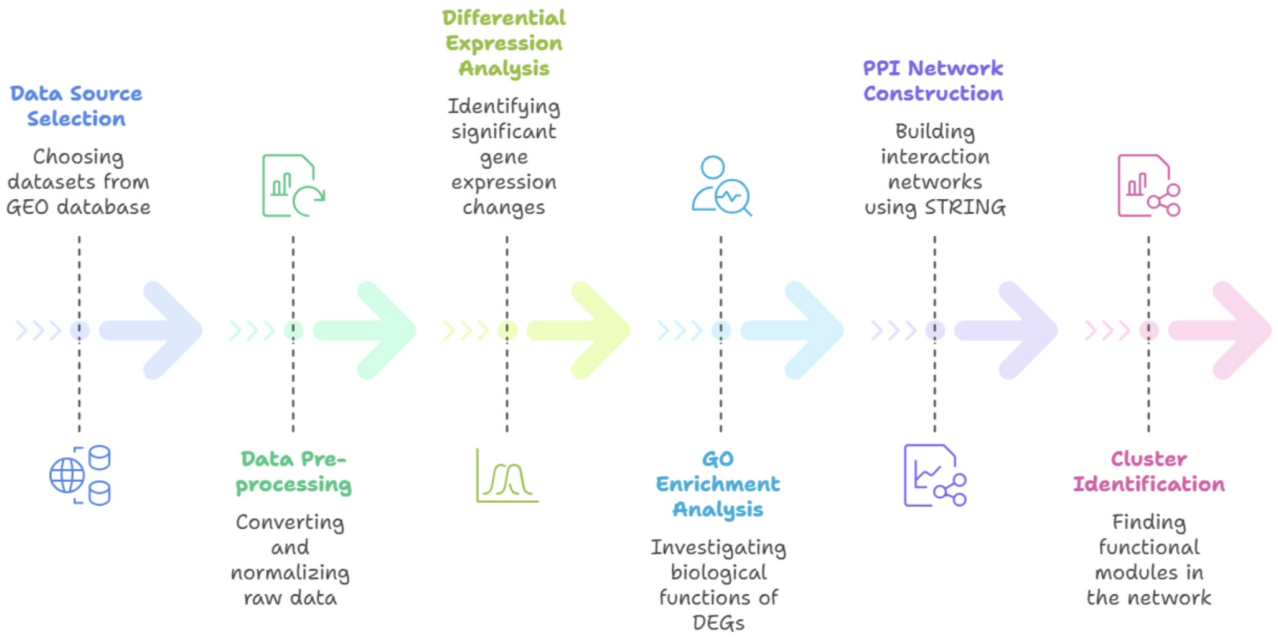

Figure 1. Schematic workflow outlining the research process from study selection to data synthesis.

Table 1. Top 10 significantly upregulated and downregulated genes in brain metastases compared with primary breast cancer (GSE43837).

