Article

Exploring the Molecular Mechanism of the Drug-Treated Breast Cancer Based on Gene Expression Microarray

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Abstract: Breast cancer (BRCA) remains the leading cause of cancer morbidity and mortality worldwide. In the present study, we identified novel biomarkers expressed during estradiol and tamoxifen treatment of BRCA. The microarray dataset of E-MTAB-4975 from Array Express database was downloaded, and the differential expressed genes (DEGs) between estradiol-treated BRCA sample and tamoxifen-treated BRCA sample were identified by limma package. The pathway and gene ontology (GO) enrichment analysis, construction of protein-protein interaction (PPI) network, module analysis, construction of target genes—miRNA interaction network and target genes-transcription factor (TF) interaction network were performed using bioinformatics tools. The expression, prognostic values, and mutation of hub genes were validated by SurvExpress database, cBioPortal, and human protein atlas (HPA) database. A total of 856 genes (421 up-regulated genes and 435 down-regulated genes) were identified in T47D (overexpressing Split Ends (SPEN) + estradiol) samples compared to T47D (overexpressing Split Ends (SPEN) + tamoxifen) samples. Pathway and GO enrichment analysis revealed that the DEGs were mainly enriched in response to lysine degradation II (pipecolate pathway), cholesterol biosynthesis pathway, cell cycle pathway, and response to cytokine pathway. DEGs (*MCM2*, *TCF4*, *OLR1*, *HSPA5*, *MAP1LC3B*, *SQSTM1*, *NEU1*, *HIST1H1B*, *RAD51*, *RFC3*, *MCM10*, *ISG15*, *TNFRSF10B*, *GBP2*, *IGFBP5*, *SOD2*, *DHF* and *MT1H*), which were significantly up- and down-regulated in estradiol and tamoxifen-treated BRCA samples, were selected as hub genes according to the results of protein-protein interaction (PPI) network, module analysis, target genes—miRNA interaction network and target genes-TF interaction network analysis. The SurvExpress database, cBioPortal, and Human Protein Atlas (HPA) database further confirmed that patients with higher expression levels of these hub genes experienced a shorter overall survival. A comprehensive bioinformatics analysis was performed, and potential therapeutic applications of estradiol and tamoxifen were predicted in BRCA samples. The data may unravel the future molecular mechanisms of BRCA.

Keywords: pathway enrichment analysis; protein-protein interaction network; microRNA

1. Introduction

Breast cancer (BRCA) is the most common type of gynecological cancer in women [1]. BRCA accounts for 2,088,849 (11.6%)of new cancer cases [2] and 626,679 (6.6%) deaths in women worldwide, as per 2018 cancer statistics [3].Surgical resection is an effective treatment to advance patient

survival time [4], but it is only suitable for a small percentage of all cases [5].A number of other therapies, including radiotherapy [6], chemotherapy [7], hormone therapy [8], and immunotherapy [9], have been developed for BRCA treatment; however, there is limited information regarding the long-term survival rate, and the mortality rate of BRCA patients remains high [10]. Therefore, examinations into new treatment strategies for patients with BRCA are needed.

Gene therapy and small molecule drugs are new strategies for cancer treatment, which have gained increasing consideration over the past few decades [11]. Currently, a number of studies have been conducted to know the underlying molecular mechanisms and find treatment targets for BRCA [12]. Specific genes associated with the DNA damage response, including BRCA1, are mutated during the development of BRCA [13]. Wang et al. [14], Gong et al. [15], Serra et al. [16], Ghayad et al. [17], and Lemée et al. [18] had verified, through microarray and RT-PCR technology, the role of VEGFR-2, AKT, HER, and MAPK as well as activated the replication and genomic instability in BRCA. The Cyclin D1 gene is overexpressed in BRCA and may act as a therapeutic target [19]. Previous studies have mainly concentrated on a certain gene or pathway; therefore, it is necessary to search the underlying molecular mechanisms and therapeutic targets for BRCA using other methods.

In the current study, the expression-profiling data E-MTAB-4975 was downloaded, and the differential expressed genes (DEGs) were analyzed between T47D (overexpressing Split Ends (SPEN)+ estradiol) samples and T47D (overexpressing Split Ends (SPEN) + tamoxifen) samples. The functions of DEGs were analyzed using pathway and gene ontology (GO) enrichment analysis. Furthermore, protein-protein interactions (PPIs) of DEGs were investigated and the topological properties of hub genes calculated as well as modules were extracted in the PPI network. In addition, target gene –miRNA interaction network and target gene- transcription factor (TF) interaction network were constructed. Therefore, the current study analyzed their expression data using a series of bioinformatics methods to diagnose important associated and novel biomarkers, that will allow the identification of the underlying mechanisms associated with BRCA.

2. Materials and Methods

2.1. Agilent Microarray Data

The microarray dataset E-MTAB-4975 was downloaded from the ArrayExpress [20] and analyzed using the Agilent 028004 SurePrint G3 Human GE 8x60K Microarray (Agilent Technologies, Inc., Santa Clara, CA, USA) platform. A total of 18 samples were present in this dataset, including 3 T47D (wild type genotype + estradiol), 3 T47D (wild type genotype + none), 3 T47D (wild type genotype + tamoxifen), 3 T47D (overexpressing Split Ends (SPEN) + estradiol), 3 T47D (overexpressing Split Ends (SPEN) +none), and 3 T47D (overexpressing Split Ends (SPEN) + tamoxifen) samples.

2.2. Data Preprocessing

Raw probe-level data was downloaded, and expression profile data preprocessing was performed based on the limma package (version 3.34.9); in R Bioconductor version 3.4.4 [20]. The matrix data of dataset achieved log2 conversion and normalization applying limma package of R/Bioconductor software [21].

2.3. Identification of DEGs

Following data preprocessing, DEGs between T47D (overexpressing Split Ends (SPEN) + estradiol) samples and T47D (overexpressing Split Ends (SPEN) + tamoxifen) samples were analyzed using Bayes methods based limma package, and raw *p*-values were revised using the Benjamini and Hochberg method [22]. The cut-off criteria for defining DEGs are $p < 0.05$, |logFC| > 1.19 (up-regulated genes), and |logFC| > −1.35 (down-regulated genes).

2.4. Pathway Enrichment Analyses of DEGs

The ToppGene provides functional classification and annotation analyses of associated genes [23] which integrates different pathway databases, such as BioCyc [24], Kyoto Encyclopedia of Genes and Genomes (KEGG) [25], Pathway Interaction Database (PID) [26], Reactome [27], GenMAPP [28], MSigDB C2 BioCarta (v6.0) [29], PantherDB [30], Pathway Ontology [31], and Small Molecule Pathway Database (SMPDB) [32] pathways. The significant pathways enriched with up-regulated and down-regulated DEGs were selected with a criterion of $p < 0.05$.

2.5. Gene Ontology (GO) Enrichment Analysis

Gene Ontology (GO) is a widely used method for consolidation of biology that compiles structured, defined, and regulated glossary for large scale gene annotation [33]. The ToppGene [23] provides a comprehensive set of functional annotation tools to identify GO terms, such as biological processes (BP), cellular component (CC), and molecular function (MF).To understand the biological functions of the DEGs, the present study used ToppGene to identify GO categories. The significant GO terms enriched with up-regulated and down-regulated DEGs were selected with a criterion of $p < 0.05$.

2.6. PPI Network Construction and Module Analysis

The online tool HIPPIE (Human Integrated Protein-Protein Interaction rEference) [34] integrates different PPI databases, such as IntAct [35], BioGRID [36], HPRD [37], MINT [38], BIND [39], MIPS [40], and DIP [41], which were applied to construct a PPI network and visualized using the Cytoscape software version 3.7.0 [42]. The importance of a protein in the PPI network was determined by its topological properties, such as degree (number of the proteins it connected) [43], betweenness centrality(measures the ability of a protein to monitor communication between other proteins) [44], stress centrality (number of nodes in the shortest path between two other nodes) [45], closeness centrality(inverse of the average length of the shortest paths to/from all the other nodes in the graph) [46], and cluster coefficient(measures the density of edges in the network neighborhood of a node) [47]. A node represents gene, and an edge represents a number of interactions between genes.

Module analysis was performed using the JAVA plugin PEWCC1 in Cytoscape with the threshold of $p < 0.001$ to obtain sub-networks (modules) [48]. For each hub, genes in modules were identified.

2.7. Construction of Target Genes-miRNA Regulatory Network

The different miRNA database, such as TarBase [49] and miRTarBase database [50], are publicly available comprehensive resource containing the predicted and the experimentally validated target gene–miRNA interaction pairs. Subsequently, the hub genes, which interact with a maximum number of miRNA, were selected. The target gene-miRNA was generated from NetworkAnalyst [51] and visualized using the Cytoscape version 3.7.0 software [42].

2.8. Construction of Target Genes-TF Regulatory Network

The TFs database, named ChEA database [52], provides data on eukaryotic transcription factors, consensus binding sequences (positional weight matrices), experimentally proven binding sites, and regulated genes. Target genes-TF regulatory network was generated from NetworkAnalyst [51] and visualized using the Cytoscape version 3.7.0 software [42]. Subsequently, the hub genes interacting with the maximum number of TFs were selected.

2.9. Survival Analysis of Hub Genes

The hub genes were identified as the intersecting genes of The Cancer Genome Atlas (TCGA) and DEGs. The hub genes were then analyzed on web tool SurvExpress, a portal for facilitating tumor subgroup gene expression and survival analyses [53]. BRCA samples were divided into two groups: (1) high expression and (2) low expression. The survival curves of samples with high gene

expression and low gene expression were compared by Kaplan-Meier survival plot, the log-rank *p*-value, and hazard ratio (HR, 95% confidence intervals). $p < 0.05$ is considered statistically significant.

2.10. Validation of Hub Genes

The mRNA expression of the DEGs was analyzed in 2 low-risk and 1 high-risk groups with the assistance of SurvExpress [53], which is an online tool to deliver customizable functionalities based on The Cancer Genome Atlas, and the translational levels of the hub genes were validated using the Human ProteinAtlas (HPA) database [54].

2.11. Mutation Analysis of Hub Genes

The cBio Cancer Genomics Portal [55] is a web tool, which provides mutation analysis, visualization, and downloads of cancer genomics datasets of various cancers. Complex cancer genomics profiles are accessible from the cBioPortal tool, thus enabling us to compare the genetic modifications of the selected ten hub genes in BRCA. The flowchart of the methodology is depicted below (Figure 1).
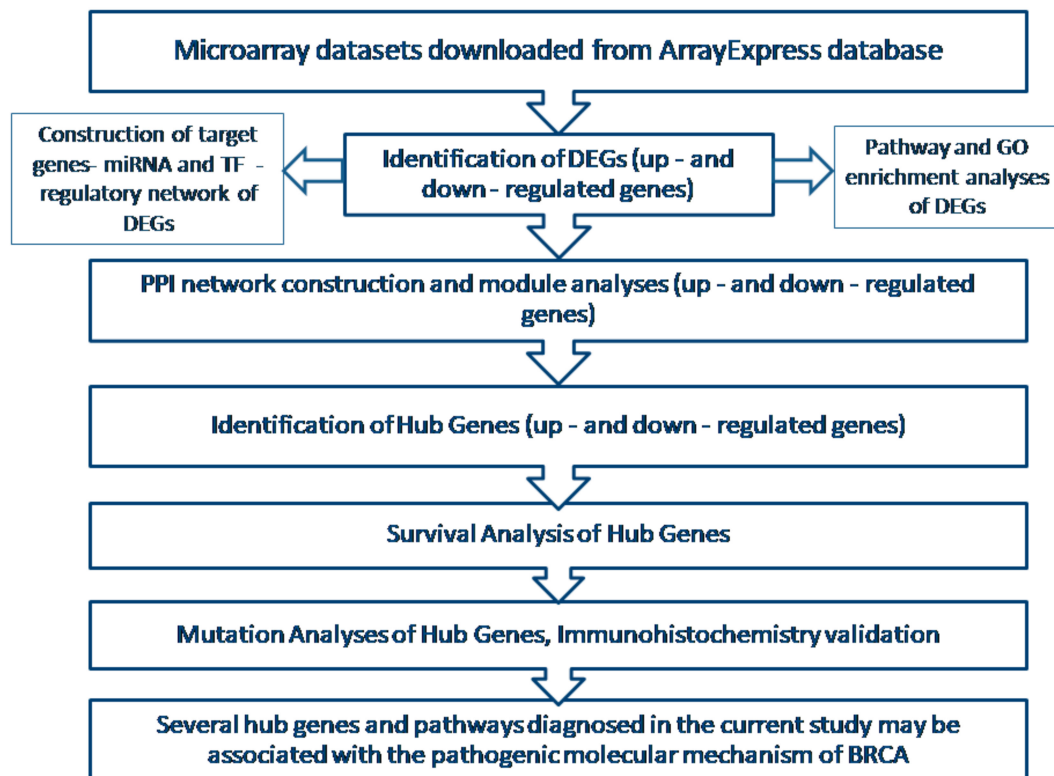

Figure 1. The workflow representing the methodology and the major outcome of the study. BRCA—breast cancer, GO—gene ontology, miRNA—MicroRNA, TF—transcription factor, DEGs—differential expressed genes.

3. Results

3.1. Data Preprocessing

Before normalization, the medians of gene expression in each sample were greatly definite (Figure 2A). However, the medians became consistent and were at an identical level following normalization (Figure 2B), suggesting that the normalization process is valid, and the normalized data may be used for additional analysis. Based on their BRCA status, samples were divided into six groups: T47D (wild type genotype + estradiol) (*n* = 3), T47D (wild type genotype + none) (*n* = 3), T47D (wild type genotype + tamoxifen) (*n* = 3), T47D (overexpressing Split Ends (SPEN) + estradiol)

(*n* = 3), T47D (overexpressing Split Ends (SPEN) + none) (*n* = 3), and T47D (overexpressing Split Ends (SPEN) + tamoxifen) (*n* = 3).
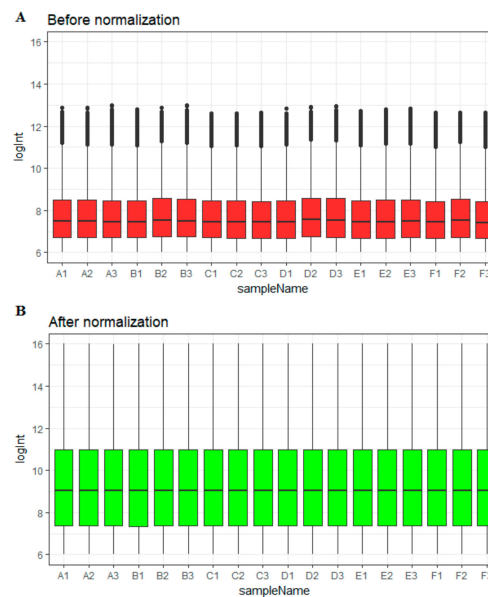

Figure 2. Box plots of the gene expression data before (**A**) and after (**B**) normalization. The horizontal axis represents the sample symbol, and the vertical axis represents the gene expression values. The black line in the box plot represents the median value of gene expression. (A1, A2, A3 = T47D (wild type genotype + estradiol); B1, B2, B3 = T47D (wild type genotype + none); C1, C2, C3 = T47D (wild type genotype + tamoxifen); D1, D2, D3 = T47D (overexpressing Split Ends (SPEN) + estradiol); E1, E2, E3 = T47D (overexpressing Split Ends (SPEN) + none); F1, F2, F3 = T47D (overexpressing Split Ends (SPEN) + tamoxifen)).

3.2. Identification of DEGs

The DEGs of E-MTAB-4975 were analyzed using the limma package following preprocessing and removing batch effects. Using $p < 0.05$ and $|\text{logFC}| > 1.19$ as the cutoff criteria for up-regulated genes, $p < 0.05$ and $|\text{logFC}| > -1.35$ for down-regulated genes, total of 856 genes (421 up-regulated genes and 435 down-regulated genes) were identified in T47D (overexpressing Split Ends (SPEN) + estradiol) samples compared to T47D (overexpressing Split Ends (SPEN) + tamoxifen) samples (Table S1). The DEGs (up- and down-regulated) are shown in the volcano plot (Figure 3). The DEGs (up- and down-regulated), according to the value of $|\text{logFC}|$, are visualized on a heatmap (Figures 4 and 5). A total of 145 housekeeping genes were identified in this dataset.
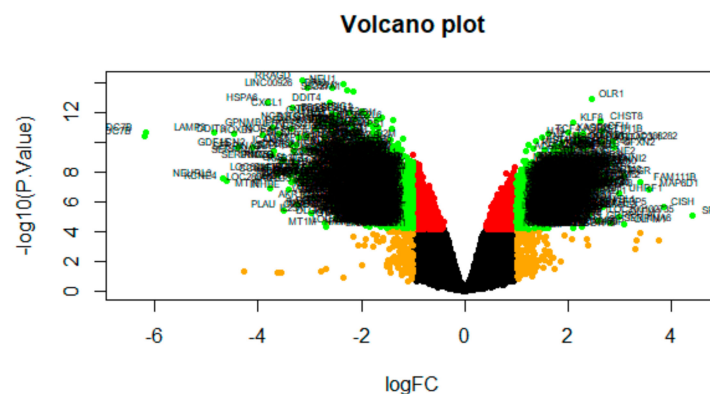

Figure 3. Volcano plot of differentially expressed genes. Genes with a significant change of more than two-fold were selected.
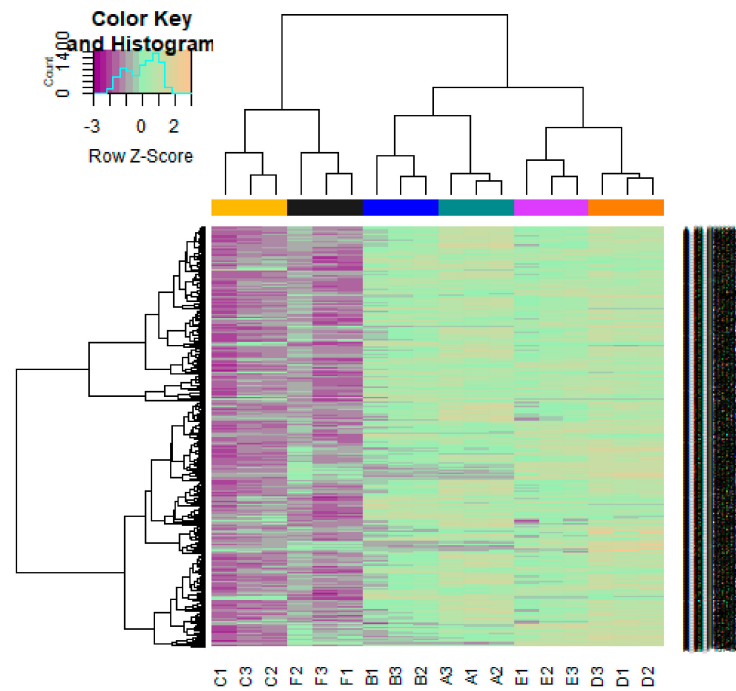
Figure 4. Heat map of up-regulated differentially expressed genes. The legend on the top left indicates log fold change of genes. (A1, A2, A3 = T47D (wild type genotype + estradiol); B1, B2, B3 = T47D (wild type genotype + none); C1, C2, C3 = T47D (wild type genotype + tamoxifen); D1, D2, D3 = T47D (overexpressing Split Ends (SPEN) + estradiol); E1, E2, E3 = T47D (overexpressing Split Ends (SPEN) + none); F1, F2, F3 = T47D (overexpressing Split Ends (SPEN) + tamoxifen)).

Figure 5. Heat map of down-regulated differentially expressed genes. The legend on the top left indicates log fold change of genes. (A1, A2, A3 = T47D (wild type genotype + estradiol); B1, B2, B3 = T47D (wild type genotype + none); C1, C2, C3 = T47D (wild type genotype + tamoxifen); D1, D2, D3 = T47D (overexpressing Split Ends (SPEN) + estradiol); E1, E2, E3 = T47D (overexpressing Split Ends (SPEN) + none); F1, F2, F3 = T47D (overexpressing Split Ends (SPEN) + tamoxifen)).
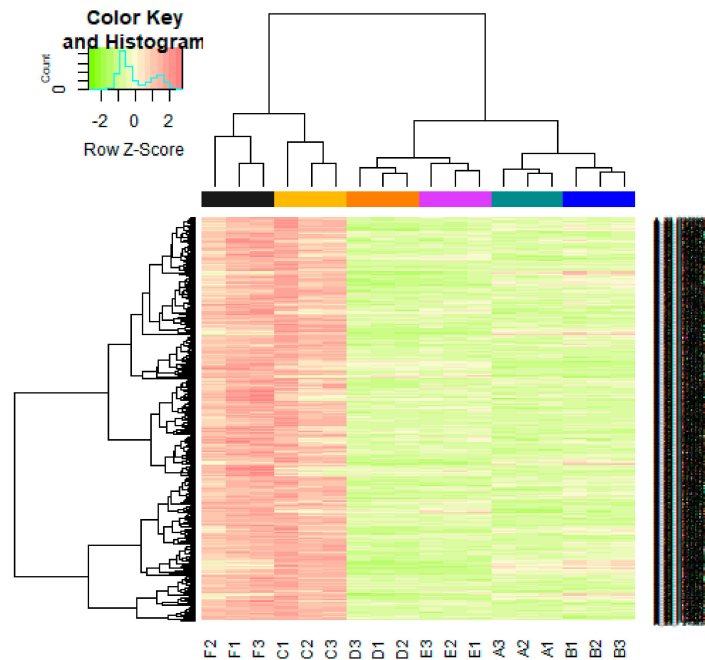
3.3. Pathway Enrichment Analysis

The DEGs (up- and down-regulated) were uploaded to the online web tool ToppGene having different pathway databases, such as BioCyc [24], KEGG [25], PID [26], Reactome [27], GenMAPP [28], MSigDB C2BioCarta [29], PantherDB [30], Pathway Ontology [31], and SMPDB [32]. Tables S2 and S3 contain the most significantly enriched pathways for up- and down-regulated genes from different pathway databases. The up-regulated genes were enriched in lysine degradation II (pipecolate pathway), pyrimidine deoxyribonucleosides salvage, DNA replication, cell cycle, E2F transcription factor network, BARD1 signaling events, mitotic, pyrimidine metabolism, carbon pool by folate, CDK regulation of DNA replication, expression of cyclins regulating progression through the cell cycle by activating cyclin-dependent kinases, tetrahydrofolate biosynthesis, mismatch repair pathway, nucleotide excision repair, and GABA-transaminase deficiency, listed in Table S2. The down-regulated genes were enriched in superpathway of cholesterol biosynthesis, cholesterol biosynthesis II (via 24,25-dihydrolanosterol), mineral absorption, squalene 2,3-epoxide => cholesterol, ATF-2 transcription factor network, direct p53 effectors, response to metal ions, sterol biosynthesis, gamma-hexachlorocyclohexane degradation, genes encoding secreted soluble factors, actions of nitric oxide in the heart, apoptosis signaling pathway, cholesterol biosynthetic, steroid biosynthetic, and risedronate pathway, listed in Table S3.

3.4. Gene Ontology (GO) Enrichment Analysis

The DEGs were uploaded to the online web tool ToppGene to pinpoint overrepresented GO categories. GO analysis results showed that up-regulated genes were significantly enriched in all GO terms, which include: cell cycle, DNA replication, chromosome, chromosomal part, chromosome, centromeric region, and DNA helicase activity (Table S4), while down-regulated genes were significantly enriched in all GO terms, which include: response to cytokine, cellular response to cytokine, endoplasmic reticulum, nuclear outer membrane-endoplasmic reticulum membrane network, cytokine activity, and cytokine receptor binding (Table S5).

3.5. PPI Network Construction and Topology Analysis

The PPI network (up-regulated) had 6479 nodes and 15,710 interactions (Figure 6). Hub genes with high node degree, such as *MCM2* (degree = 875), *CDK2* (degree = 737), *BRCA1* (degree = 561), *HIST1H3F* (degree = 454), and *HIST1H3B* (degree = 454), are listed in Table S6. R square = 0.773 and correlation coefficient = 0.987 for node degree (Figure 7A). Hub genes with high betweenness centrality, such as *TCF4* (betweenness = 0.04852), *ASPM* (betweenness = 0.012646), *CHST8* (betweenness = 0.005764), *KCNB1* (betweenness = 0.004046), and *CFH* (betweenness = 0.003746), are listed in Table S6. R square = 0.616 and correlation coefficient = 0.139 for betweenness centrality (Figure 8A). Hub genes with high stress, such as *MCM2* (stress = 127048732), *BRCA1* (stress = 87536324), *CDK2* (stress = 84519756), *HIST1H3F* (stress = 47668690), and *HIST1H3B* (stress = 47668690), are listed in Table S6. R square = 0.000 and correlation coefficient = 0.039 for stress (Figure 8B). Hub genes with high closeness centrality, such as *MCM2* (closeness = 0.414382), *FLNA* (closeness = 0.392197), *BRCA1* (closeness = 0.398937), *HIST1H3B* (closeness = 0.388514), and *HIST1H3F* (closeness = 0.388514), are listed in Table S6. R square = 0.286 and correlation coefficient = 0.400 for closeness (Figure 8C). Hub genes with low clustering coefficient, such as *OLR1* (clustering coefficient = 0), *CHST8* (clustering coefficient = 0), *KLF8* (clustering coefficient = 0), *CFH* (clustering coefficient = 0), and *XAGE2* (clustering coefficient = 0), are listed in Table S6. R square = 0.476 and correlation coefficient = 0.803 for clustering coefficient (Figure 8D).
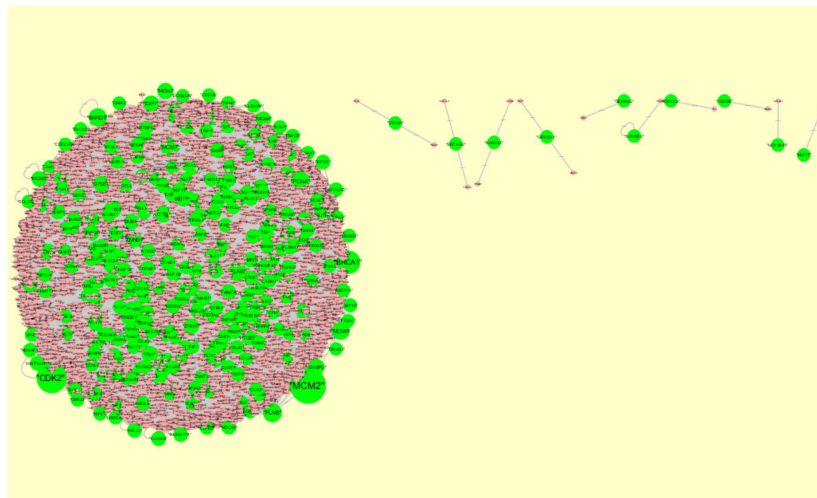
Figure 6. Protein-protein interaction network of differentially expressed genes (DEGs). Green nodes denote up-regulated genes.
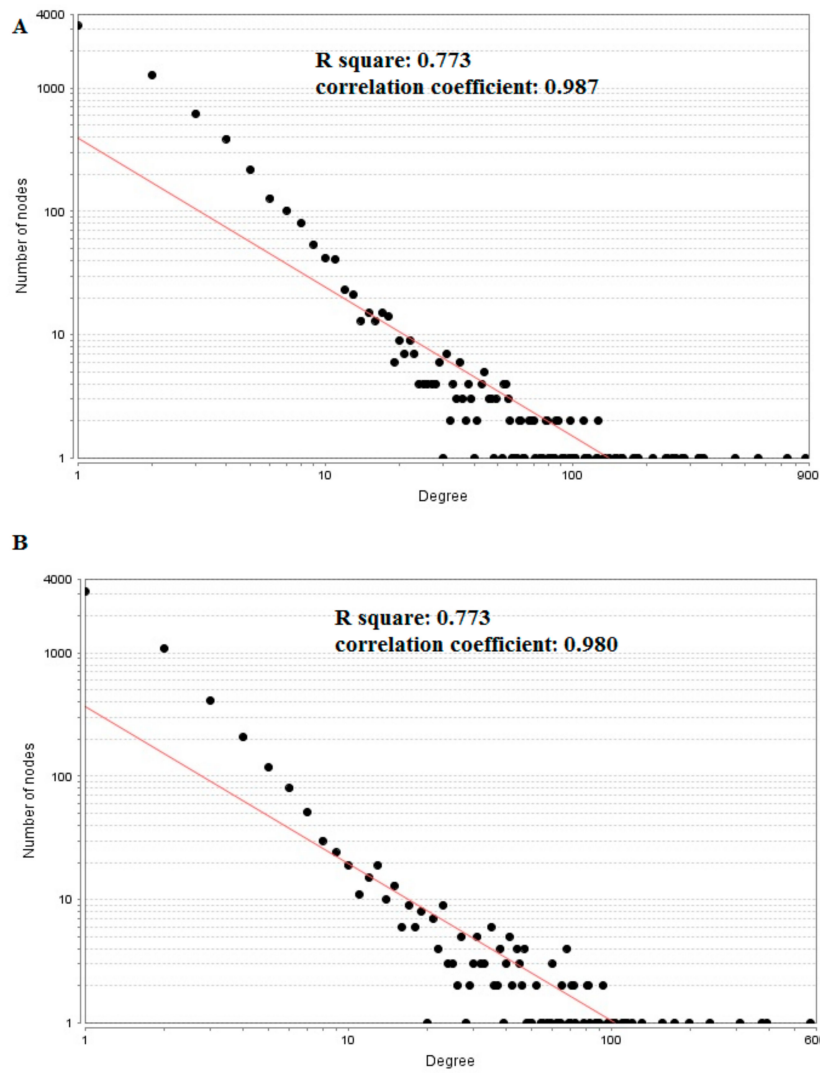

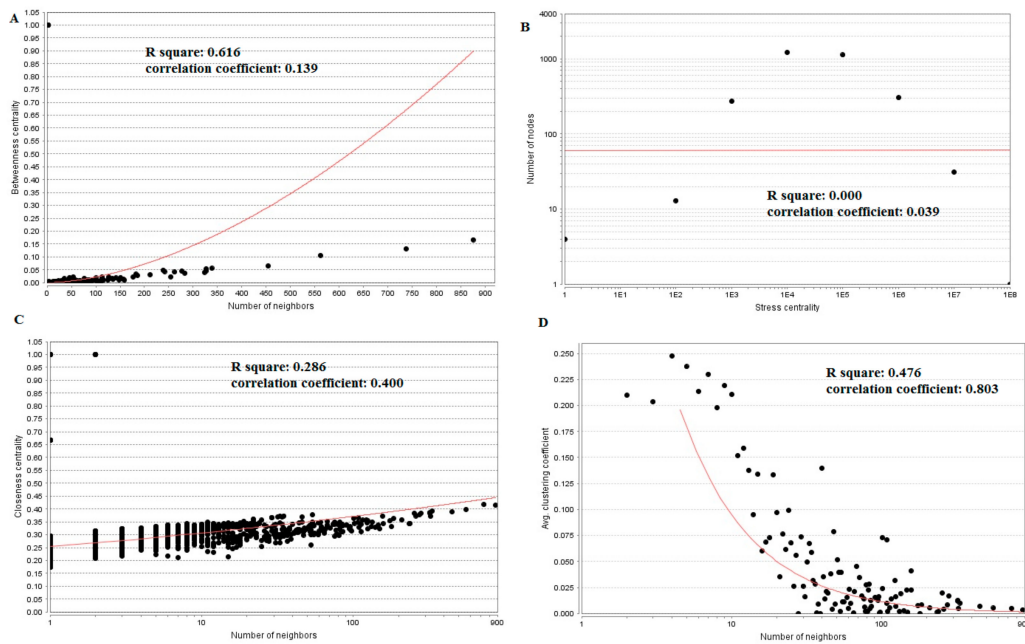**Figure 7.** Node degree distribution. (**A**) Up-regulated genes; (**B**) Down-regulated genes.

Figure 8. Regression diagrams for up-regulated genes (**A**) Betweenness centrality; (**B**) Stress centrality; (**C**) Closeness centrality; (**D**) Clustering coefficient.

The PPI network (down-regulated) had 5441 nodes and 9866 interactions (Figure 9). Hub genes with high node degree, such as *HSPA5* (degree = 572), *MAPK6* (degree = 392), *MAP1LC3B* (degree = 375), *SQSTM1* (degree = 308), and *SDCBP* (degree = 238), are listed in Table S6. R square = 0.773 and correlation coefficient = 0.980 for node degree (Figure 7B). Hub genes with high betweenness centrality, such as *MAP1LC3B* (betweenness = 1.01E-01), *SQSTM1* (betweenness = 9.98E-02), *SDCBP* (betweenness = 6.95E-02), *ISG15* (betweenness = 5.19E-02), and *ICAM1* (betweenness = 3.59E-02), are listed in Table S6. R square = 0.629 and correlation coefficient = 0.220 for betweenness centrality (Figure 10A). Hub genes with high stress genes, such as *HSPA5* (stress = 144471588), *MAPK6* (stress = 73838870), *MAP1LC3B* (stress = 51072854), *SQSTM1* (stress = 39034828), and *ICAM1* (stress = 38584000), are listed in Table S6. R square = 0.042 and correlation coefficient = 0.206 for stress (Figure 10B). Hub genes with high closeness centrality, such as *SQSTM1* (closeness = 0.369146), *MAP1LC3B* (closeness = 0.361868), *MAPK6* (closeness = 0.345146), *NDRG1* (closeness = 0.338184), and *ISG15* (closeness = 0.336858), are listed in Table S6. R square = 0.171 and correlation coefficient = 0.261 for closeness (Figure 10C). Hub genes with low clustering coefficient, such as *NEU1* (clustering coefficient = 0), *BRI3* (clustering coefficient = 0), *SLC27A1* (clustering coefficient = 0), *DDIT4* (clustering coefficient = 0), and *CXCL1* (clustering coefficient = 0), are listed in Table S6. R square = 0.540 and correlation coefficient = 0.874 for clustering coefficient (Figure 10D).
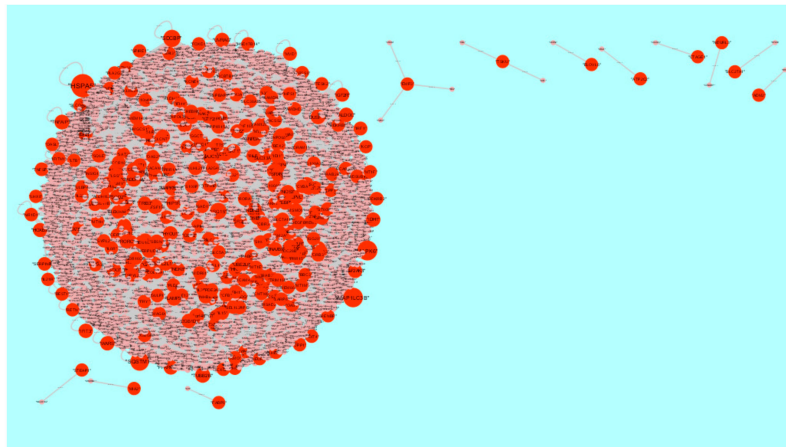
Figure 9. Protein-protein interaction network of differentially expressed genes (DEGs). Orange nodes denote down-regulated genes.
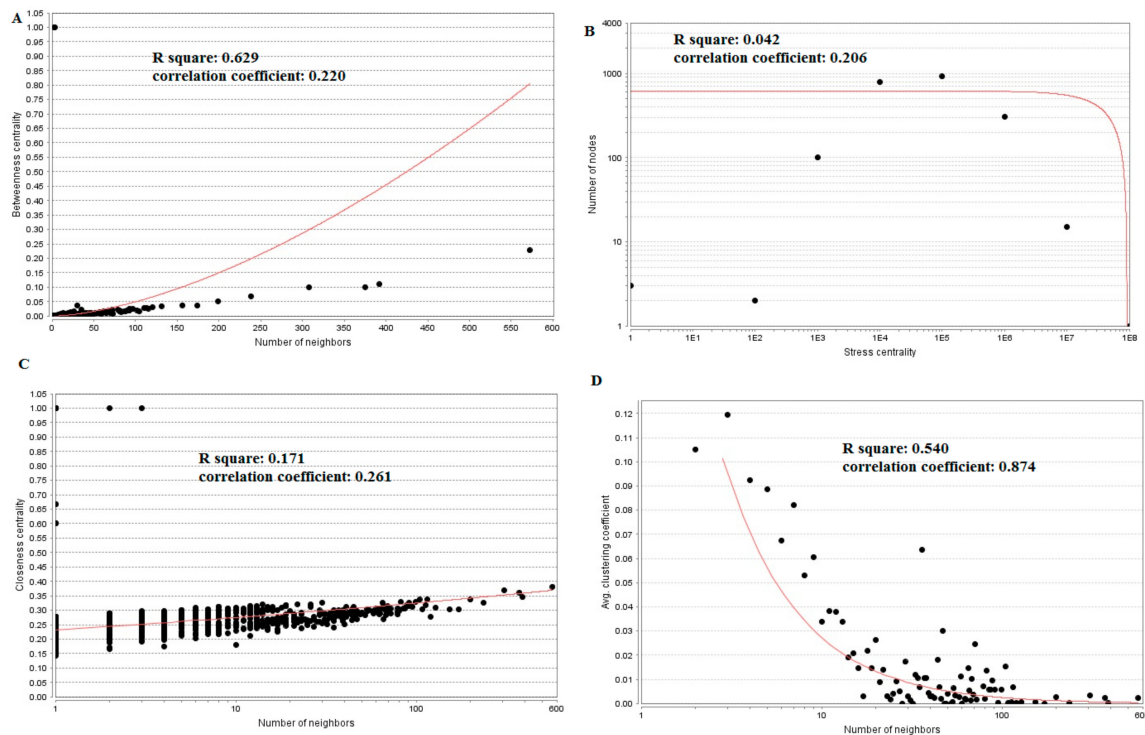

Figure 10. Regression diagrams for down-regulated genes (**A**) Betweenness centrality; (**B**) Stress centrality; (**C**) Closeness centrality; (**D**) Clustering coefficient.

3.6. Module Analysis

The PPI network (up-regulated genes) had 1835 modules. Module 15, module 23, module 44, and module 54 were highly significant (Figure 11). Module 15 had 53 nodes and 148 edges. The hub genes, such as *HIST1H1B* (degree = 74), *E2F1* (degree = 135), *POLD1* (degree = 79), *CDT1* (degree = 70), *MCM3* (degree = 157), *MYBL2* (degree = 54), *CDK2* (degree = 737), *CCNE1* (degree = 84), *CDC25A* (degree = 88), *PCNA* (degree = 326), *BRCA1* (degree = 561), and *POLA1* (degree = 54), were involved in module 15. Module 23 had 42 nodes and 119 edges. The hub genes, such as *RAD51* (degree = 126), *BLM* (degree = 93), *MSH6* (degree = 102), *BARD1* (degree = 277), *BRCA1* (degree = 561), and *PCNA* (degree = 326), were involved in module 23. Module 44 had 28 nodes and 88 edges. The hub genes, such as *RFC3* (degree = 48), *RFC5* (degree = 71), *RFC2* (degree = 68), *DSCC1* (degree = 20), and *PCNA* (degree = 326), were involved in module 44. Module 54 had 21 nodes and 95 edges. The hub genes,

such as *MCM10* (degree = 61), *CDC7* (degree = 36), *MCM4* (degree = 111), *MCM2* (degree = 875), *MCM3* (degree = 157), *MCM6* (degree = 103), and *LMNB1* (degree = 111), were involved in module 54.
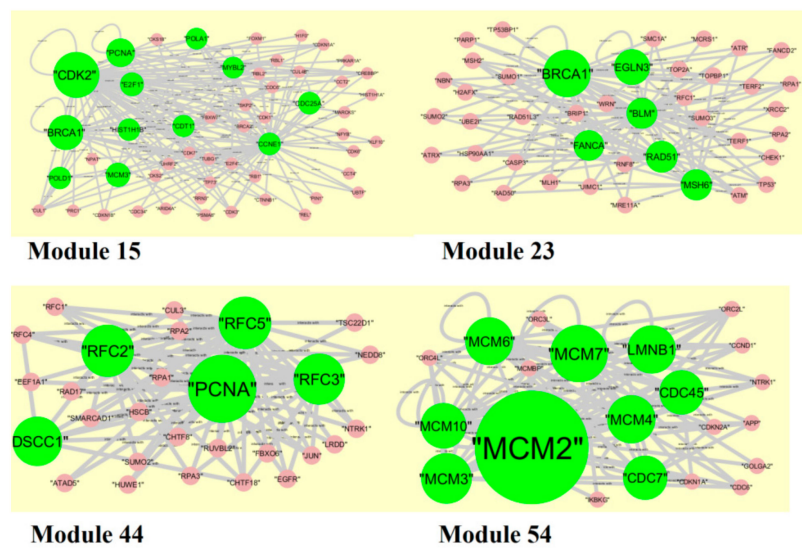

Figure 11. Modules in protein-protein interaction (PPI) network. The green nodes denote the up-regulated genes.