Gene symbol	Gene name	LogFC	P.Value	adj.P.Val	Category
POSTN	Periostin	2.920	0.0001647	0.160	Upregulated
ASPN	Aspirin	2.604	0.0014545	0.173	Upregulated
LUM	Lumican	2.323	0.0002723	0.160	Upregulated
COL6A3	collagen type VI alpha 3 chain	2.250	0.0015194	0.173	Upregulated
COL3A1	collagen type III alpha 1 chain	2.249	0.0007105	0.160	Upregulated
SFRP2	secreted frizzled related protein 2	2.207	0.0019966	0.173	Upregulated
MUCL1	mucin like 1	2.196	0.0216071	0.278	Upregulated
SULF1	sulfatase 1	2.103	0.0014886	0.173	Upregulated
COL10A1	collagen type X alpha 1 chain	1.954	0.0007472	0.160	Upregulated
TNFAIP8	TNF alpha induced protein 8	1.932	0.0002881	0.160	Upregulated
TUBB2B	tubulin beta 2B class IIb	-2.609	0.0045415	0.199	Downregulated
RPS3	ribosomal protein S3	-2.493	0.0003292	0.160	Downregulated
TUBB2B	tubulin beta 2B class IIb	-2.389	0.0030103	0.183	Downregulated
RPL7	ribosomal protein L7	-2.334	0.0155453	0.255	Downregulated
PPM1H	protein phosphatase, Mg2+/Mn2+ dependent 1H	-2.276	0.0000309	0.151	Downregulated
KDELR2	KDEL endoplasmic reticulum protein retention receptor 2	-2.200	0.0019326	0.173	Downregulated
BTBD3	BTB domain containing 3	-2.142	0.0009079	0.163	Downregulated
PPM1H	protein phosphatase, Mg2+/Mn2+ dependent 1H	-2.123	0.0000687	0.151	Downregulated
DAZAP1	DAZ associated protein 1	-2.053	0.0013438	0.170	Downregulated
MAGI1	membrane associated guanylate kinase, WW and PDZ domain containing 1	-2.010	0.0029632	0.183	Downregulated

3.2. Identification of DEGs

A total of 1262 DEGs of the GSE42568 database were examined, of which, 486 genes were upregulated and 776 were downregulated. Of the 77 DEGs examined from the GSE43837 database, 26 genes were up-regulated and 51 were down-regulated. Overall 15 common genes overlapped between the two datasets as shown in Figure 3.

3.3. PPI network analysis

Overall, among 1339 genes from the BC and BM datasets, 15 common DEGs were examined through