The PPI network (down-regulated genes) had 1003 modules. Module 4, module 8, module 16, and module 23 were highly significant (Figure 12). Module 4 had 61 nodes and 140 edges. The hub genes, such as *HSPA5* (degree = 572), *HSPA6* (degree = 104), *MAP1LC3B* (degree = 375), and *RELB* (degree = 102), were involved in module 4. Module 8 had 28 nodes and 75 edges. The hub proteins, such as *ISG15* (degree = 199), *IFIT1* (degree = 47), *IFIT2* (degree = 44), and *IFIT3* (degree = 73), were involved in module 8. Module 16 had 22 nodes and 50 edges. The hub proteins, such as *TNFRSF10B* (degree = 65), *TNFSF10* (degree = 23), *TNFAIP3* (degree = 93), and *BIRC3* (degree = 88), were involved in module 16. Module 23 had 12 nodes and 23 edges. The hub proteins, such as *GBP2* (degree = 45), *SAT1* (degree = 82), and *MVD* (degree = 35), were involved in module 23.
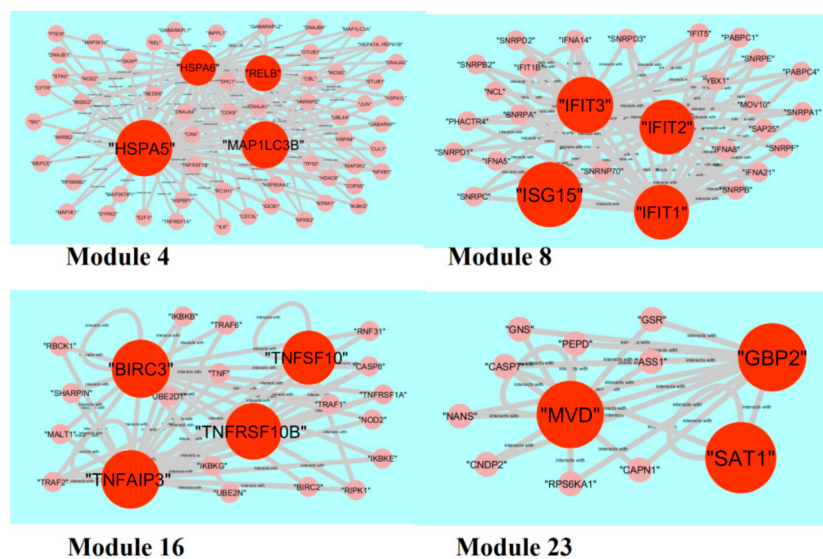

Figure 12. Modules in protein-protein interaction (PPI) network. The orange nodes denote the down-regulated genes.

3.7. Construction of the Target Genes-miRNAInteraction Network

Target genes-miRNA interaction network (up-regulated) is shown in Figure 13. Hub genes such as *IGFBP5* interacts with 143 miRNAs, *RAD51* interacts with 113 miRNAs, *DSN1* interacts with 111 miRNAs, *RRM2* interacts with102 miRNAs, and *ZWINT* interacts with 98 miRNAs (Table S7). Target genes-miRNA interaction network (down-regulated) is shown in Figure 14. Hub genes such as *SOD2* interacts with 257 miRNAs, *DNAJC10* interacts with 195 miRNAs, *PEG10* interacts with 139 miRNAs, *LDLR* interacts with 123 miRNAs, and *RORA* interacts with 110 miRNAs (Table S7).
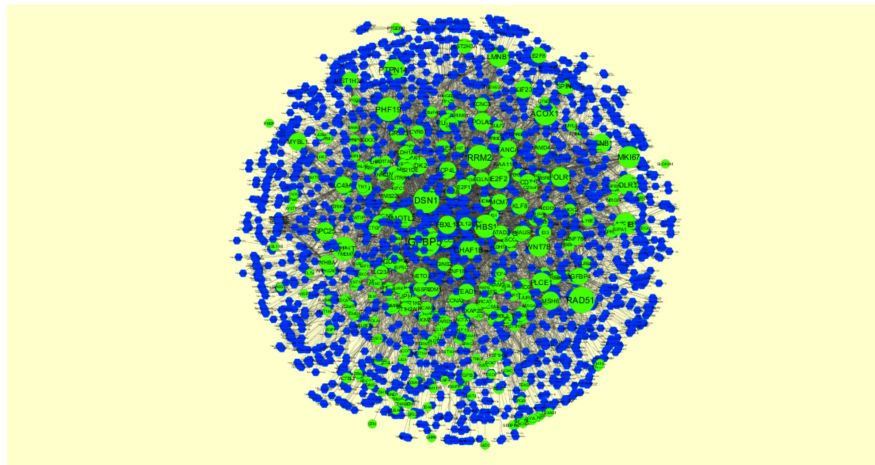

Figure 13. The network of up-regulated differential expressed genes (DEGs) and their related miRNAs. The green circle nodes are the up-regulated DEGs, and blue diamond nodes are the miRNAs.
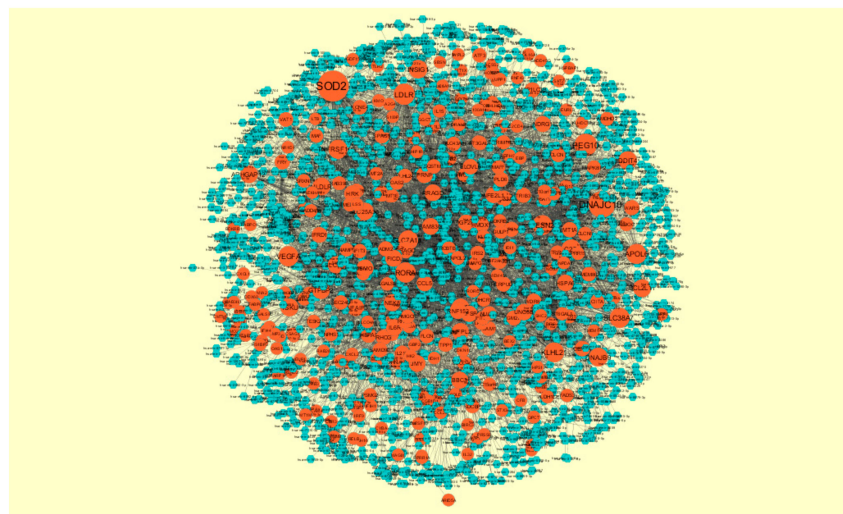
Figure 14. The network of down-regulated differential expressed genes (DEGs) and their related miRNAs. The orange-red circle nodes are the down-regulated DEGs, and blue diamond nodes are the miRNAs.

3.8. Construction of the Target Genes-TF Interaction Network

Target genes-TF interaction network (up-regulated) is shown in Figure 15. Hub genes such as *DHF* interacts with 178 TFs, *TBXAS1* interacts with 177 TFs, *MCEE* interacts with 154 TFs, *ETNK2* interacts with 144 TFs, and *CENPM* interacts with 137 TFs (Table S8). Target genes-TF interaction network (down-regulated) is shown in Figure 16. Hub genes such as *MT1H* interacts with 172 TFs, KRTAP5-4 interacts with 163 TFs, *RETN* interacts with 143 TFs, *HSD17B14* interacts with 132 TFs, and *SEPHS2* interacts with 124 TFs (Table S8).

Figure 15. The network of up-regulated differential expressed genes (DEGs) and their related transcription factors (TFs). (Lavender triangles—TFs, and green circles—target up-regulated genes).
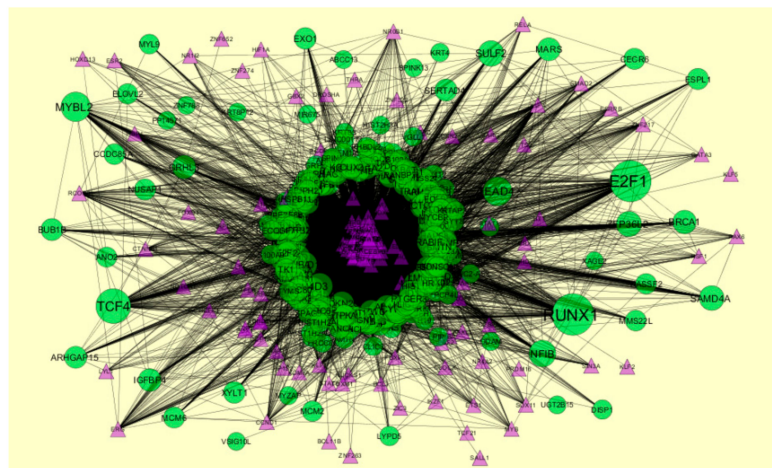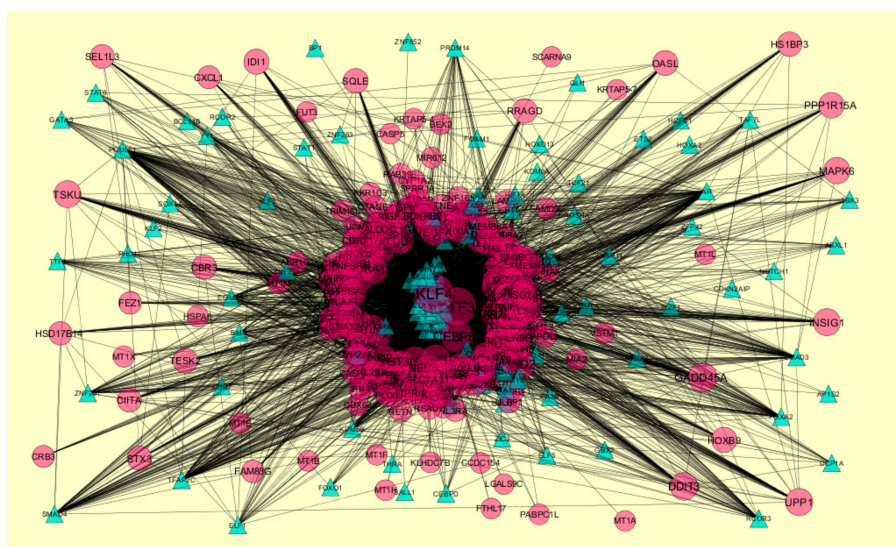

Figure 16. The network of down-regulated differential expressed genes (DEGs) and their related transcription factors (TFs). (Blue triangles—TFs, and pink circles—target down-regulated genes).

3.9. Survival Analysis of Hub Genes

To evaluate if the identified prognostic markers are valuable in predicting patient survival, we focused on the hub genes (up- and down-regulated genes). We utilized SurvExpress [54], an online tool developed for conveniently exploring survival correlations with gene expression data from 502 cancer studies performed by The Cancer Genome Atlas (TCGA). Genes, such as *BRCA1*, *FLNA*, *FLNB*, *HSPA5*, *MAP1LC3B*, *NDRG1*, *PCNA*, and *TUBB2B*, which are overexpressed in BRCA, showed a positive correlation with patient survival. Patients with higher expression of these genes had favorable overall survival (*p*-value < 0.05) (Figure 17). Genes, such as *HIST1H3B* and *MAPK6*, which are overexpressed in BRCA, showed a negative correlation with patient survival. Patients with higher expression of these genes had worse overall survival (*p*-value < 0.05) (Figure 18).

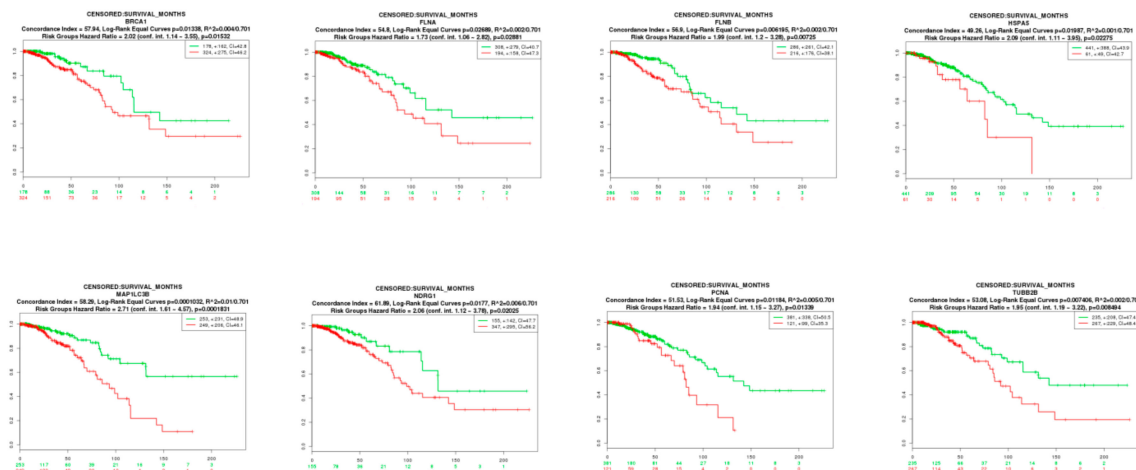**Figure 17.** Kaplan-Meier survival curves using The Cancer Genome Atlas (TCGA) data validate the prognostic value of genes having favorable overall survival in BRCA (Green—low expression; Red—high expression).
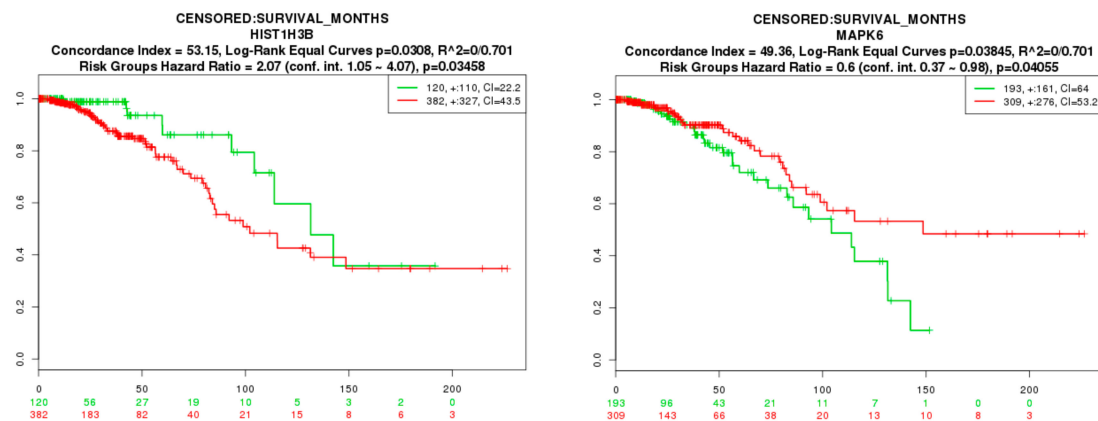
Figure 18. Kaplan-Meier survival curves using The Cancer Genome Atlas (TCGA) data validate the prognostic value of genes having worse overall survival in BRCA (Green—low expression; Red—high expression).

3.10. Validation of Hub Genes

The expression level of hub genes was assessed in 2 low-risk and1 high-risk groups. The data showed that the hub gene expression of *BRCA1*, *HIST1H3B*, *MAPK6*, *NDRG1*, and *PCNA* were increased (Figure 19), while that of *FLNA*, *FLNB*, *HSPA5*, *MAP1LC3B*, and *TUBB2B* were reduced (Figure 20) in the high-risk group compared with those in the low-risk group. The outcome of the validation of the hub genes on a translational level through the HPA database are displayed in Figure 21.

3.11. Mutation Analysis of Hub Genes

The mutation analysis results made the ten hub genes we screened out reliable. As for genetic mutation, ten hub genes were altered in 98.6% of 1093 patients. Figure 22 depicts the alteration information of the ten hub genes. *BRCA1*, *FLNA*, *FLNB*, *HIST1H3B*, *HSPA5*, *MAP1LC3B*, *MAPK6*, *NDRG1*, *PCNA*, and *TUBB2B* were altered most often (4%, 3%, 2.4%, 2.9%, 2.2%, 3%, 2.3%, 12%, 1.1%, and 2.3%, respectively), and these include inframe mutation, missense mutation, truncating mutation, amplification, and deep deletion.

Figure 19. Box plots of hub genes (*BRCA1*, *HIST1H3B*, *MAPK6*, *NDRG1*, and *PCNA*). Red—high-risk; Green—low-risk.

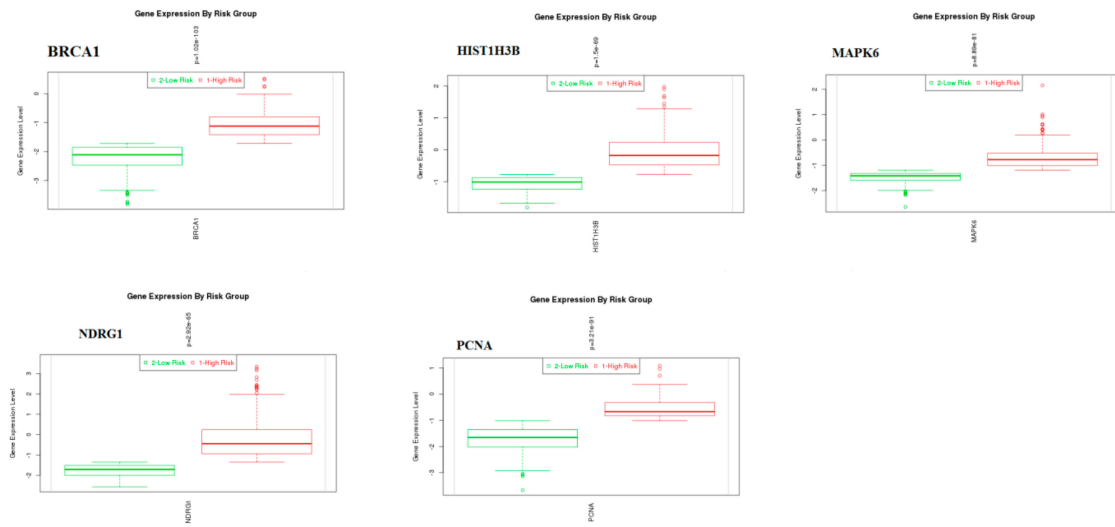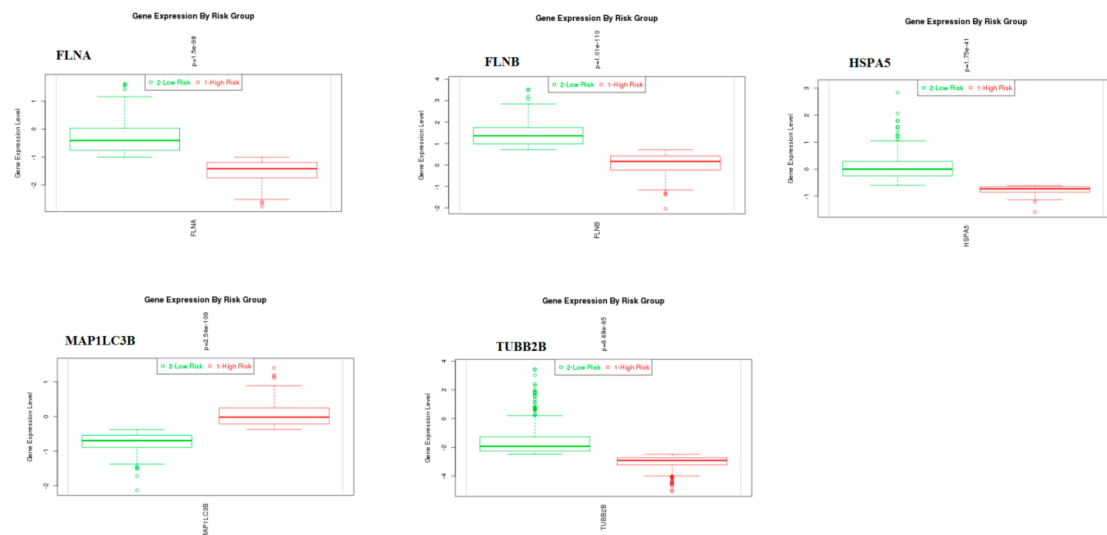**Figure 20.** Box plots of hub genes (*FLNA*, *FLNB*, *HSPA5*, *MAP1LC3B*, and *TUBB2B*). Red—high-risk; Green—low-risk.
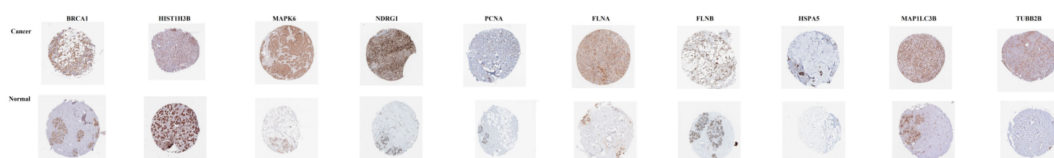