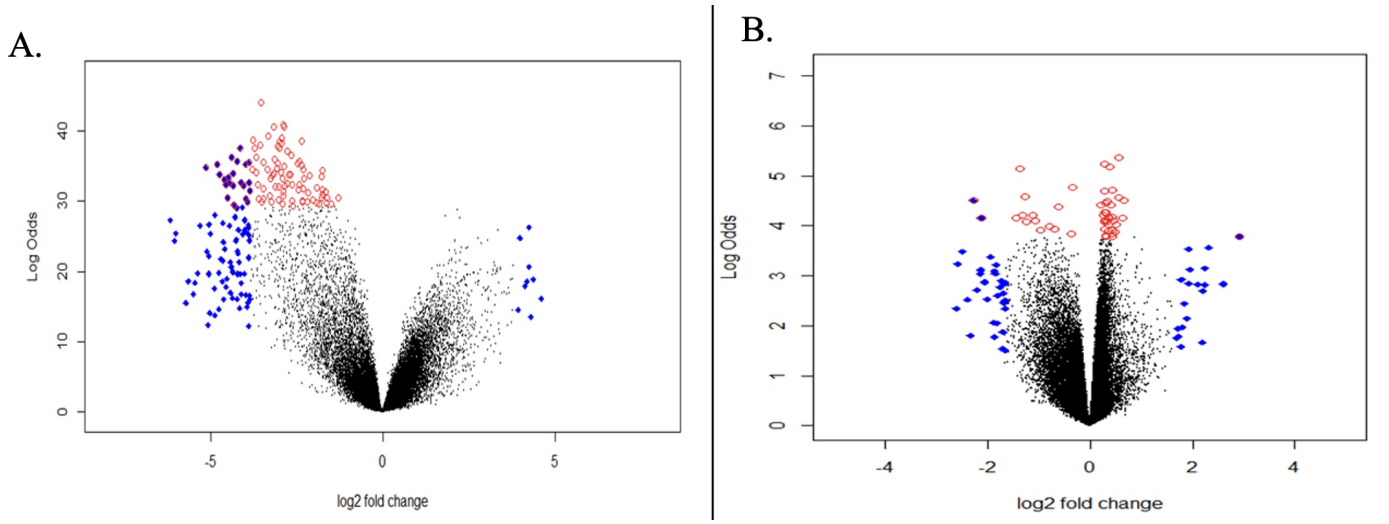

Figure 2. Volcano plots of differentially expressed genes (DEGs): (A) Dataset 1 (normal breast versus breast cancer) and (B) Dataset 2 (breast cancer versus brain metastases). x-axis is log2 fold-change (log2FC) and y-axis is –log10 adjusted p-value. Red dots mark significantly upregulated genes, green dots mark significantly downregulated genes, and grey dots are non-significant genes (thresholds: $|\log2FC| > 1.5$ and adjusted $p < 0.05$). These plots illustrate the global transcriptional differences between normal breast tissue, primary breast cancer, and brain metastases.

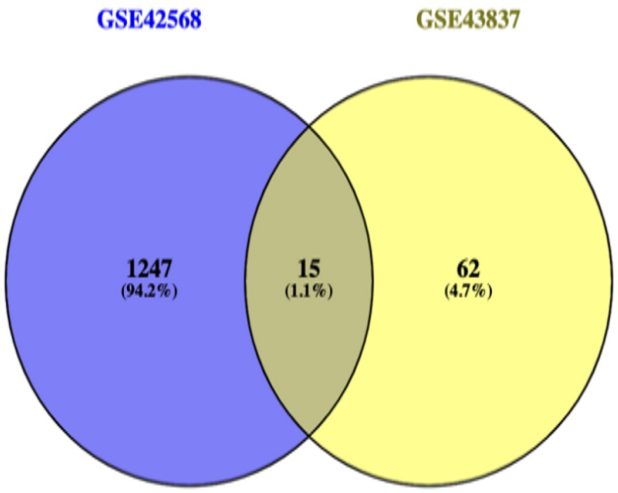

Figure 3. Venn diagram showing 15 overlapping differentially expressed genes (DEGs) between breast cancer (GSE42568) and brain metastases (GSE43837) datasets. Different colored areas represent different datasets. The overlapping area represents the common DEGs. DEGs were identified using the t-test; statistically significant DEGs were defined with [log2FC]>1.5 as the cutoff criterion

the DEGs PPI network complex, which revealed 15 nodes and 8 edges [Figure 4.A.]. The 62 unique BM genes examined through the DEGs PPI network complex showed 59 nodes and 64 edges [Figure 4B]. The 77 common genes were examined in a combined PPI network complex, which revealed 74 nodes and 104 edges [Figure 4.C.].

Biological function of shared DEGs was identified using PPI network analysis. The top 10 shared genes ranked according to network centrality scores. Of note, MMP1 and COL1A2 had the highest degree of interaction and were therefore likely to be hub genes to be engaged in breast cancer initiation to brain metastasis [Table 2].

Genes identified to be present only in the brain metastasis dataset were explored in detail using PPI network analysis. Top 10 genes by degree of interaction and centrality metrics. Core ribosomal proteins [RPL8, RPL7, RPS3A, EEF1A1] and signaling factors [FASLG] were central nodes of high connectivity, suggesting their possible role in brain metastasis biology. When the DEGs specific for brain metastasis and the shared

Table 2. Top 10 unique brain metastasis associated genes ranked by network centrality measures in the PPI network.

Gene Symbol	Betweenness Centrality	Closeness Centrality	Degree	Eccentricity	Neighborhood Connectivity
ACTB	0.59975369	0.3372093	9	7	4.66666667
RPL8	0.09400657	0.29896907	8	8	7.5
RPL7	0.09400657	0.29896907	8	8	7.5
RPS3A	0.09400657	0.29896907	8	8	7.5
EEF1A1	0.04655172	0.29	8	8	7
PSMD2	0.01600985	0.24786325	7	9	6.85714286
RPS3	0.00640394	0.25438596	7	9	7.42857143
RPL18	0.00640394	0.25438596	7	9	7.42857143
RPN2	0.19211823	0.25217391	6	9	6.66666667
FASLG	0.27914614	0.24786325	4	9	3.5

DEGs were analyzed together in an integrated PPI network, certain hub genes became apparent. The top 10 ranked according to degree of interaction. Highly interacting ribosomal proteins [RPS3, RPL7, RPL8, EEF1A1] were again predominant, further testifying to these as key players of metastatic spread.

GO enrichment of the genes that are specific for brain metastasis indicated their implication in significant biological processes Significant GO terms such as phosphate symporter activity, chromatin assembly, regulation of apoptosis, and extracellular matrix organization and related genes. KEGG and Reactome database enrichment pathway analysis of rare brain metastasis genes identified enrichment in pathways of ribosome biogenesis, protein metabolism, and extracellular matrix remodeling. The key pathways and their corresponding gene members. GO enrichment analysis of common DEGs found between brain metastasis and breast cancer datasets identified significant biological processes. The enriched GO terms like collagen trimer formation, histone modification, and ion transport regulation, indicating the general functional themes in metastatic development [Table 3].

KEGG and Reactome pathway enrichment of the common DEGs also highly supported processes in protein digestion and absorption, collagen breakdown, and extracellular matrix remodeling. Enriched Reactome and KEGG pathways and signify possible convergence of metastatic signaling pathways.

The network was generated using Cytoscape and the MCODE plug-in was used to perform module analysis of the PPI network. Two significant clusters were extracted from the constructed PPI network [clusters 1 and 2] [Figure 5.A, B]. Cluster 1 contained 8 genes, namely, EEF1A1, PSMD2, RPL7, RPL8, RPL18, RPS3, RPS3A, and RPN2, whereas Cluster 2 consisted of 12 genes, namely, ASPN, COL3A1, VCAM, H3F3B, GBP1, H3F3A, CXCL9, KMT2D, FASLG, DAXX and LUM.

3.4. Cluster analysis through GO function plus KEGG enrichment pathways

There are three classes of DEGs based on GO analysis, including biological, cellular component, and molecular pathways. For cluster 1, GO functions included [GO: 1900022], [GO: 1905051], and [GO: 0032358]. The [GO: 1900022] regulates D-erythro-sphingosine kinase activity, whereas the [GO: 1905051] maintains regulation of the cellular base-excision repair process. The [GO: 0032358] is involved in oxidized pyrimidine DNA binding. In contrast, cluster 2 GO functions included [GO: 0031508], [GO: 0031509], [GO: 0005201], [GO: 0030021], and [GO: 0030021] . The [GO: 0031508] is responsible for pericentric heterochromatin assembly and [GO: 0031509] has a role in telomeric heterochromatin assembly. The [GO: 0005586] promotes collagen type III trimer, while [GO: 0005201] maintains the structural composition of the extracellular matrix. Finally, [GO: 0030021] regulates the structural composition of the extracellular matrix, conferring compression resistance [Table 4].

According to the KEGG and Reactome enrichment pathways, cluster 1 genes were associated with nonsense-mediated decay independent of the exon