Figure 21. Validation of the hub genes using the Human Protein Atlas (HPA) database.
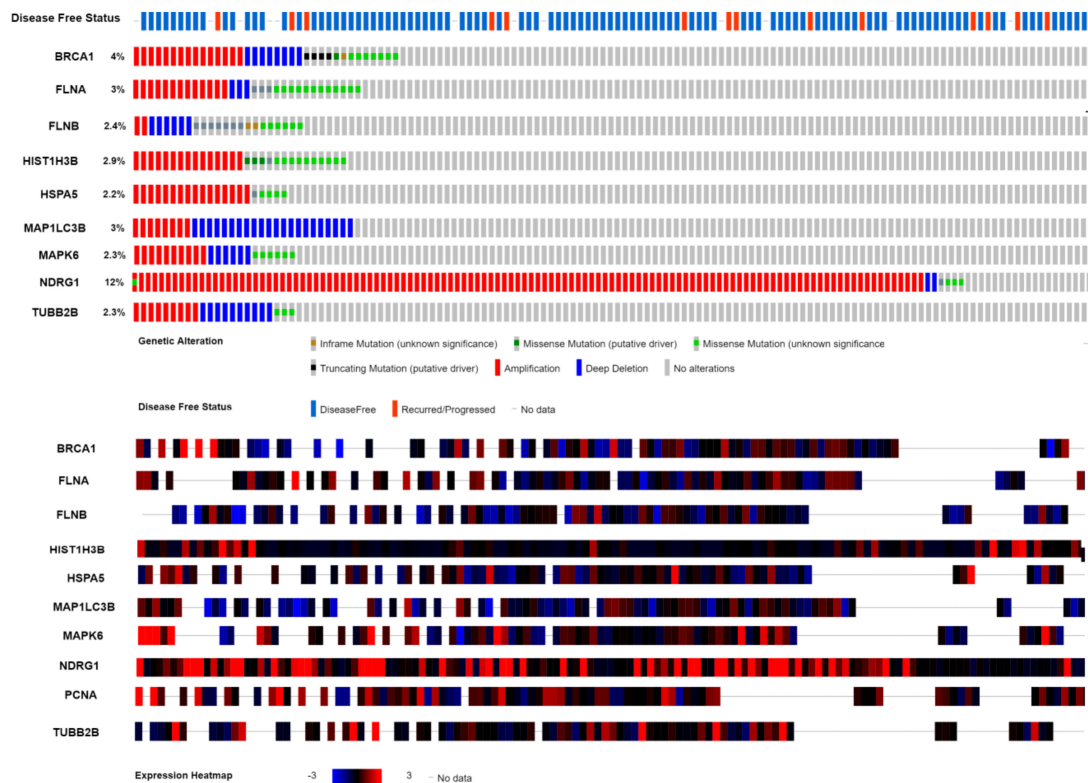
Figure 22. A visual summary, which displays genetic alteration of the ten hub genes in The Cancer Genome Atlas-Breast cancer (TCGA-BRCA) patients.

4. Discussion

Breast cancer is one of the most common cancer to affect women. BRCA is a heterogeneous disease presenting distinct subtypes (Triple Negative, Luminal A, Luminal B, human epidermal growth factor receptor (HER2+)). Increased estradiol level is associated with breast cancer development through regulation of the progesterone receptor [56,57]. Estradiol antagonist tamoxifen has been the first line treatment for all stages of estrogen-receptor-positive BRCA [55]. In most cases, somatic mutations in breast cells acquired during a person's lifetime lead to breast cancer [58]. BRCA occurs due to the accumulation of different genetic mutations, thus, a high level of molecular heterogeneity in BRCA demands thorough investigation of the molecular markers and signaling pathways associated with pathogenesis of BRCA; this may be of benefit for the examination of targeted molecular therapy to assist early diagnosis and prognosis, and may also afford a molecular basis for treatment. In the current study, the integrated analysis was performed on the gene expression profiles in estradiol- and tamoxifen-treated BRCA cell lines. Using the microarray platforms, we identified 856 DEGs (421 up-regulated and 435 down-regulated). BRCA arises from the accumulation of different gene modifications, and it is important to characterize the genetic changes during the advancement of BRCA [59]. Methylation inactivation of tumor suppressor *KCNB1* is responsible for the development of gliomas [60], but this gene may be identified with the development of BRCA. *COL12A1* is diagnosed with the pathogenesis of gastric cancer [61], but this gene may be associated with the pathogenesis of BRCA. *DIAPH3* is important for metastasis of hepatocellular carcinoma cells through stimulation of the beta-catenin/TCF signaling pathway [62], but this gene may be linked with metastasis of BRCA. *SFXN2* is important for the invasion of oral squamous cell carcinoma [63], but this gene may be responsible for the invasion of BRCA cells. *GLDC* is involved in the pathogenesis of non-small cell lung cancer cell proliferation through pyrimidine metabolism [64], but this gene may be linked with changes in amino acid and nucleic acid metabolism in BRCA. *DDIT4* is liable for the proliferation of gastric cancer cell through activation of p53 and MAPK pathways [65], but this gene may be associated

with the proliferation of BRCA cells. Loss of genes, such as *INSIG1* and *ACSS2*, is responsible for the advancement of gastric cancer [66,67], but inactivation of these genes may be linked with the development of BRCA. *IFIT3* is responsible for inflammatory stimulus in pancreatic cancer [68], but this gene may be associated with inflammation in BRCA. Methylation inactivation of tumor suppressor genes, such as *FLCN* [69] and *DDIT3* [70], is important for the development of many cancer, such as renal cancer and gastric cancer, but inactivation of these genes may be responsible for the advancement of BRCA. *PRSS8* is liable for the development of ovarian cancer [71], but this gene may identify with the pathogenesis of BRCA. Genes, such as *KLF8* [72], *TCF4* [73], *H19* [74], *NEU1* [75], *CXCL1* [76], *TRIB3* [77], *FTL* [78], and *UBE2L6* [79], are responsible for the pathogenesis of BRCA.

In pathway enrichment analysis, lysine degradation II (pipecolate pathway), DNA replication, E2F transcription factor network, cell cycle, pyrimidine metabolism, CDK regulation of DNA replication, mismatch repair pathway, and pyrimidine metabolism are the most significant pathways for up-regulated genes. *CRYM* is responsible for the development of prostate cancer [80], but this gene may be identified with the pathogenesis of BRCA. Single nucleotide polymorphisms (SNP) in genes, such as *ALDH7A1* [81], *POLA2* [82], *LIG1* [83], and *ERCC6L* [84], are important for the development of various cancers, such as esophageal squamous cell carcinoma, lung cancer, and oral cancer, but these polymorphic genes may be linked with pathogenesis of BRCA. Genes, such as *MCM3* [85], *MCM5* [86], *MCM7* [87], and *DSN1* [88], are associated with the pathogenesis of various cancers, such as salivary gland cancer, cervical cancer, and hepatocellular carcinoma, through regulation of cell cycle, but these genes may be involved in progression of BRCA. Mutations in genes, such as *POLD1* [89], *CDKN2C* [90], and *HIST1H3B* [91], are involved in the pathogenesis of various cancers, such as colorectal cancer, melanoma, and gliomas, but a mutation in these genes may be important for the progression of BRCA. Genes, such as *POLE2* [92], *RFC5* [93], *MYBL2* [94], *SPC25* [95], *KIF23* [96], *NCAPG* [97], *CENPU* [98], and *ESCO2* [99], are linked with the proliferation of various cancer cells, such as lung cancer, cervical cancer, hepatocellular carcinoma, bladder cancer, and gastric cancer, but these genes may be responsible for the proliferation of BRCA cells. Genes, such as *ORC6* [100] and *GTSE1* [101], are linked with drug resistance in various cancers, such as colon cancer and gastric cancer, but these genes may be liable for drug resistance in BRCA. Genes, such as *SPC24* [102] and *PKMYT1* [103], are linked with the invasion of hepatocellular carcinoma cells, but these genes may be important for the invasion of BRCA cells. *AJUBA* is diagnosed with the growth of colorectal cancer through apoptosis inhibition [104], but this gene may be responsible for the advancement of BRCA, through inhibition of apoptosis. Genes, such as *MCM2* [105], *PCNA* [106], *RFC3* [107], *RRM2* [108], *TYMS* [109], *BRCA1* [110], *DHFR* [111], *RBBP8* [112], *E2F1* [113], *CCNA2* [114], *CCNE1* [115], *TK1* [116], *CCNE2* [117], *CDC25A* [118], *CDK2* [119], *HJURP* [120], *CDC7* [121], *NDC80* [122], *PSMC3IP* [123], *GINS2* [124], *ESPL1* [125], *BARD1* [126], *BLM* [127], *BUB1B* [128], *CDT1* [129], *RAD51* [130], *KIF20A* [131], *EXO1* [132], *AURKB* [133], *MCM10* [134], *CDCA5* [135], *LMNB1* [136], and *MSH6* [137], are responsible for the pathogenesis of BRCA. *MCM6*, *POLA1*, *RFC2*, *MND1*, *HIST2H3A*, *SYCE2*, *CDC45*, *HAUS8*, *HIST1H2BF*, *FBXL18*, *HIST1H4D*, *CENPM*, *GINS3*, *RMI2*, *GINS4*, *NDC1*, *KNTC1*, *GINS1*, *FBXO5*, *HIST1H3F*, *ZWINT*, and *CTPS1* are identified as novel molecular markers for the pathogenesis of BRCA in these pathways. While superpathway of cholesterol biosynthesis, mineral absorption, ATF-2 transcription factor network, cholesterol biosynthesis, sterol biosynthesis, genes encoding secreted soluble factors, and steroid biosynthesis are the most significant pathways for down-regulated genes. Genes, such as *HMGCS1* and *HMGCR*, are associated with the proliferation of prostate cancer cell [138], but these genes may be responsible for the proliferation of BRCA cells. Genes, such as *HMOX1* [139] and *VEGFB* [140], are important for the invasion of various cancer cells, such as bladder cancer and colorectal cancer, but these genes may be associated with the invasion of BRCA cells. Methylation inactivation in tumor suppressors genes, such as *MT1M* [141], *MT1H* [142], *MT1X* [143], and *HRK* [144], is responsible for the development of various cancers, such as prostate cancer, liver cancer, colorectal cancer, and gastric cancer, but loss of these genes may be linked with the pathogenesis of BRCA. *FGF13* is responsible for chemoresistance in cervical cancer [145], but this gene may be associated with drug resistance in

BRCA. *CCL20* is linked with the development of gastric cancer [146], but this gene may be liable for the progression of BRCA. SNP in tumor suppressor genes, such as *TNFSF10* [147] and *TNFSF9* [148], are identified with the pathogenesis of various cancers, such as ovarian cancer and hepatocellular carcinoma, but these polymorphic genes may be answerable for the development of BRCA. Genes, such as *SQLE* [149], *EBP* [150], *STEAP1* [151], *MT1E* [152], *MT1F* [153], *MT2A* [154], *PLAU* [155], *ATF3* [156], *GADD45A* [157], *PPARGC1A* [158], *S100A14* [159], *S100P* [160], *CCL5* [161], *VEGFA* [162], *GDF15* [163], *IL-15* [164], *CXCL2* [165], *CXCL3* [166], *LTB* [167], and *S100A3* [168], are responsible for the pathogenesis of BRCA. *MSMO1*, *FDPS*, *IDI1*, *MVD*, *CYP51A1*, *DHCR7*, *LSS*, *BRCA*, *MT1A*, *MT1B*, *IL23A*, and *INHBE* are identified as novel molecular markers for the pathogenesis of BRCA in these pathways.

In GO enrichment analysis, cell cycle, chromosome, and DNA helicase activity are the most significant GO terms for up-regulated genes. Genes, such as *CHAF1B* [169], *INHBA* [170], *TGFB2* [171], *SKA3* [172], and *HELLS* [173], are responsible for the invasion of various cancer cells, such as hepatocellular carcinoma, gastric cancer cells, renal cell carcinoma, prostate cancer, head and neck cancer, but these genes may be involved in the invasion of BRCA cells. *TRIP13* is responsible for the development of chemoresistance in head and neck cancer [174], but this gene may be linked with the drug resistance in BRCA. *DSCC1* is associated with the development of colorectal cancer through inhibition of apoptosis [175], but this gene may be responsible for the inhibition of apoptosis in BRCA. SNP in tumor suppressor RAD54L is important for the development of pancreatic cancer [176], but this polymorphic gene may be identified with the development of BRCA. Genes, such as *CDCA3* [177], *KIF15* [178], and *TCF19* [179], are linked with the proliferation of various cancer cells, such as oral cancer, pancreatic cancer, and hepatocellular carcinoma cells, but these genes may be responsible for the proliferation of BRCA cells. Genes, such as *BOP1* [180], *KIF11* [181], and *MMS22L* [182], are associated with the progression of various cancers, such as colorectal cancer, gastric cancer, lung, and esophageal cancer, but these genes may be linked with the development of BRCA. Genes, such as *PDGFB* [183], *ANLN* [184], *RECQL4* [185], *MKI67* [186], *FGFR2* [187], *FLNA* [188], *DTL* [189], *ID3* [190], *XRCC3* [191], *SIPA1* [192], *SPAG5* [193], *EGFL6* [194], *UHRF1* [195], *CTGF* [196], *STARD13* [197], *RASSF2* [198], *PBK* [199], *NEDD9* [200], *KIFC1* [201], *E2F8* [202], *THBS1* [203], *FANCI* [204], *NUSAP1* [205], *SATB1* [206], *ASF1B* [207], and *KDM4B* [208], are responsible for the pathogenesis of BRCA. *FANCA*, *AUNIP*, *ASPM*, *DCLRE1B*, *PCLAF*, *CIT*, *HIST1H2AI*, *HIST1H2AL*, *ANKRD2*, *TONSL*, *WDHD1*, and *HIST1H1D* are identified as novel molecular markers for the pathogenesis of BRCA in these GO categories.

While the response to cytokine, endoplasmic reticulum, and cytokine activity are the most significant GO terms for down-regulated genes. Genes, such as *SERPINA3* [209], *BIRC3* [210], and *CREBRF* [211], are liable for the proliferation of various cancer cells, such as endometrial cancer and gastric cancer, but these genes may be linked with the proliferation of BRCA cells. Genes, such as *IFIT2* [212], *CCR10* [213], and *TMEM97* [214], are important for the invasion of various cancer cells, such as oral cancer, melanoma, and glioma, but these genes may be responsible for the invasion of BRCA cells. Decreased expression of genes, such as *TNFRSF10B* [210], *MIA2* [215], and *BBC3* [216], are answerable for the progression of various cancers, such as lung cancer, hepatocellular carcinoma, head, and neck cancer, but low expression of these genes may be responsible for the development of BRCA. Genes, such as *OAS2* [217], *ULBP1* [218], *HERPUD1* [219], and *CASP4* [220], are diagnosed with the growth of various cancers, such as oral cancer, cervical cancer, and gliomas, but these genes may identify with the development of BRCA. SNP in genes, such as *PPP1R15A* [221], *PLA2G4C* [222], *CMTM8* [223], and *IFNL3* [224], are responsible for the growth of various cancers, such as colorectal cancer, osteosarcoma, and hepatocellular carcinoma, but SNP in these genes may be associated with the pathogenesis of BRCA. Mutation in *UVRAG* [225] and *RNF43* [226] is liable for the advancement of various cancers, such as gastric cancer, colorectal, and endometrial cancers, but variation in these genes may be linked with the advancement of BRCA. Methylation inactivation of tumor suppressor *ST6GAL1* [227] is responsible for the pathogenesis of bladder cancer, but the loss of this gene may be associated with the development of BRCA. Genes, such as *CEBPB* [228],

ACP5 [229], *KLF4* [230], *ACSL1* [231], *IRF9* [232], *HSPA5* [233], *ICAM1* [234], *IFITM1* [235], *IFIT1* [236], *ISG15* [237], *LAMP3* [238], *IL6R* [239], *GBP2* [240], *IRF1* [241], *CEACAM1* [242], *CD70* [243], *RORA* [244], *TNFAIP3* [245], *CIITA* [246], *SLC7A11* [247], *F7* [248], *ELOVL6* [249], *EIF2AK3* [250], *SDCBP* [251], *HYOU1* [252], *PRNP* [253], *CYP1A2* [254], *SQSTM1* [255], *NUCB2* [256], *IL32* [257], *IL15* [258], and *NAMPT* [259], are responsible for the pathogenesis of BRCA. Elevated levels of *SQSTM1* have been demonstrated in oncogenesis and resistance to cancer chemotherapy. *SQSTM1* regulates autophagy and apoptosis and acts as a signaling hub, which regulates cell viability in response to cytotoxic stress, thus playing a vital role in cancer. *SQSTM1* is a key component and player in VANGL2–JNK signaling pathway and this signaling pathway is associated with the proliferation of breast cancer cells [260]. Pleiotropic cytokine TNFα is associated with tumor cell growth, invasion, and metastasis. TNFα plays a vital role in the progression of triple negative breast cancer (TNBC) via up-regulation of *TNFAIP3*. Pleiotropic DNA damage response protein, such as BRCA1, operates in both checkpoint activation and DNA repair. In our study, survival analysis revealed that high expression of *BRCA1* was linked with breast cancer.

PDE2A, *IFI30*, *VLDLR*, *RSAD2*, *IL21R*, *OASL*, *IL3RA*, *MX1*, *CYBA*, *ISG20*, *SLC27A1*, *OAS1*, *RELB*, *CLGN*, *DNAJB9*, *DNAJC10*, *SDR16C5*, *APOL2*, *COL16A1*, *ERO1B*, *STARD4*, *ERO1A*, *RDH16*, *PLPP3*, *CERS1*, *SLC36A1*, *INSIG1*, *BDKRB1*, *LPIN1*, *SEC24D*, *NFE2L1*, *GPAT3*, *HS1BP3*, *FADS3*, *SLC33A1*, *RELB*, *VSTM1*, and *IFNL2* are identified as novel molecular markers for the pathogenesis of BRCA in these GO category.

In PPI network, hub genes (up-regulated), such as *MCM2*, *CDK2*, *HIST1H3F*, *HIST1H3B*, *TCF4*, *ASPM*, *CHST8*, *KCNB1*, *CFH*, *FLNA*, and *BRCA1*, are identified with high node degree, high betweenness, high stress, and high closeness. *CFH* is important for the development of lung cancer [261], but this gene may be associated with the progression of BRCA. Hub genes, such as *OLR1*, *CHST8*, *KLF8*, *CFH*, and *XAGE2*, are identified with the lowest clustering coefficient. *XAGE2* is identified as a novel molecular marker for the pathogenesis of BRCA. While hub genes (down-regulated), such as *HSPA5*, *MAPK6*, *MAP1LC3B*, *SQSTM1*, *SDCBP*, *ISG15*, *ICAM1*, and *NDRG1*, are identified with high node degree, high betweenness, high stress, and high closeness. Genes, such as *MAP1LC3B* [262], *MAPK6* [263], and *NDRG1* [264], are responsible for the development of BRCA. Hub genes, such as *NEU1*, *BRI3*, *SLC27A1*, *DDIT4*, and *CXCL1*, are identified with the lowest clustering coefficient. *DDIT4* and *BRI3* are identified as novel molecular markers for the pathogenesis of BRCA.

In module analysis, hub genes(up-regulated), such as *HIST1H1B*, *E2F1*, *POLD1*, *CDT1*, *MCM3*, *MYBL2*, *CDK2*, *CCNE1*, *CDC25A*, *PCNA*, *RAD51*, *BLM*, *MSH6*, *BARD1*, *BRCA1*, *POLA1*, *RFC3*, *RFC5*, *RFC2*, *DSCC1*, *MCM10*, *CDC7*, *MCM4*, *MCM2*, *MCM6*, and *LMNB1*, are identified in all four modules. *HIST1H1B* is identified as a novel molecular marker for the pathogenesis of BRCA. *MCM4* is associated with the pathogenesis of BRCA [265]. Meanwhile, hub genes (down-regulated), such as *HSPA5*, *HSPA6*, *MAP1LC3B*, *RELB*, *ISG15*, *IFIT1*, *IFIT2* and *IFIT3*, *TNFRSF10B*, *TNFSF10*, *TNFAIP3*, *BIRC3*, *GBP2*, *SAT1*, and *MVD*, are identified in all four modules. *HSPA6*, *MAFF*, *MAFG*, and *SAT1* are identified as novel molecular markers for the pathogenesis of BRCA.

In target genes-miRNA network, target genes (up-regulated), such as *IGFBP5*, *RAD51*, *DSN1*, *RRM2*, and *ZWINT*, are identified with a high degree. Expression of *IGFBP5* is responsible for the development of BRCA [266]. Meanwhile, target genes (down-regulated), such as *SOD2*, *DNAJC10*, *PEG10*, *LDLR*, and *RORA*, are identified with a high degree. Genes, such as *SOD2* [267], and *PEG10* [268], are associated with the pathogenesis of BRCA. *LDLR* is responsible for the advancement of prostate cancer cells [269], but this gene may be associated with the development of BRCA.

In target genes-TF network (up-regulated), target genes, such as *DHFR*, *TBXAS1*, *MCEE*, *ETNK2*, and *CENPM*, are identified with a high degree. *TBXAS1* is responsible for the development of BRCA [270]. *MCEE* and *ETNK2* are identified as novel molecular markers for the pathogenesis of BRCA. Meanwhile, target genes (down-regulated), such as *MT1H*, *KRTAP5-4*, *RETN*, *HSD17B14*, and *SEPHS2*, are identified with a high degree. *KRTAP5-4* and *HSD17B14* are identified as novel molecular markers for the pathogenesis of BRCA.

Survival analysis revealed that genes, such as *BRCA1*, *FLNA*, *FLNB*, *HSPA5*, *MAP1LC3B*, *NDRG1*, *PCNA*, and *TUBB2B*, are predicting longer survival of BRCA, while genes, such as *HIST1H3B* and *MAPK6*, are predicting shorter survival of BRCA. High expression of genes, such as *BRCA1*, *HIST1H3B*, *MAPK6*, *NDRG1*, and *PCNA*, is linked with BRCA; while low expression of genes, such as *FLNA*, *FLNB*, *HSPA5*, *MAP1LC3B*, and *TUBB2B*, are linked with BRCA.

5. Conclusions

In this study, key genes were identified for the first time in estradiol and tamoxifen drug-treated BRCA by integrated bioinformatics analysis. By analyzing the pathway and GO enrichment analysis, we found that DEGs were mainly enriched in the lysine degradation II (pipecolate pathway), cholesterol biosynthesis, cell cycle, and response to cytokine, which provide a theoretical basis for studying the biological processes of BRCA. We successfully constructed a PPI network, miRNA-target gene regulatory network, and TF-target gene regulatory network of DEGs in BRCA and screened several key genes encoding proteins in the networks that are associated in the process of BRCA in the form of molecular populations. These findings promote our understanding of the molecular pathogenesis of BRCA during estradiol and tamoxifen drug treatment and may provide an enhanced perceptive of the molecular mechanisms that underlie breast cancer. However, further molecular biological experiments are required to confirm the action of the diagnosed genes that are linked with BRCA during estradiol and tamoxifen drug treatment.

References

1. O'Brien, K.M.; Cole, S.R.; Tse, C.K.; Perou, C.M.; Carey, L.A.; Foulkes, W.D.; Dressler, L.G.; Geradts, J.; Millikan, R.C. Intrinsic breast tumor subtypes, race, and long-term survival in the Carolina Breast Cancer Study. *Clin. Cancer Res.* **2010**, *16*, 6100–6110. [CrossRef] [PubMed]

2. Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R.L.; Torre, L.A.; Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* **2018**, *68*, 394–424. [CrossRef] [PubMed]

3. Ferlay, J.; Colombet, M.; Soerjomataram, I.; Mathers, C.; Parkin, D.M.; Piñeros, M.; Znaor, A.; Bray, F. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int. J. Cancer* **2019**, *144*, 1941–1953. [CrossRef] [PubMed]

4. Fields, R.C.; Jeffe, D.B.; Trinkaus, K.; Zhang, Q.; Arthur, C.; Aft, R.; Dietz, J.R.; Eberlein, T.J.; Gillanders, W.E.; Margenthaler, J.A. Surgical resection of the primary tumor is associated with increased long-term survival in patients with stage IV breast cancer after controlling for site of metastasis. *Ann. Surg. Oncol.* **2007**, *14*, 3345–3351. [CrossRef] [PubMed]

5. Schnitt, S.J.; Abner, A.; Gelman, R.; Connolly, J.L.; Recht, A.; Duda, R.B.; Eberlein, T.J.; Mayzel, K.; Silver, B.; Harris, J.R. The relationship between microscopic margins of resection and the risk of local recurrence in patients with breast cancer treated with breast-conserving surgery and radiation therapy. *Cancer* **1994**, *74*, 1746–1751. [CrossRef]

6. Høst, H.; Brennhovd, I.O.; Loeb, M. Postoperative radiotherapy in breast cancer—Long-term results from the Oslo study. *Int. J. Radiat. Oncol. Biol. Phys.* **1986**, *12*, 727–732. [CrossRef]

7. Smith, I.C.; Heys, S.D.; Hutcheon, A.W.; Miller, I.D.; Payne, S.; Gilbert, F.J.; Ah-See, A.K.; Eremin, O.; Walker, L.G.; Sarkar, T.K.; et al. Neoadjuvant chemotherapy in breast cancer: Significantly enhanced response with docetaxel. *J. Clin. Oncol.* **2002**, *20*, 1456–1466. [CrossRef] [PubMed]

8. Shapiro, S.; Farmer, R.D.; Stevenson, J.C.; Burger, H.G.; Mueck, A.O.; Gompel, A. Does hormone replacement therapy (HRT) cause breast cancer? An application of causal principles to three studies. *J. Fam. Plann. Reprod. Health Care* **2013**, *39*, 80–88. [CrossRef] [PubMed]

9. Fendly, B.M.; Kotts, C.; Vetterlein, D.; Lewis, G.D.; Winget, M.; Carver, M.E.; Watson, S.R.; Sarup, J.; Saks, S.; Ullrich, A.; et al. The extracellular domain of HER2/neu is a potential immunogen for active specific immunotherapy of breast cancer. *J. Biol. Response Mod.* **1990**, *9*, 449–455. [PubMed]

10. Cuzick, J.; Stewart, H.; Rutqvist, L.; Houghton, J.; Edwards, R.; Redmond, C.; Peto, R.; Baum, M.; Fisher, B.; Host, H.; et al. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. *J. Clin. Oncol.* **1994**, *12*, 447–453. [CrossRef]

11. Ross, J.S.; Fletcher, J.A.; Bloom, K.J.; Linette, G.P.; Stec, J.; Symmans, W.F.; Pusztai, L.; Hortobagyi, G.N. Targeted therapy in breast cancer: The HER-2/neu gene and protein. *Mol. Cell. Proteom.* **2004**, *3*, 379–398. [CrossRef] [PubMed]

12. Mego, M.; Mani, S.A.; Cristofanilli, M. Molecular mechanisms of metastasis in breast cancer–clinical applications. *Nat. Rev. Clin. Oncol.* **2010**, *7*, 693–701. [CrossRef] [PubMed]

13. Zhong, Q.; Chen, C.F.; Li, S.; Chen, Y.; Wang, C.C.; Xiao, J.; Chen, P.L.; Sharp, Z.D.; Lee, W.H. Association of BRCA1 with the hRad50-hMre11-p95 complex and the DNA damage response. *Science* **1999**, *285*, 747–750. [CrossRef] [PubMed]

14. Wang, N.; Wang, Z.Y.; Mo, S.L.; Loo, T.Y.; Wang, D.M.; Luo, H.B.; Yang, D.P.; Chen, Y.L.; Shen, J.G.; Chen, J.P. Ellagic acid, a phenolic compound, exerts anti-angiogenesis effects via VEGFR-2 signaling pathway in breast cancer. *Breast Cancer Res. Treat.* **2012**, *134*, 943–955. [CrossRef] [PubMed]

15. Gong, L.; Li, Y.; Nedeljkovic-Kurepa, A.; Sarkar, F.H. Inactivation of NF-kappaB by genistein is mediated via Akt signaling pathway in breast cancer cells. *Oncogene* **2013**, *22*, 4702–4709. [CrossRef] [PubMed]

16. Serra, V.; Scaltriti, M.; Prudkin, L.; Eichhorn, P.J.; Ibrahim, Y.H.; Chandarlapaty, S.; Markman, B.; Rodriguez, O.; Guzman, M.; Rodriguez, S.; et al. PI3K inhibition results in enhanced HER signaling and acquired ERK dependency in HER2-overexpressing breast cancer. *Oncogene* **2011**, *30*, 2547–2557. [CrossRef]

17. Ghayad, S.E.; Vendrell, J.A.; Ben Larbi, S.; Dumontet, C.; Bieche, I.; Cohen, P.A. Endocrine resistance associated with activated ErbB system in breast cancer cells is reversed by inhibiting MAPK or PI3K/Akt signaling pathways. *Int. J. Cancer* **2010**, *126*, 545–562. [CrossRef]

18. Lemée, F.; Bergoglio, V.; Fernandez-Vidal, A.; Machado-Silva, A.; Pillaire, M.J.; Bieth, A.; Gentil, C.; Baker, L.; Martin, A.L.; Leduc, C.; et al. DNA polymerase theta up-regulation is associated with poor survival in breast cancer, perturbs DNA replication, and promotes genetic instability. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 13390–13395. [CrossRef]

19. Gillett, C.; Fantl, V.; Smith, R.; Fisher, C.; Bartek, J.; Dickson, C.; Barnes, D.; Peters, G. Amplification and overexpression of cyclin D1 in breast cancer detected by immunohistochemical staining. *Cancer Res.* **1994**, *54*, 1812–1817.

20. Kolesnikov, N.; Hastings, E.; Keays, M.; Melnichuk, O.; Tang, Y.A.; Williams, E.; Dylag, M.; Kurbatova, N.; Brandizi, M.; Burdett, T.; et al. ArrayExpress update—Simplifying data submissions. *Nucleic Acids Res.* **2015**, *43*, D1113–D1116. [CrossRef]

21. Ritchie, M.E.; Phipson, B.; Wu, D.; Hu, Y.; Law, C.W.; Shi, W.; Smyth, G.K. Limma powers differential expression analyses for RNA-sequencing and microarray studies. *Nucleic Acids. Res.* **2015**, *43*, e47. [CrossRef] [PubMed]

22. Efron, B.; Tibshirani, R. Empirical bayes methods and false discovery rates for microarrays. *Genet. Epidemiol.* **2002**, *23*, 70–86. [CrossRef] [PubMed]

23. Chen, J.; Bardes, E.E.; Aronow, B.J.; Jegga, A.G. ToppGene Suite for gene list enrichment analysis and candidate gene prioritization. *Nucleic Acids Res.* **2009**, *37*, W305–W311. [CrossRef] [PubMed]

24. Caspi, R.; Altman, T.; Dreher, K.; Fulcher, C.A.; Subhraveti, P.; Keseler, I.M.; Kothari, A.; Krummenacker, M.; Latendresse, M.; Mueller, L.A.; et al. The MetaCyc database of metabolic pathways and enzymes and the BioCyc collection of pathway/genome databases. *Nucleic Acids Res.* **2016**, *44*, D471–D480. [CrossRef] [PubMed]

25. Tanabe, M.; Kanehisa, M. Using the KEGG database resource. *Curr. Protoc. Bioinform.* **2012**. [CrossRef]

26. Schaefer, C.F.; Anthony, K.; Krupa, S.; Buchoff, J.; Day, M.; Hannay, T.; Buetow, K.H. PID: The Pathway Interaction Database. *Nucleic Acids Res.* **2009**, *37*, D674–D679. [CrossRef] [PubMed]

27. Sidiropoulos, K.; Viteri, G.; Sevilla, C.; Jupe, S.; Webber, M.; Orlic-Milacic, M.; Jassal, B.; May, B.; Shamovsky, V.; Duenas, C.; et al. Reactome enhanced pathway visualization. *Bioinformatics* **2017**, *33*, 3461–3467. [CrossRef] [PubMed]

28. Dahlquist, K.D.; Salomonis, N.; Vranizan, K.; Lawlor, S.C.; Conklin, B.R. GenMAPP, a new tool for viewing and analyzing microarray data on biological pathways. *Nat. Genet.* **2002**, *31*, 19–20. [CrossRef]

29. Subramanian, A.; Tamayo, P.; Mootha, V.K.; Mukherjee, S.; Ebert, B.L.; Gillette, M.A.; Paulovich, A.; Pomeroy, S.L.; Golub, T.R.; Lander, E.S.; et al. Gene set enrichment analysis: A knowledge-based approach for interpreting genome-wide expression profiles. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 15545–15550. [CrossRef]

30. Mi, H.; Huang, X.; Muruganujan, A.; Tang, H.; Mills, C.; Kang, D.; Thomas, P.D. PANTHER version 11: Expanded annotation data from Gene Ontology and Reactome pathways, and data analysis tool enhancements. *Nucleic Acids Res.* **2017**, *45*, D183–D189. [CrossRef]

31. Petri, V.; Jayaraman, P.; Tutaj, M.; Hayman, G.T.; Smith, J.R.; De Pons, J.; Laulederkind, S.J.; Lowry, T.F.; Nigam, R.; Wang, S.J.; et al. The pathway ontology—Updates and applications. *J. Biomed. Semant.* **2014**, *5*, 7. [CrossRef] [PubMed]

32. Jewison, T.; Su, Y.; Disfany, F.M.; Liang, Y.; Knox, C.; Maciejewski, A.; Poelzer, J.; Huynh, J.; Zhou, Y.; Arndt, D.; et al. SMPDB 2.0: Big improvements to the Small Molecule Pathway Database. *Nucleic Acids Res.* **2014**, *42*, D478–D484. [CrossRef] [PubMed]

33. Cheng, L.; Lin, H.; Hu, Y.; Wang, J.; Yang, Z. Gene function prediction based on the Gene Ontology hierarchical structure. *PLoS ONE* **2014**, *9*, e107187. [CrossRef] [PubMed]

34. Alanis-Lobato, G.; Andrade-Navarro, M.A.; Schaefer, M.H. HIPPIE v2.0: Enhancing meaningfulness and reliability of protein-protein interaction networks. *Nucleic Acids Res.* **2017**, *45*, D408–D414. [CrossRef] [PubMed]

35. Orchard, S.; Ammari, M.; Aranda, B.; Breuza, L.; Briganti, L.; Broackes-Carter, F.; Campbell, N.H.; Chavali, G.; Chen, C.; del-Toro, N.; et al. The MIntAct project–IntAct as a common curation platform for 11 molecular interaction databases. *Nucleic Acids Res.* **2014**, *42*, D358–D363. [CrossRef] [PubMed]

36. Chatr-Aryamontri, A.; Oughtred, R.; Boucher, L.; Rust, J.; Chang, C.; Kolas, N.K.; O'Donnell, L.; Oster, S.; Theesfeld, C.; Sellam, A.; et al. The BioGRID interaction database: 2017 update. *Nucleic Acids Res.* **2017**, *45*, D369–D379. [CrossRef]

37. Keshava Prasad, T.S.; Goel, R.; Kandasamy, K.; Keerthikumar, S.; Kumar, S.; Mathivanan, S.; Telikicherla, D.; Raju, R.; Shafreen, B.; Venugopal, A.; et al. Human Protein Reference Database—2009 update. *Nucleic Acids Res.* **2009**, *37*, D767–D772. [CrossRef]

38. Licata, L.; Briganti, L.; Peluso, D.; Perfetto, L.; Iannuccelli, M.; Galeota, E.; Sacco, F.; Palma, A.; Nardozza, A.P.; Santonico, E.; et al. MINT, the molecular interaction database: 2012 update. *Nucleic Acids Res.* **2012**, *40*, D857–D861. [CrossRef]

39. Isserlin, R.; El-Badrawi, R.A.; Bader, G.D. The Biomolecular Interaction Network Database in PSI-MI 2.5. *Database* **2011**, *2011*, baq037. [CrossRef]

40. Pagel, P.; Kovac, S.; Oesterheld, M.; Brauner, B.; Dunger-Kaltenbach, I.; Frishman, G.; Montrone, C.; Mark, P.; Stümpflen, V.; Mewes, H.W.; et al. The MIPS mammalian protein-protein interaction database. *Bioinformatics* **2005**, *21*, 832–834. [CrossRef]

41. Salwinski, L.; Miller, C.S.; Smith, A.J.; Pettit, F.K.; Bowie, J.U.; Eisenberg, D. The Database of Interacting Proteins: 2004 update. *Nucleic Acids Res.* **2004**, *32*, D449–D451. [CrossRef] [PubMed]

42. Shannon, P.; Markiel, A.; Ozier, O.; Baliga, N.S.; Wang, J.T.; Ramage, D.; Amin, N.; Schwikowski, B.; Ideker, T. Cytoscape: A software environment for integrated models of biomolecular interaction networks. *Genome Res.* **2003**, *3*, 2498–2504. [CrossRef] [PubMed]

43. Przulj, N. Biological network comparison using graphlet degree distribution. *Bioinformatics* **2007**, *23*, e177–e183. [CrossRef] [PubMed]

44. Hahn, M.W.; Kern, A.D. Comparative genomics of centrality and essentiality in three eukaryotic protein-interaction networks. *Mol. Biol. Evol.* **2005**, *22*, 803–806. [CrossRef] [PubMed]

45. Zhuang, D.Y.; Jiang, L.; He, Q.Q.; Zhou, P.; Yue, T. Identification of hub subnetwork based on topological features of genes in breast cancer. *Int. J. Mol. Med.* **2015**, *35*, 664–674. [CrossRef] [PubMed]

46. Ozgür, A.; Vu, T.; Erkan, G.; Radev, D.R. Identifying gene-disease associations using centrality on a literature mined gene-interaction network. *Bioinformatics* **2008**, *24*, i277–i285. [CrossRef]

47. Stelzl, U.; Worm, U.; Lalowski, M.; Haenig, C.; Brembeck, F.H.; Goehler, H.; Stroedicke, M.; Zenkner, M.; Schoenherr, A.; Koeppen, S.; et al. A human protein-protein interaction network: A resource for annotating the proteome. *Cell* **2005**, *122*, 957–968. [CrossRef]

48. Zaki, N.; Efimov, D.; Berengueres, J. Protein complex detection using interaction reliability assessment and weighted clustering coefficient. *BMC Bioinform.* **2013**, *14*, 163. [CrossRef]

49. Sethupathy, P.; Corda, B.; Hatzigeorgiou, A.G. TarBase: A comprehensive database of experimentally supported animal microRNA targets. *RNA* **2006**, *12*, 192–197. [CrossRef]

50. Chou, C.H.; Shrestha, S.; Yang, C.D.; Chang, N.W.; Lin, Y.L.; Liao, K.W.; Huang, W.C.; Sun, T.H.; Tu, S.J.; Lee, W.H.; et al. miRTarBase update 2018: A resource for experimentally validated microRNA-target interactions. *Nucleic Acids Res.* **2018**, *46*, D296–D302. [CrossRef]

51. Xia, J.; Benner, M.J.; Hancock, R.E. NetworkAnalyst—Integrative approaches for protein-protein interaction network analysis and visual exploration. *Nucleic Acids Res.* **2014**, *42*, W167–W174. [CrossRef] [PubMed]

52. Lachmann, A.; Xu, H.; Krishnan, J.; Berger, S.I.; Mazloom, A.R.; Ma'ayan, A. ChEA: Transcription factor regulation inferred from integrating genome-wide ChIP-X experiments. *Bioinformatics* **2010**, *26*, 2438–2444. [CrossRef] [PubMed]

53. Aguirre-Gamboa, R.; Gomez-Rueda, H.; Martínez-Ledesma, E.; Martínez-Torteya, A.; Chacolla-Huaringa, R.; Rodriguez-Barrientos, A.; Tamez-Peña, J.G.; Treviño, V. SurvExpress: An online biomarker validation tool and database for cancer gene expression data using survival analysis. *PLoS ONE* **2013**, *8*, e74250. [CrossRef] [PubMed]

54. Uhlén, M.; Fagerberg, L.; Hallström, B.M.; Lindskog, C.; Oksvold, P.; Mardinoglu, A.; Sivertsson, Å.; Kampf, C.; Sjöstedt, E.; Asplund, A.; et al. Proteomics. Tissue-based map of the human proteome. *Science* **2015**, *347*, 1260419. [CrossRef] [PubMed]