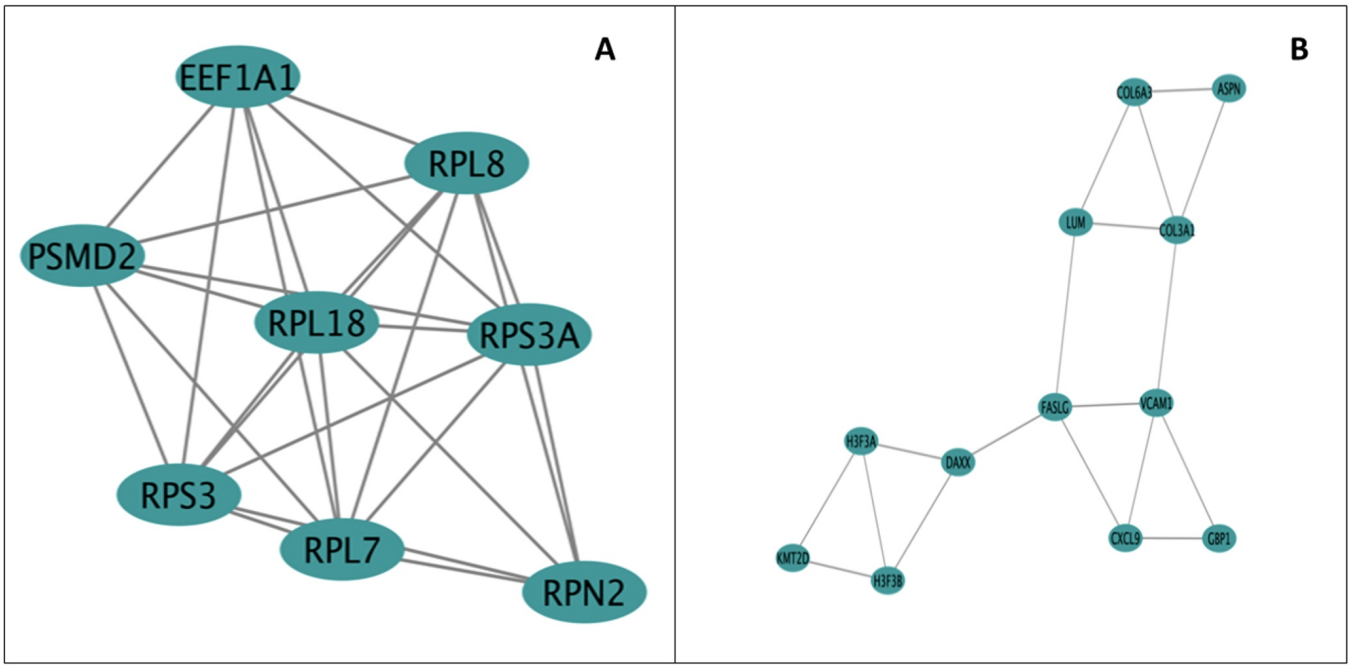

Figure 4. PPI clusters from genes shared by primary tumors and brain metastases. Nodes are genes; gray lines are interaction edges from the PPI analysis, reflecting functional associations (greater line density = more cohesive/strongly connected module). (A) Ribosome/proteostasis. (B) ECM–immune/chromatin.

Table 3. Gene ontology (GO) functional annotations of unique brain metastasis associated genes.

GO ID	Biological Function	Associated Genes
GO:0015317	phosphate:proton symporter activity	SLC25A3
GO:0031508	pericentric heterochromatin assembly	H3-3A, H3-3B
GO:0031509	telomeric heterochromatin assembly	H3-3A, H3-3B
GO:0038044	transforming growth factor-beta secretion	ITGB6
GO:0061185	negative regulation of dermatome development	SFRP2
GO:1900022	regulation of D-erythro-sphingosine kinase activity	EEF1A1
GO:1902340	negative regulation of chromosome condensation	H3-3A, H3-3B
GO:1905051	regulation of base-excision repair	RPS3
GO:1905053	positive regulation of base-excision repair	RPS3
GO:2001272	positive regulation of cysteine-type endopeptidase activity involved in execution phase of apoptosis	RPS3
GO:0005586	collagen type III trimer	COL3A1
GO:0034685	integrin alphav-beta6 complex	ITGAV, ITGB6
GO:0150002	distal dendrite	MAP2, METAP2
GO:0150014	apical distal dendrite	MAP2, METAP2
GO:0032358	oxidized pyrimidine DNA binding	RPS3

junction complex. The cluster 1 genes control SLITs, ROBO expression, and ROBO signaling receptors. EEF1A1, PSMD, RPL8, RPL7, RPS3A, RPS3, RPL18, and RPN2 were involved in these signaling pathways. In contrast to the enrichment pathways of cluster 2, these genes were related to the extracellular matrix