55. Gao, J.; Aksoy, B.A.; Dogrusoz, U.; Dresdner, G.; Gross, B.; Sumer, S.O.; Sun, Y.; Jacobsen, A.; Sinha, R.; Larsson, E.; et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. *Sci. Signal.* **2013**, *6*, pl1. [CrossRef] [PubMed]

56. Yager, J.D.; Davidson, N.E. Estrogen carcinogenesis in breast cancer. *N. Engl. J. Med.* **2006**, *354*, 270–282. [CrossRef] [PubMed]

57. Jordan, V.C. Tamoxifen: A most unlikely pioneering medicine. *Nat. Rev. Drug Discov.* **2003**, *2*, 205–213. [CrossRef] [PubMed]

58. Veer, L.J.; Dai, H.; Vijver, M.J.; He, Y.D.; Hart, A.A.; Mao, M.; Peterse, H.L.; van der Kooy, K.; Marton, M.J.; Witteveen, A.T.; et al. Gene expression profiling predicts clinical outcome of breast cancer. *Nature* **2002**, *415*, 530–536. [CrossRef]

59. Wang, H.Y.; Wang, W.; Liu, Y.W.; Li, M.Y.; Liang, T.Y.; Li, J.Y.; Hu, H.M.; Lu, Y.; Yao, C.; Ye, Y.Y.; et al. Role of KCNB1 in the prognosis of gliomas and autophagy modulation. *Sci. Rep.* **2017**, *7*, 14. [CrossRef]

60. Duan, S.; Gong, B.; Wang, P.; Huang, H.; Luo, L.; Liu, F. Novel prognostic biomarkers of gastric cancer based on gene expression microarray: COL12A1, GSTA3, FGA and FGG. *Mol. Med. Rep.* **2018**, *18*, 3727–3736. [CrossRef]

61. Dong, L.; Li, Z.; Xue, L.; Li, G.; Zhang, C.; Cai, Z.; Li, H.; Guo, R. DIAPH3 promoted the growth, migration and metastasis of hepatocellular carcinoma cells by activating beta-catenin/TCF signaling. *Mol. Cell Biochem.* **2018**, *438*, 183–190. [CrossRef] [PubMed]

62. Murase, R.; Abe, Y.; Takeuchi, T.; Nabeta, M.; Imai, Y.; Kamei, Y.; Kagawa-Miki, L.; Ueda, N.; Sumida, T.; Hamakawa, H.; et al. Serum autoantibody to sideroflexin 3 as a novel tumor marker for oral squamous cell carcinoma. *Proteom. Clin. Appl.* **2008**, *2*, 517–527. [CrossRef] [PubMed]

63. Zhang, W.C.; Shyh-Chang, N.; Yang, H.; Rai, A.; Umashankar, S.; Ma, S.; Soh, B.S.; Sun, L.L.; Tai, B.C.; Nga, M.E.; et al. Glycine decarboxylase activity drives non-small cell lung cancer tumor-initiating cells and tumorigenesis. *Cell* **2012**, *148*, 259–272. [CrossRef] [PubMed]

64. Du, F.; Sun, L.; Chu, Y.; Li, T.; Lei, C.; Wang, X.; Jiang, M.; Min, Y.; Lu, Y.; Zhao, X.; et al. DDIT4 promotes gastric cancer proliferation and tumorigenesis through the p53 and MAPK pathways. *Cancer Commun.* **2018**, *38*, 45. [CrossRef] [PubMed]

65. Kaneda, A.; Kaminishi, M.; Nakanishi, Y.; Sugimura, T. Reduced expression of the insulin-induced protein 1 and p41 Arp2/3 complex genes in human gastric cancers. *Int. J. Cancer* **2002**, *100*, 57–62. [CrossRef] [PubMed]

66. Hur, H.; Kim, Y.B.; Ham, I.H.; Lee, D. Loss of ACSS2 expression predicts poor prognosis in patients with gastric cancer. *J. Surg. Oncol.* **2015**, *112*, 585–591. [CrossRef] [PubMed]

67. Niess, H.; Camaj, P.; Mair, R.; Renner, A.; Zhao, Y.; Jäckel, C.; Nelson, P.J.; Jauch, K.W.; Bruns, C.J. Overexpression of IFN-induced protein with tetratricopeptide repeats 3 (IFIT3) in pancreatic cancer: Cellular "pseudoinflammation" contributing to an aggressive phenotype. *Oncotarget* **2015**, *6*, 3306–3318. [CrossRef] [PubMed]

68. Hong, S.B.; Oh, H.; Valera, V.A.; Stull, J.; Ngo, D.T.; Baba, M.; Merino, M.J.; Linehan, W.M.; Schmidt, L.S. Tumor suppressor FLCN inhibits tumorigenesis of a FLCN-null renal cancer cell line and regulates expression of key molecules in TGF-beta signaling. *Mol. Cancer* **2010**, *9*, 160. [CrossRef]

69. Xie, M.; Sun, M.; Zhu, Y.N.; Xia, R.; Liu, Y.W.; Ding, J.; Ma, H.W.; He, X.Z.; Zhang, Z.H.; Liu, Z.J.; et al. Long noncoding RNA HOXA-AS2 promotes gastric cancer proliferation by epigenetically silencing P21/PLK3/DDIT3 expression. *Oncotarget* **2015**, *6*, 33587–33601. [CrossRef]

70. Tamir, A.; Gangadharan, A.; Balwani, S.; Tanaka, T.; Patel, U.; Hassan, A.; Benke, S.; Agas, A.; D'Agostino, J.; Shin, D.; et al. The serine protease prostasin (PRSS8) is a potential biomarker for early detection of ovarian cancer. *J. Ovarian Res.* **2016**, *9*, 20. [CrossRef]

71. Wang, X.; Lu, H.; Urvalek, A.M.; Li, T.; Yu, L.; Lamar, J.; DiPersio, C.M.; Feustel, P.J.; Zhao, J. KLF8 promotes human breast cancer cell invasion and metastasis by transcriptional activation of MMP9. *Oncogene* **2011**, *30*, 1901–1911. [CrossRef] [PubMed]

72. Ravindranath, A.; Yuen, H.F.; Chan, K.K.; Grills, C.; Fennell, D.A.; Lappin, T.R.; El-Tanani, M. Wnt-β-catenin-Tcf-4 signaling-modulated invasiveness is dependent on osteopontin expression in breast cancer. *Br. J. Cancer* **2011**, *105*, 542–551. [CrossRef] [PubMed]

73. Berteaux, N.; Lottin, S.; Monté, D.; Pinte, S.; Quatannens, B.; Coll, J.; Hondermarck, H.; Curgy, J.J.; Dugimont, T.; Adriaenssens, E. H19 mRNA-like noncoding RNA promotes breast cancer cell proliferation through positive control by E2F1. *J. Biol. Chem.* **2005**, *280*, 29625–29636. [CrossRef] [PubMed]

74. Kim, S.K.; Jung, W.H.; Koo, J.S. Differential expression of enzymes associated with serine/glycine metabolism in different breast cancer subtypes. *PLoS ONE* **2014**, *9*, e101004. [CrossRef] [PubMed]

75. Divella, R.; Daniele, A.; Savino, E.; Palma, F.; Bellizzi, A.; Giotta, F.; Simone, G.; Lioce, M.; Quaranta, M.; Paradiso, A.; et al. Circulating levels of transforming growth factor-βeta (TGF-β) and chemokine (C-X-C motif) ligand-1 (CXCL1) as predictors of distant seeding of circulating tumor cells in patients with metastatic breast cancer. *Anticancer Res.* **2013**, *33*, 1491–1497. [PubMed]

76. Izrailit, J.; Berman, H.K.; Datti, A.; Wrana, J.L.; Reedijk, M. High throughput kinase inhibitor screens reveal TRB3 and MAPK-ERK/TGFβ pathways as fundamental Notch regulators in breast cancer. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 1714–1719. [CrossRef] [PubMed]

77. Shpyleva, S.I.; Tryndyak, V.P.; Kovalchuk, O.; Starlard-Davenport, A.; Chekhun, V.F.; Beland, F.A.; Pogribny, I.P. Role of ferritin alterations in human breast cancer cells. *Breast Cancer Res. Treat.* **2011**, *126*, 63–71. [CrossRef]

78. Tripathi, M.K.; Chaudhuri, G. Down-regulation of UCRP and UBE2L6 in BRCA2 knocked-down human breast cells. *Biochem. Biophys. Res. Commun.* **2005**, *328*, 43–48. [CrossRef]

79. Malinowska, K.; Cavarretta, I.T.; Susani, M.; Wrulich, O.A.; Uberall, F.; Kenner, L.; Culig, Z. Identification of mu-crystallin as an androgen-regulated gene in human prostate cancer. *Prostate* **2009**, *69*, 1109–1118. [CrossRef]

80. Wang, H.; Tong, L.; Wei, J.; Pan, W.; Li, L.; Ge, Y.; Yuan, Q.; Zhou, C.; Yang, M. The ALDH7A1 genetic polymorphisms contribute to development of esophageal squamous cell carcinoma. *Tumour Biol.* **2014**, *35*, 12665–12670. [CrossRef]

81. Koh, V.; Kwan, H.Y.; Tan, W.L.; Mah, T.L.; Yong, W.P. Knockdown of POLA2 increases gemcitabine resistance in lung cancer cells. *BMC Genom.* **2016**, *17*, 1029. [CrossRef] [PubMed]

82. Li, D.; Li, R.; Zhang, J.; Li, K.; Wu, Y. Association Between the LIG1 Polymorphisms and Lung Cancer Risk: A Meta-analysis of Case-Control Studies. *Cell Biochem. Biophys.* **2015**, *73*, 381–387. [CrossRef] [PubMed]

83. Chiu, C.F.; Tsai, M.H.; Tseng, H.C.; Wang, C.L.; Tsai, F.J.; Lin, C.C.; Bau, D.T. A novel single nucleotide polymorphism in ERCC6 gene is associated with oral cancer susceptibility in Taiwanese patients. *Oral Oncol.* **2008**, *44*, 582–586. [CrossRef] [PubMed]

84. Ashkavandi, Z.J.; Najvani, A.D.; Tadbir, A.A.; Pardis, S.; Ranjbar, M.A.; Ashraf, M.J. MCM3 as a novel diagnostic marker in benign and malignant salivary gland tumors. *Asian Pac. J. Cancer Prev.* **2013**, *14*, 3479–3482. [CrossRef] [PubMed]

85. Murphy, N.; Ring, M.; Heffron, C.C.; King, B.; Killalea, A.G.; Hughes, C.; Martin, C.M.; McGuinness, E.; Sheils, O.; O'Leary, J.J. p16INK4A, CDC6, and MCM5: Predictive biomarkers in cervical preinvasive neoplasia and cervical cancer. *J. Clin. Pathol.* **2005**, *58*, 525–534. [CrossRef] [PubMed]

86. Qu, K.; Wang, Z.; Fan, H.; Li, J.; Liu, J.; Li, P.; Liang, Z.; An, H.; Jiang, Y.; Lin, Q.; et al. MCM7 promotes cancer progression through cyclin D1-dependent signaling and serves as a prognostic marker for patients with hepatocellular carcinoma. *Cell Death Dis.* **2017**, *8*, e2603. [CrossRef] [PubMed]

87. Sun, C.; Huang, S.; Ju, W.; Hou, Y.; Wang, Z.; Liu, Y.; Wu, L.; He, X. Elevated DSN1 expression is associated with poor survival in patients with hepatocellular carcinoma. *Hum. Pathol.* **2018**, *81*, 113–120. [CrossRef]

88. Valle, L.; Hernández-Illán, E.; Bellido, F.; Aiza, G.; Castillejo, A.; Castillejo, M.I.; Navarro, M.; Seguí, N.; Vargas, G.; Guarinos, C.; et al. New insights into POLE and POLD1 germline mutations in familial colorectal cancer and polyposis. *Hum. Mol. Genet.* **2014**, *23*, 3506–3512. [CrossRef]

89. Platz, A.; Hansson, J.; Ringborg, U. Screening of germline mutations in the CDK4, CDKN2C and TP53 genes in familial melanoma: A clinic-based population study. *Int. J. Cancer* **1998**, *78*, 13–15. [CrossRef]

90. Castel, D.; Philippe, C.; Calmon, R.; Le Dret, L.; Truffaux, N.; Boddaert, N.; Pagès, M.; Taylor, K.R.; Saulnier, P.; Lacroix, L.; et al. Histone H3F3A and HIST1H3B K27M mutations define two subgroups of diffuse intrinsic pontine gliomas with different prognosis and phenotypes. *Acta Neuropathol.* **2015**, *130*, 815–827. [CrossRef]

91. Li, J.; Wang, J.; Yu, J.; Zhao, Y.; Dong, Y.; Fan, Y.; Li, N.; Zhang, Y.; Wang, Y. Knockdown of POLE2 expression suppresses lung adenocarcinoma cell malignant phenotypes in vitro. *Oncol. Rep.* **2018**, *40*, 2477–2486. [CrossRef] [PubMed]

92. Wang, M.; Xie, T.; Wu, Y.; Yin, Q.; Xie, S.; Yao, Q.; Xiong, J.; Zhang, Q. Identification of RFC5 as a novel potential prognostic biomarker in lung cancer through bioinformatics analysis. *Oncol. Lett.* **2018**, *16*, 4201–4210. [CrossRef] [PubMed]

93. Astbury, K.; McEvoy, L.; Brian, H.; Spillane, C.; Sheils, O.; Martin, C.; O'Leary, J.J. MYBL2 (B-MYB) in cervical cancer: Putative biomarker. *Int. J. Gynecol. Cancer* **2011**, *21*, 206–212. [CrossRef] [PubMed]

94. Chen, J.; Chen, H.; Yang, H.; Dai, H. SPC25 upregulation increases cancer stem cell properties in non-small cell lung adenocarcinoma cells and independently predicts poor survival. *Biomed. Pharmacother.* **2018**, *100*, 233–239. [CrossRef] [PubMed]

95. Kato, T.; Wada, H.; Patel, P.; Hu, H.P.; Lee, D.; Ujiie, H.; Hirohashi, K.; Nakajima, T.; Sato, M.; Kaji, M.; et al. Overexpression of KIF23 predicts clinical outcome in primary lung cancer patients. *Lung Cancer* **2016**, *92*, 53–61. [CrossRef]

96. Zhang, Q.; Su, R.; Shan, C.; Gao, C.; Wu, P. Non-SMC Condensin I Complex, Subunit G (NCAPG) is a Novel Mitotic Gene Required for Hepatocellular Cancer Cell Proliferation and Migration. *Oncol. Res.* **2018**, *26*, 269–276. [CrossRef] [PubMed]

97. Wang, S.; Liu, B.; Zhang, J.; Sun, W.; Dai, C.; Sun, W.; Li, Q. Centromere protein U is a potential target for gene therapy of human bladder cancer. *Oncol. Rep.* **2017**, *38*, 735–744. [CrossRef]

98. Chen, H.; Zhang, L.; He, W.; Liu, T.; Zhao, Y.; Chen, H.; Li, Y. ESCO2 knockdown inhibits cell proliferation and induces apoptosis in human gastric cancer cells. *Biochem. Biophys. Res. Commun.* **2018**, *496*, 475–481. [CrossRef]

99. Gavin, E.J.; Song, B.; Wang, Y.; Xi, Y.; Ju, J. Reduction of Orc6 expression sensitizes human colon cancer cells to 5-fluorouracil and cisplatin. *PLoS ONE* **2008**, *3*, e4054. [CrossRef]

100. Subhash, V.V.; Tan, S.H.; Tan, W.L.; Yeo, M.S.; Xie, C.; Wong, F.Y.; Kiat, Z.Y.; Lim, R.; Yong, W.P. GTSE1 expression represses apoptotic signaling and confers cisplatin resistance in gastric cancer cells. *BMC Cancer* **2015**, *15*, 550. [CrossRef]

101. Zhu, P.; Jin, J.; Liao, Y.; Li, J.; Yu, X.Z.; Liao, W.; He, S. A novel prognostic biomarker SPC24 up-regulated in hepatocellular carcinoma. *Oncotarget* **2015**, *6*, 41383–41397. [CrossRef] [PubMed]

102. Liu, L.; Wu, J.; Wang, S.; Luo, X.; Du, Y.; Huang, D.; Gu, D.; Zhang, F. PKMYT1 promoted the growth and motility of hepatocellular carcinoma cells by activating beta-catenin/TCF signaling. *Exp. Cell Res.* **2017**, *358*, 209–216. [CrossRef] [PubMed]

103. Jia, H.; Song, L.; Cong, Q.; Wang, J.; Xu, H.; Chu, Y.; Li, Q.; Zhang, Y.; Zou, X.; Zhang, C.; et al. The LIM protein AJUBA promotes colorectal cancer cell survival through suppression of JAK1/STAT1/IFIT2 network. *Oncogene* **2017**, *36*, 2655–2666. [CrossRef] [PubMed]

104. Gonzalez, M.A.; Pinder, S.E.; Callagy, G.; Vowler, S.L.; Morris, L.S.; Bird, K.; Bell, J.A.; Laskey, R.A.; Coleman, N. Minichromosome maintenance protein 2 is a strong independent prognostic marker in breast cancer. *J. Clin. Oncol.* **2003**, *21*, 4306–4313. [CrossRef] [PubMed]

105. Juríková, M.; Danihel, Ľ.; Polák, Š.; Varga, I. Ki67, PCNA, and MCM proteins: Markers of proliferation in the diagnosis of breast cancer. *Acta Histochem.* **2016**, *118*, 544–552. [CrossRef] [PubMed]

106. Zhou, J.; Zhang, W.W.; Peng, F.; Sun, J.Y.; He, Z.Y.; Wu, S.G. Down regulation of hsa_circ_0011946 suppresses the migration and invasion of the breast cancer cell line MCF-7 by targeting RFC3. *Cancer Manag. Res.* **2018**, *10*, 535–544. [CrossRef] [PubMed]

107. Putluri, N.; Maity, S.; Kommagani, R.; Creighton, C.J.; Putluri, V.; Chen, F.; Nanda, S.; Bhowmik, S.K.; Terunuma, A.; Dorsey, T.; et al. Pathway-centric integrative analysis identifies RRM2 as a prognostic marker in breast cancer associated with poor survival and tamoxifen resistance. *Neoplasia* **2014**, *16*, 390–402. [CrossRef] [PubMed]

108. Naushad, S.M.; Reddy, C.A.; Kumaraswami, K.; Divyya, S.; Kotamraju, S.; Gottumukkala, S.R.; Digumarti, R.R.; Kutala, V.K. Impact of hyperhomocysteinemia on breast cancer initiation and progression: Epigenetic perspective. *Cell Biochem. Biophys.* **2014**, *68*, 397–406. [CrossRef]

109. Byrski, T.; Gronwald, J.; Huzarski, T.; Grzybowska, E.; Budryk, M.; Stawicka, M.; Mierzwa, T.; Szwiec, M.; Wisniowski, R.; Siolek, M.; et al. Pathologic complete response rates in young women with BRCA1-positive breast cancers after neoadjuvant chemotherapy. *J. Clin. Oncol.* **2010**, *28*, 375–379. [CrossRef]

110. Cowan, K.H.; Goldsmith, M.E.; Levine, R.M.; Aitken, S.C.; Douglass, E.; Clendeninn, N.; Nienhuis, A.W.; Lippman, M.E. Dihydrofolate reductase gene amplification and possible rearrangement in estrogen-responsive methotrexate-resistant human breast cancer cells. *J. Biol. Chem.* **1982**, *257*, 15079–15086.

111. Soria-Bretones, I.; Sáez, C.; Ruíz-Borrego, M.; Japón, M.A.; Huertas, P. Prognostic value of CtIP/RBBP8 expression in breast cancer. *Cancer Med.* **2013**, *2*, 774–783. [CrossRef] [PubMed]

112. Han, S.; Park, K.; Bae, B.N.; Kim, K.H.; Kim, H.J.; Kim, Y.D.; Kim, H.Y. E2F1 expression is related with the poor survival of lymph node-positive breast cancer patients treated with fluorouracil, doxorubicin and cyclophosphamide. *Breast Cancer Res. Treat.* **2003**, *82*, 11–16. [CrossRef] [PubMed]

113. Gao, T.; Han, Y.; Yu, L.; Ao, S.; Li, Z.; Ji, J. CCNA2 is a prognostic biomarker for ER+ breast cancer and tamoxifen resistance. *PLoS ONE* **2014**, *9*, e91771. [CrossRef] [PubMed]

114. Luo, Q.; Li, X.; Li, J.; Kong, X.; Zhang, J.; Chen, L.; Huang, Y.; Fang, L. MiR-15a is underexpressed and inhibits the cell cycle by targeting CCNE1 in breast cancer. *Int. J. Oncol.* **2013**, *43*, 1212–1218. [CrossRef] [PubMed]

115. He, Q.; Zou, L.; Zhang, P.A.; Lui, J.X.; Skog, S.; Fornander, T. The clinical significance of thymidine kinase 1 measurement in serum of breast cancer patients using anti-TK1 antibody. *Int. J. Biol. Markers* **2000**, *15*, 139–146. [CrossRef] [PubMed]

116. Pegoraro, S.; Ros, G.; Ciani, Y.; Sgarra, R.; Piazza, S.; Manfioletti, G. A novel HMGA1-CCNE2-YAP axis regulates breast cancer aggressiveness. *Oncotarget* **2015**, *6*, 19087–19101. [CrossRef]

117. Cangi, M.G.; Cukor, B.; Soung, P.; Signoretti, S.; Moreira, G.; Ranashinge, M.; Cady, B.; Pagano, M.; Loda, M. Role of the Cdc25A phosphatase in human breast cancer. *J. Clin. Investig.* **2000**, *106*, 753–761. [CrossRef]

118. Nakayama, S.; Torikoshi, Y.; Takahashi, T.; Yoshida, T.; Sudo, T.; Matsushima, T.; Kawasaki, Y.; Katayama, A.; Gohda, K.; Hortobagyi, G.N.; et al. Prediction of paclitaxel sensitivity by CDK1 and CDK2 activity in human breast cancer cells. *Breast Cancer Res.* **2009**, *11*, R12. [CrossRef]

119. Hu, Z.; Huang, G.; Sadanandam, A.; Gu, S.; Lenburg, M.E.; Pai, M.; Bayani, N.; Blakely, E.A.; Gray, J.W.; Mao, J.H. The expression level of HJURP has an independent prognostic impact and predicts the sensitivity to radiotherapy in breast cancer. *Breast Cancer Res.* **2010**, *12*, R18. [CrossRef]

120. Choschzick, M.; Lebeau, A.; Marx, A.H.; Tharun, L.; Terracciano, L.; Heilenkötter, U.; Jaenicke, F.; Bokemeyer, C.; Simon, R.; Sauter, G.; et al. Overexpression of cell division cycle 7 homolog is associated with gene amplification frequency in breast cancer. *Hum. Pathol.* **2010**, *41*, 358–365. [CrossRef]

121. Bièche, I.; Vacher, S.; Lallemand, F.; Tozlu-Kara, S.; Bennani, H.; Beuzelin, M.; Driouch, K.; Rouleau, E.; Lerebours, F.; Ripoche, H.; et al. Expression analysis of mitotic spindle checkpoint genes in breast carcinoma: Role of NDC80/HEC1 in early breast tumorigenicity, and a two-gene signature for aneuploidy. *Mol. Cancer* **2011**, *10*, 23. [CrossRef] [PubMed]

122. Capdevila-Busquets, E.; Badiola, N.; Arroyo, R.; Alcalde, V.; Soler-López, M.; Aloy, P. Breast cancer genes PSMC3IP and EPSTI1 play a role in apoptosis regulation. *PLoS ONE* **2015**, *10*, e0115352. [CrossRef] [PubMed]

123. Rantala, J.K.; Edgren, H.; Lehtinen, L.; Wolf, M.; Kleivi, K.; Vollan, H.K.; Aaltola, A.R.; Laasola, P.; Kilpinen, S.; Saviranta, P.; et al. Integrative functional genomics analysis of sustained polyploidy phenotypes in breast cancer cells identifies an oncogenic profile for GINS2. *Neoplasia* **2010**, *12*, 877–888. [CrossRef] [PubMed]

124. Finetti, P.; Guille, A.; Adelaide, J.; Birnbaum, D.; Chaffanet, M.; Bertucci, F. ESPL1 is a candidate oncogene of luminal B breast cancers. *Breast Cancer Res. Treat.* **2014**, *147*, 51–59. [CrossRef] [PubMed]

125. Karppinen, S.M.; Heikkinen, K.; Rapakko, K.; Winqvist, R. Mutation screening of the BARD1 gene: Evidence for involvement of the Cys557Ser allele in hereditary susceptibility to breast cancer. *J. Med. Genet.* **2004**, *41*, e114. [CrossRef] [PubMed]

126. Prokofyeva, D.; Bogdanova, N.; Dubrowinskaja, N.; Bermisheva, M.; Takhirova, Z.; Antonenkova, N.; Turmanov, N.; Datsyuk, I.; Gantsev, S.; Christiansen, H.; et al. Nonsense mutation p.Q548X in BLM, the gene mutated in Bloom's syndrome, is associated with breast cancer in Slavic populations. *Breast Cancer Res. Treat.* **2013**, *137*, 533–539. [CrossRef] [PubMed]

127. Myrie, K.A.; Percy, M.J.; Azim, J.N.; Neeley, C.K.; Petty, E.M. Mutation and expression analysis of human BUB1 and BUB1B in aneuploid breast cancer cell lines. *Cancer Lett.* **2000**, *152*, 193–199. [CrossRef]

128. Mahadevappa, R.; Neves, H.; Yuen, S.M.; Bai, Y.; McCrudden, C.M.; Yuen, H.F.; Wen, Q.; Zhang, S.D.; Kwok, H.F. The prognostic significance of Cdc6 and Cdt1 in breast cancer. *Sci. Rep.* **2017**, *7*, 985. [CrossRef]

129. Wong, A.K.; Pero, R.; Ormonde, P.A.; Tavtigian, S.V.; Bartel, P.L. RAD51 interacts with the evolutionarily conserved BRC motifs in the human breast cancer susceptibility gene brca2. *J. Biol. Chem.* **1997**, *272*, 31941–31944. [CrossRef]

130. Khongkow, P.; Gomes, A.R.; Gong, C.; Man, E.P.; Tsang, J.W.; Zhao, F.; Monteiro, L.J.; Coombes, R.C.; Medema, R.H.; Khoo, U.S.; et al. Paclitaxel targets FOXM1 to regulate KIF20A in mitotic catastrophe and breast cancer paclitaxel resistance. *Oncogene* **2016**, *35*, 990–1002. [CrossRef]

131. Wang, H.C.; Chiu, C.F.; Tsai, R.Y.; Kuo, Y.S.; Chen, H.S.; Wang, R.F.; Tsai, C.W.; Chang, C.H.; Lin, C.C.; Bau, D.T. Association of genetic polymorphisms of EXO1 gene with risk of breast cancer in Taiwan. *Anticancer Res.* **2009**, *29*, 3897–3901. [PubMed]

132. Tchatchou, S.; Wirtenberger, M.; Hemminki, K.; Sutter, C.; Meindl, A.; Wappenschmidt, B.; Kiechle, M.; Bugert, P.; Schmutzler, R.K.; Bartram, C.R.; et al. Aurora kinases A and B and familial breast cancer risk. *Cancer Lett.* **2007**, *247*, 266–272. [CrossRef] [PubMed]

133. Mahadevappa, R.; Neves, H.; Yuen, S.M.; Jameel, M.; Bai, Y.; Yuen, H.F.; Zhang, S.D.; Zhu, Y.; Lin, Y.; Kwok, H.F. DNA Replication Licensing Protein MCM10 Promotes Tumor Progression and Is a Novel Prognostic Biomarker and Potential Therapeutic Target in Breast Cancer. *Cancers* **2018**, *10*, 282. [CrossRef] [PubMed]

134. Phan, N.N.; Wang, C.Y.; Li, K.L.; Chen, C.F.; Chiao, C.C.; Yu, H.G.; Huang, P.L.; Lin, Y.C. Distinct expression of CDCA3, CDCA5, and CDCA8 leads to shorter relapse free survival in breast cancer patient. *Oncotarget* **2018**, *9*, 6977–6992. [CrossRef] [PubMed]

135. Wazir, U.; Ahmed, M.H.; Bridger, J.M.; Harvey, A.; Jiang, W.G.; Sharma, A.K.; Mokbel, K. The clinicopathological significance of lamin A/C, lamin B1 and lamin B receptor mRNA expression in human breast cancer. *Cell. Mol. Biol. Lett.* **2013**, *18*, 595–611. [CrossRef] [PubMed]

136. Moelans, C.B.; Verschuur-Maes, A.H.; Diest, P.J. Frequent promoter hypermethylation of BRCA2, CDH13, MSH6, PAX5, PAX6 and WT1 in ductal carcinoma in situ and invasive breast cancer. *J. Pathol.* **2011**, *225*, 222–231. [CrossRef] [PubMed]

137. Ashida, S.; Kawada, C.; Inoue, K. Stromal regulation of prostate cancer cell growth by mevalonate pathway enzymes HMGCS1 and HMGCR. *Oncol. Lett.* **2017**, *14*, 6533–6542. [CrossRef] [PubMed]

138. Yim, M.S.; Ha, Y.S.; Kim, I.Y.; Yun, S.J.; Choi, Y.H.; Kim, W.J. HMOX1 is an important prognostic indicator of nonmuscle invasive bladder cancer recurrence and progression. *J. Urol.* **2011**, *185*, 701–705. [CrossRef]

139. Hanrahan, V.; Currie, M.J.; Gunningham, S.P.; Morrin, H.R.; Scott, P.A.; Robinson, B.A.; Fox, S.B. The angiogenic switch for vascular endothelial growth factor (VEGF)-A, VEGF-B, VEGF-C, and VEGF-D in the adenoma-carcinoma sequence during colorectal cancer progression. *J. Pathol.* **2003**, *200*, 183–194. [CrossRef] [PubMed]

140. Ji, X.F.; Fan, Y.C.; Gao, S.; Yang, Y.; Zhang, J.J.; Wang, K. MT1M and MT1G promoter methylation as biomarkers for hepatocellular carcinoma. *World J. Gastroenterol.* **2014**, *20*, 4723–4729. [CrossRef]

141. Han, Y.C.; Zheng, Z.L.; Zuo, Z.H.; Yu, Y.P.; Chen, R.; Tseng, G.C.; Nelson, J.B.; Luo, J.H. Metallothionein 1 h tumour suppressor activity in prostate cancer is mediated by euchromatin methyltransferase 1. *J. Pathol.* **2013**, *230*, 184–193. [CrossRef] [PubMed]

142. Liu, Z.; Ye, Q.; Wu, L.; Gao, F.; Xie, H.; Zhou, L.; Zheng, S.; Xu, X. Metallothionein 1 family profiling identifies MT1X as a tumor suppressor involved in the progression and metastatic capacity of hepatocellular carcinoma. *Mol. Carcinog.* **2018**, *57*, 1435–1444. [CrossRef] [PubMed]

143. Obata, T.; Toyota, M.; Satoh, A.; Sasaki, Y.; Ogi, K.; Akino, K.; Suzuki, H.; Murai, M.; Kikuchi, T.; Mita, H.; et al. Identification of HRK as a target of epigenetic inactivation in colorectal and gastric cancer. *Clin. Cancer Res.* **2003**, *9*, 6410–6418. [PubMed]

144. Okada, T.; Murata, K.; Hirose, R.; Matsuda, C.; Komatsu, T.; Ikekita, M.; Nakawatari, M.; Nakayama, F.; Wakatsuki, M.; Ohno, T.; et al. Upregulated expression of FGF13/FHF2 mediates resistance to platinum drugs in cervical cancer cells. *Sci. Rep.* **2013**, *3*, 2899. [CrossRef] [PubMed]

145. Ohtani, H.; Nakayama, T.; Yoshie, O. In situ expression of the CCL20-CCR6 axis in lymphocyte-rich gastric cancer and its potential role in the formation of lymphoid stroma. *Pathol. Int.* **2011**, *61*, 645–651. [CrossRef] [PubMed]

146. Charbonneau, B.; Block, M.S.; Bamlet, W.R.; Vierkant, R.A.; Kalli, K.R.; Fogarty, Z.; Rider, D.N.; Sellers, T.; Tworoger, S.S.; Poole, E.; et al. Risk of ovarian cancer and the NF-κB pathway: Genetic association with IL1A and TNFSF10. *Cancer Res.* **2014**, *74*, 852–861. [CrossRef] [PubMed]

147. Shen, Y.L.; Gan, Y.; Gao, H.F.; Fan, Y.C.; Wang, Q.; Yuan, H.; Song, Y.F.; Wang, J.D.; Tu, H. TNFSF9 exerts an inhibitory effect on hepatocellular carcinoma. *J. Dig. Dis.* **2017**, *18*, 395–403. [CrossRef] [PubMed]

148. Helms, M.W.; Kemming, D.; Pospisil, H.; Vogt, U.; Buerger, H.; Korsching, E.; Liedtke, C.; Schlotter, C.M.; Wang, A.; Chan, S.Y.; et al. Squalene epoxidase, located on chromosome 8q24.1, is upregulated in 8q+ breast cancer and indicates poor clinical outcome in stage I and II disease. *Br. J. Cancer* **2008**, *99*, 774–780. [CrossRef]

149. Simony-Lafontaine, J.; Esslimani, M.; Bribes, E.; Gourgou, S.; Lequeux, N.; Lavail, R.; Grenier, J.; Kramar, A.; Casellas, P. Immunocytochemical assessment of sigma-1 receptor and human sterol isomerase in breast cancer and their relationship with a series of prognostic factors. *Br. J. Cancer* **2000**, *82*, 1958–1966. [CrossRef]

150. Maia, C.J.; Socorro, S.; Schmitt, F.; Santos, C.R. STEAP1 is over-expressed in breast cancer and down-regulated by 17beta-estradiol in MCF-7 cells and in the rat mammary gland. *Endocrine* **2008**, *34*, 108–116. [CrossRef]

151. Friedline, J.A.; Garrett, S.H.; Somji, S.; Todd, J.H.; Sens, D.A. Differential expression of the MT-1E gene in estrogen-receptor-positive and -negative human breast cancer cell lines. *Am. J. Pathol.* **1998**, *152*, 23–27. [PubMed]

152. Jadhav, R.R.; Ye, Z.; Huang, R.L.; Liu, J.; Hsu, P.Y.; Huang, Y.W.; Rangel, L.B.; Lai, H.C.; Roa, J.C.; Kirma, N.B.; et al. Genome-wide DNA methylation analysis reveals estrogen-mediated epigenetic repression of metallothionein-1 gene cluster in breast cancer. *Clin. Epigenet.* **2015**, *7*, 13. [CrossRef] [PubMed]

153. Krześlak, A.; Forma, E.; Jóźwiak, P.; Szymczyk, A.; Smolarz, B.; Romanowicz-Makowska, H.; Różański, W.; Bryś, M. Metallothionein 2A genetic polymorphisms and risk of ductal breast cancer. *Clin. Exp. Med.* **2014**, *14*, 107–113. [CrossRef] [PubMed]

154. Duffy, M.J.; Reilly, D.; O'Sullivan, C.; O'Higgins, N.; Fennelly, J.J.; Andreasen, P. Urokinase-plasminogen activator, a new and independent prognostic marker in breast cancer. *Cancer Res.* **1990**, *50*, 6827–6829. [PubMed]

155. Yin, X.; Wolford, C.C.; Chang, Y.S.; McConoughey, S.J.; Ramsey, S.A.; Aderem, A.; Hai, T. ATF3, an adaptive-response gene, enhances TGF{beta} signaling and cancer-initiating cell features in breast cancer cells. *J. Cell Sci.* **2010**, *123*, 3558–3565. [CrossRef] [PubMed]

156. Wang, W.; Huper, G.; Guo, Y.; Murphy, S.K.; Olson, J.A.; Marks, J.R. Analysis of methylation-sensitive transcriptome identifies GADD45a as a frequently methylated gene in breast cancer. *Oncogene* **2005**, *24*, 2705–2714. [CrossRef]

157. Wirtenberger, M.; Tchatchou, S.; Hemminki, K.; Schmutzhard, J.; Sutter, C.; Schmutzler, R.K.; Meindl, A.; Wappenschmidt, B.; Kiechle, M.; Arnold, N.; et al. Associations of genetic variants in the estrogen receptor coactivators PPARGC1A, PPARGC1B and EP300 with familial breast cancer. *Carcinogenesis* **2006**, *27*, 2201–2208. [CrossRef] [PubMed]

158. Xu, C.; Chen, H.; Wang, X.; Gao, J.; Che, Y.; Li, Y.; Ding, F.; Luo, A.; Zhang, S.; Liu, Z. S100A14, a member of the EF-hand calcium-binding proteins, is overexpressed in breast cancer and acts as a modulator of HER2 signaling. *J. Biol. Chem.* **2014**, *289*, 827–837. [CrossRef]

159. Wang, G.; Platt-Higgins, A.; Carroll, J.; de Silva Rudland, S.; Winstanley, J.; Barraclough, R.; Rudland, P.S. Induction of metastasis by S100P in a rat mammary model and its association with poor survival of breast cancer patients. *Cancer Res.* **2006**, *66*, 1199–1207. [CrossRef]

160. Pinilla, S.; Alt, E.; Abdul Khalek, F.J.; Jotzu, C.; Muehlberg, F.; Beckmann, C.; Song, Y.H. Tissue resident stem cells produce CCL5 under the influence of cancer cells and thereby promote breast cancer cell invasion. *Cancer Lett.* **2009**, *284*, 80–85. [CrossRef]

161. Zhu, N.; Zhang, D.; Xie, H.; Zhou, Z.; Chen, H.; Hu, T.; Bai, Y.; Shen, Y.; Yuan, W.; Jing, Q.; et al. Endothelial-specific intron-derived miR-126 is down-regulated in human breast cancer and targets both VEGFA and PIK3R2. *Mol. Cell. Biochem.* **2011**, *351*, 157–164. [CrossRef] [PubMed]

162. Joshi, J.P.; Brown, N.E.; Griner, S.E.; Nahta, R. Growth differentiation factor 15 (GDF15)-mediated HER2 phosphorylation reduces trastuzumab sensitivity of HER2-overexpressing breast cancer cells. *Biochem. Pharmacol.* **2011**, *82*, 1090–1099. [CrossRef] [PubMed]

163. Roberti, M.P.; Barrio, M.M.; Bravo, A.I.; Rocca, Y.S.; Arriaga, J.M.; Bianchini, M.; Mordoh, J.; Levy, E.M. IL-15 and IL-2 increase Cetuximab-mediated cellular cytotoxicity against triple negative breast cancer cell lines expressing EGFR. *Breast Cancer Res. Treat.* **2011**, *130*, 465–475. [CrossRef] [PubMed]

164. Bachmeier, B.E.; Mohrenz, I.V.; Mirisola, V.; Schleicher, E.; Romeo, F.; Höhneke, C.; Jochum, M.; Nerlich, A.G.; Pfeffer, U. Curcumin downregulates the inflammatory cytokines CXCL1 and -2 in breast cancer cells via NFkappaB. *Carcinogenesis* **2008**, *29*, 779–789. [CrossRef] [PubMed]

165. See, A.L.; Chong, P.K.; Lu, S.Y.; Lim, Y.P. CXCL3 is a potential target for breast cancer metastasis. *Curr. Cancer Drug Targets* **2014**, *14*, 294–309. [CrossRef]

166. Martinet, L.; Filleron, T.; Le Guellec, S.; Rochaix, P.; Garrido, I.; Girard, J.P. High endothelial venule blood vessels for tumor-infiltrating lymphocytes are associated with lymphotoxin β-producing dendritic cells in human breast cancer. *J. Immunol.* **2013**, *191*, 2001–2008. [CrossRef] [PubMed]

167. Lloyd, B.H.; Ruddell, C.; Rudland, P.S.; Barraclough, R. S100A3 mRNA expression displays an inverse correlation to breast cancer progression. *Biochem. Soc. Trans.* **1996**, *24*, 340S. [CrossRef]

168. Peng, X.; Fu, H.; Yin, J.; Zhao, Q. CHAF1B knockdown blocks migration in a hepatocellular carcinoma model. *Oncol. Rep.* **2018**, *40*, 405–413. [CrossRef]

169. Wang, Q.; Wen, Y.G.; Li, D.P.; Xia, J.; Zhou, C.Z.; Yan, D.W.; Tang, H.M.; Peng, Z.H. Upregulated INHBA expression is associated with poor survival in gastric cancer. *Med. Oncol.* **2012**, *29*, 77–83. [CrossRef]