Table 4. KEGG and Reactome signaling pathway enrichment analysis of unique brain metastasis

Pathway ID	Functional Pathway	Associated Genes
KEGG:03010	Ribosome	RPL18,RPL7,RPL8,RPS3,RPS3A
R-HSA-2408557	Selenocysteine synthesis	RPL18,RPL7,RPL8,RPS3,RPS3A
R-HSA-975957	Nonsense-Mediated Decay (NMD) enhanced by the Exon Junction Complex (EJC)	RPL18,RPL7,RPL8,RPS3,RPS3A
R-HSA-9010553	Regulation of expression of SLITs and ROBOs	PSMD2,RPL18,RPL7,RPL8,RPS3,RPS3A
R-HSA-376176	Signaling by ROBO receptors	PSMD2,RPL18,RPL7,RPL8,RPS3,RPS3A
R-HSA-392499	Metabolism of proteins	LYZ,MUCL1,ACTB,DAXX,DDB1,EEF1A1,EPRS
R-HSA-216083	Integrin cell surface interactions	COL3A1,COL6A3,LUM,VCAM1,ITGB6
R-HSA-3000178	ECM proteoglycans	ASPN,COL3A1,COL6A3,LUM,ITGB6

[ECM] proteoglycans in African trypanosomiasis. These genes, including ASPN, COL3A1, VCAM1, LUM, COL6A3, and FASLG, are also involved in interactions of cell surface integrin and extracellular matrix organization.

4 Discussion

BC is a major cause of death in women. BM is a main mortality risk for patients with BC [21,22]. BC can metastasize to the brain, but the basic mechanisms underlying BC metastasis to the brain are still unknown [21]. Progression to BM may result from angiogenesis, immunity, signaling kinase, and genes such as COX2 and ST6GALNAC5. In recent studies, long noncoding RNA was also associated with metastatic BC to the brain [23–27]. A previous study identified five DEGs, namely, MMP2, MMP11, VCAM1, CXCL12, and MME, implicated in primary brain cancer and BC metastasis to the brain. These genes play essential roles in metastases processes [28]. In this study, VCAM1, a gene that is expressed in cytokine activated endothelium and encodes a cell surface sialoglycoprotein, was found in cluster 1. VCAM1 protein regulates adhesion between leukocytes and endothelial cells and contributes significantly to signal transduction. It has been associated with atherosclerosis and rheumatoid arthritis progression and three alternative splice variants have been reported, which encode several isoforms. VCAM1 contributes to leukocyte circulation from blood to tissue during the inflammatory response and may be expressed abnormally in multiple types of cancers. It includes breast cancer, melanomas, and gastric cancer [29]. Thus, VCAM1 may contribute in the progression of BC and BM. A recent study has identified 12 differentially expressed collagen genes between metastatic brain cancer and the primary BC. These genes are COL1A1, COL15A1, COL1A2, COL3A1, COL6A3, COL14A1, COL6A1, COL5A1, COL8A2, COL6A2, COL5A2, and COL10A1. Each of these genes were expressed considerably more in BC than in BM [21]. Collagen shows for 35% of all the proteins produced by humans [30]. Collagen I, II, III, V, plus collage IX levels were increased at BC progression [31]. In our study, we also identified four collagen genes, namely, COL1A2, COL3A1, COL6A3, and COL10A1. Abnormal expression of collagen genes may have a cotribution to metastatic brain cancer development in patients with BC.

Another study supports the concept that EEF1A1 may be pro-tumorigenic for particular cancers, including kidney cancer, liver cancer, gliomas, and glioblastomas. EEF1A1 expression is more likely to be a good prognostic indicator for several cancer types, including breast, brain, lung, and kidney cancers, and EEF1A1 has also been commonly described as a pro-apoptotic protein [32]. In this study, EEF1A1 was detected and may have been identified as either CCS3, EE1A1, EF1A, PTI1, or CCS-3. Other names such as LENG7, EEF1A, GRAF-1EF, EEF-1, EF-Tu, and eEF1A-1 may also be associated with EEF1A1. In addition, the alpha domain of the elongation factor-1 is encoded by EEF1A1. Alpha-1 isoform facilitates aminoacyl tRNA distribution to the ribosome. Its expression is widely demonstrated in the brain, placenta, lungs, liver, and kidney. In this study, we also identified 12 genes ASPN, FASLG, H3-3A, H3.3B, LUM, PSMD, RPL8, RPL7, RPS3A, RPS3 RPL18, and RPN2. PSMD2 is a type of proteasome that spreads among eukaryotic cells at high concentrations. They degrade

peptides in a non-lysosomal pathway specifically through an ATP/ubiquitin-dependent manner. The modified proteasome has a particular role as an immunoproteasome. The immunoproteasome refers to the preparation process of class I MHC peptides. The immunoproteasome also contributes to the TNF signaling pathway. PSMD2 demonstrates ubiquitous expression in the brain [RPKM 40.8]. RPL8, RPL7, RPS3A, RPS3 RPL18, and RPN2 are ribosomal proteins identified in our study and they may have a role in brain metastases, along with PSMD2, because they are involved in the regulation of SLIT and ROBO expression.

ASPN encodes a cartilage extracellular protein, which belongs to the leucine-rich proteoglycan family, and contributes to chondrogenesis regulation. In cartilage, it acts as a suppressor for transforming growth factor-beta 1. It connects calcium and collagen to promote collagen mineralization. ASPN polymorphism is associated with osteoarthritis susceptibility through the aspartic acid repeat domain and is also associated with intervertebral disc disease. Several transcript variants are initiated as a result of alternative splicing of ASPN. FASLG gene encodes a transmembrane protein that is essential for inducing apoptosis initiated by binding to FAS. The FAS/FASLG signaling pathway has a basic role in immune system regulation as it regulates activation-induced cell death which occurs in T cells. It also initiates cytotoxic T lymphocyte-induced cell death. Additionally, FASLG has been implicated in the progression of several cancers and may be correlated with metastases of breast cancer to the brain.

H3-3A and H3-3B genes control the nucleosome composition of the chromosomal fiber. These genes comprise introns and their mRNA is polyadenylated, unlike that of most histone genes. The encoded protein is a replication-independent element of the histone H3 group. As histone modification indicates epigenetic mechanisms, H3-3A and H3-3B genes might have a potential association with BC and the development of BM. LUM was upregulated in this study which encodes a unit of the SLRP cascade. This involves keratocan, osteoglycin, biglycan, decorin, epiphycan, and fibromodulin. The protein attaches to collagen fibrils in these bifunctional molecules. They are maintaining interfibrillar spacing through increased charged hydrophilic glycosaminoglycans. Lumican is a primary keratan sulfate proteoglycan. However, it is found likewise at interstitial collagenous matrices. It also facilitates the regulation of collagen organization and growth.

5 Conclusion

In conclusion, in this study, we performed various bioinformatic analyses to determine the potential molecular contributions between BC and metastatic brain cancer. Twenty significant genes, namely, EEF1A1, RPL8, RPS3A, RPN2, PSMD2, RPL18, RPL7, RPS3, ASPN, COL6A3, COL3A1, LUM, VCAM1, FASLG, GBP1, CXCL9, DAXX, H3F3A, H3F3B, and KMT2D, in two PPI clusters were identified. However, further validations are necessary to support these findings. Further studies should involve both in vivo likewise in vitro analyses for validating the results obtained at this study. The genes identified are associated with the structural composition of the extracellular matrix which confers compression resistance, which demonstrates the significance of these gene clusters.

Conflicts of Interest

The author declare that they have no conflicts of interest.

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