170. Lu, R.; Ji, Z.; Li, X.; Qin, J.; Cui, G.; Chen, J.; Zhai, Q.; Zhao, C.; Zhang, W.; Yu, Z. Tumor suppressive microRNA-200a inhibits renal cell carcinoma development by directly targeting TGFB2. *Tumour Biol.* **2015**, *36*, 6691–6700. [CrossRef]

171. Lee, M.; Williams, K.A.; Hu, Y.; Andreas, J.; Patel, S.J.; Zhang, S.; Crawford, N.P. GNL3 and SKA3 are novel prostate cancer metastasis susceptibility genes. *Clin. Exp. Metastasis* **2015**, *32*, 769–782. [CrossRef] [PubMed]

172. Waseem, A.; Ali, M.; Odell, E.W.; Fortune, F.; Teh, M.T. Downstream targets of FOXM1: CEP55 and HELLS are cancer progression markers of head and neck squamous cell carcinoma. *Oral Oncol.* **2010**, *46*, 536–542. [CrossRef] [PubMed]

173. Banerjee, R.; Russo, N.; Liu, M.; Basrur, V.; Bellile, E.; Palanisamy, N.; Scanlon, C.S.; van Tubergen, E.; Inglehart, R.C.; Metwally, T.; et al. Corrigendum: TRIP13 promotes error-prone nonhomologous end joining and induces chemoresistance in head and neck cancer. *Nat. Commun.* **2016**, *7*, 10726. [CrossRef] [PubMed]

174. Yamaguchi, K.; Yamaguchi, R.; Takahashi, N.; Ikenoue, T.; Fujii, T.; Shinozaki, M.; Tsurita, G.; Hata, K.; Niida, A.; Imoto, S.; et al. Overexpression of cohesion establishment factor DSCC1 through E2F in colorectal cancer. *PLoS ONE* **2014**, *9*, e85750. [CrossRef] [PubMed]

175. Li, D.; Frazier, M.; Evans, D.B.; Hess, K.R.; Crane, C.H.; Jiao, L.; Abbruzzese, J.L. Single nucleotide polymorphisms of RecQ1, RAD54L, and ATM genes are associated with reduced survival of pancreatic cancer. *J. Clin. Oncol.* **2006**, *24*, 1720–1728. [CrossRef] [PubMed]

176. Uchida, F.; Uzawa, K.; Kasamatsu, A.; Takatori, H.; Sakamoto, Y.; Ogawara, K.; Shiiba, M.; Tanzawa, H.; Bukawa, H. Overexpression of cell cycle regulator CDCA3 promotes oral cancer progression by enhancing cell proliferation with prevention of G1 phase arrest. *BMC Cancer* **2012**, *12*, 321. [CrossRef]

177. Wang, J.; Guo, X.; Xie, C.; Jiang, J. KIF15 promotes pancreatic cancer proliferation via the MEK-ERK signalling pathway. *Br. J. Cancer* **2017**, *117*, 245–255. [CrossRef]

178. Zeng, C.X.; Fu, S.B.; Feng, W.S.; Zhao, J.Y.; Li, F.X.; Gao, P. TCF19 enhances cell proliferation in hepatocellular carcinoma by activating the ATK/FOXO1 signaling pathway. *Neoplasma* **2018**. [CrossRef]

179. Killian, A.; Sarafan-Vasseur, N.; Sesboüé, R.; Le Pessot, F.; Blanchard, F.; Lamy, A.; Laurent, M.; Flaman, J.M.; Frébourg, T. Contribution of the BOP1 gene, located on 8q24, to colorectal tumorigenesis. *Genes Chromosomes Cancer* **2006**, *45*, 874–881. [CrossRef]

180. Imai, T.; Oue, N.; Nishioka, M.; Mukai, S.; Oshima, T.; Sakamoto, N.; Sentani, K.; Matsusaki, K.; Yoshida, K.; Yasui, W. Overexpression of KIF11 in Gastric Cancer with Intestinal Mucin Phenotype. *Pathobiology* **2017**, *84*, 16–24. [CrossRef]

181. Nguyen, M.H.; Ueda, K.; Nakamura, Y.; Daigo, Y. Identification of a novel oncogene, MMS22L, involved in lung and esophageal carcinogenesis. *Int. J. Oncol.* **2012**, *41*, 1285–1296. [CrossRef] [PubMed]

182. Coltrera, M.D.; Wang, J.; Porter, P.L.; Gown, A.M. Expression of platelet-derived growth factor B-chain and the platelet-derived growth factor receptor beta subunit in human breast tissue and breast carcinoma. *Cancer Res.* **1995**, *55*, 2703–2708. [PubMed]

183. Zhou, W.; Wang, Z.; Shen, N.; Pi, W.; Jiang, W.; Huang, J.; Hu, Y.; Li, X.; Sun, L. Knockdown of ANLN by lentivirus inhibits cell growth and migration in human breast cancer. *Mol. Cell. Biochem.* **2015**, *398*, 11–19. [CrossRef] [PubMed]

184. Arora, A.; Agarwal, D.; Abdel-Fatah, T.M.; Lu, H.; Croteau, D.L.; Moseley, P.; Aleskandarany, M.A.; Green, A.R.; Ball, G.; Rakha, E.A.; et al. RECQL4 helicase has oncogenic potential in sporadic breast cancers. *J. Pathol.* **2016**, *238*, 495–501. [CrossRef] [PubMed]

185. Cheang, M.C.; Chia, S.K.; Voduc, D.; Gao, D.; Leung, S.; Snider, J.; Watson, M.; Davies, S.; Bernard, P.S.; Parker, J.S.; et al. Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. *J. Natl. Cancer Inst.* **2009**, *101*, 736–750. [CrossRef] [PubMed]

186. Hunter, D.J.; Kraft, P.; Jacobs, K.B.; Cox, D.G.; Yeager, M.; Hankinson, S.E.; Wacholder, S.; Wang, Z.; Welch, R.; Hutchinson, A.; et al. A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. *Nat. Genet.* **2007**, *39*, 870–874. [CrossRef] [PubMed]

187. Zhong, Z.; Yeow, W.S.; Zou, C.; Wassell, R.; Wang, C.; Pestell, R.G.; Quong, J.N.; Quong, A.A. Cyclin D1/cyclin-dependent kinase 4 interacts with filamin A and affects the migration and invasion potential of breast cancer cells. *Cancer Res.* **2010**, *70*, 2105–2114. [CrossRef] [PubMed]

188. Perez-Peña, J.; Corrales-Sánchez, V.; Amir, E.; Pandiella, A.; Ocana, A. Ubiquitin-conjugating enzyme E2T (UBE2T) and denticleless protein homolog (DTL) are linked to poor outcome in breast and lung cancers. *Sci. Rep.* **2017**, *7*, 17530. [CrossRef]

189. Mern, D.S.; Hoppe-Seyler, K.; Hoppe-Seyler, F.; Hasskarl, J.; Burwinkel, B. Targeting Id1 and Id3 by a specific peptide aptamer induces E-box promoter activity, cell cycle arrest, and apoptosis in breast cancer cells. *Breast Cancer Res. Treat.* **2010**, *124*, 623–633. [CrossRef]

190. Krupa, R.; Synowiec, E.; Pawlowska, E.; Wozniak, K.; Blasiak, J. Polymorphism of the homologous recombination repair genes RAD51 and XRCC3 in breast cancer. *Exp. Mol. Pathol.* **2009**, *87*, 32–35. [CrossRef]

191. Crawford, N.P.; Ziogas, A.; Peel, D.J.; Hess, J.; Anton-Culver, H.; Hunter, K.W. Germline polymorphisms in SIPA1 are associated with metastasis and other indicators of poor prognosis in breast cancer. *Breast Cancer Res.* **2006**, *8*, R16. [CrossRef] [PubMed]

192. Abdel-Fatah, T.M.A.; Agarwal, D.; Liu, D.X.; Russell, R.; Rueda, O.M.; Liu, K.; Xu, B.; Moseley, P.M.; Green, A.R.; Pockley, A.G.; et al. SPAG5 as a prognostic biomarker and chemotherapy sensitivity predictor in breast cancer: A retrospective, integrated genomic, transcriptomic, and protein analysis. *Lancet Oncol.* **2016**, *17*, 1004–1018. [CrossRef]

193. Larimer, B.M.; Deutscher, S.L. Identification of a Peptide from In vivo Bacteriophage Display with Homology to EGFL6: A Candidate Tumor Vasculature Ligand in Breast Cancer. *J. Mol. Biomark. Diagn.* **2014**, *5*. [CrossRef]

194. Yan, F.; Tan, X.Y.; Geng, Y.; Ju, H.X.; Gao, Y.F.; Zhu, M.C. Inhibition effect of siRNA-downregulated UHRF1 on breast cancer growth. *Cancer Biother. Radiopharm.* **2011**, *26*, 183–189. [CrossRef]

195. Xie, D.; Nakachi, K.; Wang, H.; Elashoff, R.; Koeffler, H.P. Elevated levels of connective tissue growth factor, WISP-1, and CYR61 in primary breast cancers associated with more advanced features. *Cancer Res.* **2001**, *61*, 8917–8923. [PubMed]

196. Tang, F.; Zhang, R.; He, Y.; Zou, M.; Guo, L.; Xi, T. MicroRNA-125b induces metastasis by targeting STARD13 in MCF-7 and MDA-MB-231 breast cancer cells. *PLoS ONE* **2012**, *7*, e35435. [CrossRef]

197. Cooper, W.N.; Dickinson, R.E.; Dallol, A.; Grigorieva, E.V.; Pavlova, T.V.; Hesson, L.B.; Bieche, I.; Broggini, M.; Maher, E.R.; Zabarovsky, E.R.; et al. Epigenetic regulation of the ras effector/tumour suppressor RASSF2 in breast and lung cancer. *Oncogene* **2008**, *27*, 1805–1811. [CrossRef]

198. Park, J.H.; Lin, M.L.; Nishidate, T.; Nakamura, Y.; Katagiri, T. PDZ-binding kinase/T-LAK cell-originated protein kinase, a putative cancer/testis antigen with an oncogenic activity in breast cancer. *Cancer Res.* **2006**, *66*, 9186–9195. [CrossRef]

199. Kong, C.; Wang, C.; Wang, L.; Ma, M.; Niu, C.; Sun, X.; Du, J.; Dong, Z.; Zhu, S.; Lu, J.; et al. NEDD9 is a positive regulator of epithelial-mesenchymal transition and promotes invasion in aggressive breast cancer. *PLoS ONE* **2011**, *6*, e22666. [CrossRef]

200. Li, Y.; Lu, W.; Chen, D.; Boohaker, R.J.; Zhai, L.; Padmalayam, I.; Wennerberg, K.; Xu, B.; Zhang, W. KIFC1 is a novel potential therapeutic target for breast cancer. *Cancer Biol. Ther.* **2015**, *16*, 1316–1322. [CrossRef]

201. Ye, L.; Guo, L.; He, Z.; Wang, X.; Lin, C.; Zhang, X.; Wu, S.; Bao, Y.; Yang, Q.; Song, L.; et al. Upregulation of E2F8 promotes cell proliferation and tumorigenicity in breast cancer by modulating G1/S phase transition. *Oncotarget* **2016**, *7*, 23757–23771. [CrossRef] [PubMed]

202. Weinstat-Saslow, D.L.; Zabrenetzky, V.S.; VanHoutte, K.; Frazier, W.A.; Roberts, D.D.; Steeg, P.S. Transfection of thrombospondin 1 complementary DNA into a human breast carcinoma cell line reduces primary tumor growth, metastatic potential, and angiogenesis. *Cancer Res.* **1994**, *54*, 6504–6511. [PubMed]

203. García, M.J.; Fernández, V.; Osorio, A.; Barroso, A.; Fernández, F.; Urioste, M.; Benítez, J. Mutational analysis of FANCL, FANCM and the recently identified FANCI suggests that among the 13 known Fanconi Anemia genes, only FANCD1/BRCA2 plays a major role in high-risk breast cancer predisposition. *Carcinogenesis* **2009**, *30*, 1898–1902. [CrossRef] [PubMed]

204. Zhang, X.; Pan, Y.; Fu, H.; Zhang, J. Nucleolar and Spindle Associated Protein 1 (NUSAP1) Inhibits Cell Proliferation and Enhances Susceptibility to Epirubicin In Invasive Breast Cancer Cells by Regulating Cyclin D Kinase (CDK1) and DLGAP5 Expression. *Med. Sci. Monit.* **2018**, *24*, 8553–8564. [CrossRef] [PubMed]

205. McInnes, N.; Sadlon, T.J.; Brown, C.Y.; Pederson, S.; Beyer, M.; Schultze, J.L.; McColl, S.; Goodall, G.J.; Barry, S.C. FOXP3 and FOXP3-regulated microRNAs suppress SATB1 in breast cancer cells. *Oncogene* **2012**, *31*, 1045–1054. [CrossRef] [PubMed]

206. Corpet, A.; De Koning, L.; Toedling, J.; Savignoni, A.; Berger, F.; Lemaître, C.J.; O'Sullivan, R.J.; Karlseder, J.; Barillot, E.; Asselain, B.; et al. Asf1b, the necessary Asf1 isoform for proliferation, is predictive of outcome in breast cancer. *EMBO J.* **2011**, *30*, 480–493. [CrossRef]

207. Ye, Q.; Holowatyj, A.; Wu, J.; Liu, H.; Zhang, L.; Suzuki, T.; Yang, Z.Q. Genetic alterations of KDM4 subfamily and therapeutic effect of novel demethylase inhibitor in breast cancer. *Am. J. Cancer Res.* **2015**, *5*, 1519–1530. [PubMed]

208. Yang, G.D.; Yang, X.M.; Lu, H.; Ren, Y.; Ma, M.Z.; Zhu, L.Y.; Wang, J.H.; Song, W.W.; Zhang, W.M.; Zhang, R.; et al. SERPINA3 promotes endometrial cancer cells growth by regulating G2/M cell cycle checkpoint and apoptosis. *Int. J. Clin. Exp. Pathol.* **2014**, *7*, 1348–1358.

209. Neubauer, N.L.; Ward, E.C.; Patel, P.; Lu, Z.; Lee, I.; Blok, L.J.; Schink, J.; Kim, J.J. Progesterone receptor-B induction of BIRC3 protects endometrial cancer cells from AP1-59-mediated apoptosis. *Horm. Cancer* **2011**, *2*, 170–181. [CrossRef]

210. Han, J.; Zhang, L.; Zhang, J.; Jiang, Q.; Tong, D.; Wang, X.; Gao, X.; Zhao, L.; Huang, C. CREBRF promotes the proliferation of human gastric cancer cells via the AKT signaling pathway. *Cell. Mol. Biol.* **2018**, *64*, 40–45. [CrossRef]

211. Lai, K.C.; Liu, C.J.; Lin, T.J.; Mar, A.C.; Wang, H.H.; Chen, C.W.; Hong, Z.X.; Lee, T.C. Blocking TNF-α inhibits angiogenesis and growth of IFIT2-depleted metastatic oral squamous cell carcinoma cells. *Cancer Lett.* **2016**, *370*, 207–215. [CrossRef] [PubMed]

212. Simonetti, O.; Goteri, G.; Lucarini, G.; Filosa, A.; Pieramici, T.; Rubini, C.; Biagini, G.; Offidani, A. Potential role of CCL27 and CCR10 expression in melanoma progression and immune escape. *Eur. J. Cancer* **2006**, *42*, 1181–1187. [CrossRef] [PubMed]

213. Qiu, G.; Sun, W.; Zou, Y.; Cai, Z.; Wang, P.; Lin, X.; Huang, J.; Jiang, L.; Ding, X.; Hu, G. RNA interference against TMEM97 inhibits cell proliferation, migration, and invasion in glioma cells. *Tumour Biol.* **2015**, *36*, 8231–8238. [CrossRef] [PubMed]

214. Zhao, C.; Yin, S.; Dong, Y.; Guo, X.; Fan, L.; Ye, M.; Hu, H. Autophagy-dependent EIF2AK3 activation compromises ursolic acid-induced apoptosis through upregulation of MCL1 in MCF-7 human breast cancer cells. *Autophagy* **2013**, *9*, 196–207. [CrossRef] [PubMed]

215. Hellerbrand, C.; Amann, T.; Schlegel, J.; Wild, P.; Bataille, F.; Spruss, T.; Hartmann, A.; Bosserhoff, A.K. The novel gene MIA2 acts as a tumour suppressor in hepatocellular carcinoma. *Gut* **2008**, *57*, 243–251. [CrossRef] [PubMed]

216. Tajnik, M.; Stražišar, M.; Volavšek, M.; Boštjančič, E.; Glavač, D. BBC3 is down-regulated with increased tumor size independently of p53 expression in head and neck cancer. *Cancer Biomark.* **2012**, *11*, 197–208. [CrossRef] [PubMed]

217. Dar, A.A.; Pradhan, T.N.; Kulkarni, D.P.; Shah, S.U.; Rao, K.V.; Chaukar, D.A.; D'Cruz, A.K.; Chiplunkar, S.V. Extracellular 2′5′-oligoadenylate synthetase 2 mediates T-cell receptor CD3-ζ chain down-regulation via caspase-3 activation in oral cancer. *Immunology* **2016**, *147*, 251–264. [CrossRef]

218. Cho, H.; Chung, J.Y.; Kim, S.; Braunschweig, T.; Kang, T.H.; Kim, J.; Chung, E.J.; Hewitt, S.M.; Kim, J.H. MICA/B and ULBP1 NKG2D ligands are independent predictors of good prognosis in cervical cancer. *BMC Cancer* **2014**, *14*, 957. [CrossRef]

219. Yang, L.; Mu, Y.; Cui, H.; Liang, Y.; Su, X. MiR-9-3p augments apoptosis induced by H2O2 through down regulation of Herpud1 in glioma. *PLoS ONE* **2017**, *12*, e0174839. [CrossRef]

220. Scapoli, L.; Girardi, A.; Rubini, C.; Martinelli, M.; Spinelli, G.; Palmieri, A.; Lo Muzio, L.; Carinci, F. LOH at PDCD4, CTNNB1, and CASP4 loci contributes to stage progression of oral cancer. *Int. J. Immunopathol. Pharmacol.* **2011**, *24*, 89–93. [CrossRef]

221. Roh, S.A.; Park, I.J.; Yoon, Y.S.; Kwon, Y.H.; Chung, J.H.; Kim, T.W.; Cho, D.H.; Lim, B.H.; Kim, S.K.; Kim, S.Y.; et al. Feasibility of novel PPP1R15A and proposed ANXA11 single nucleotide polymorphisms as predictive markers for bevacizumab regimen in metastatic colorectal cancer. *J. Cancer Res. Clin. Oncol.* **2016**, *142*, 1705–1714. [CrossRef] [PubMed]

222. Olsen, R.S.; Andersson, R.E.; Zar, N.; Löfgren, S.; Wågsäter, D.; Matussek, A.; Dimberg, J. Prognostic significance of PLA2G4C gene polymorphism in patients with stage II colorectal cancer. *Acta Oncol.* **2016**, *55*, 474–479. [CrossRef] [PubMed]

223. Both, J.; Krijgsman, O.; Bras, J.; Schaap, G.R.; Baas, F.; Ylstra, B.; Hulsebos, T.J. Focal chromosomal copy number aberrations identify CMTM8 and GPR177 as new candidate driver genes in osteosarcoma. *PLoS ONE* **2014**, *9*, e115835. [CrossRef] [PubMed]

224. Lee, M.H.; Yang, H.I.; Lu, S.N.; Lin, Y.J.; Jen, C.L.; Wong, K.H.; Chan, S.Y.; Chen, L.C.; Wang, L.Y.; L'Italien, G.; et al. Polymorphisms near the IFNL3 Gene Associated with HCV RNA Spontaneous Clearance and Hepatocellular Carcinoma Risk. *Sci. Rep.* **2015**, *5*, 17030. [CrossRef] [PubMed]

225. Kim, M.S.; Jeong, E.G.; Ahn, C.H.; Kim, S.S.; Lee, S.H.; Yoo, N.J. Frameshift mutation of UVRAG, an autophagy-related gene, in gastric carcinomas with microsatellite instability. *Hum. Pathol.* **2008**, *39*, 1059–1063. [CrossRef] [PubMed]

226. Giannakis, M.; Hodis, E.; Jasmine Mu, X.; Yamauchi, M.; Rosenbluh, J.; Cibulskis, K.; Saksena, G.; Lawrence, M.S.; Qian, Z.R.; Nishihara, R.; et al. RNF43 is frequently mutated in colorectal and endometrial cancers. *Nat. Genet.* **2014**, *46*, 1264–1266. [CrossRef]

227. Antony, P.; Rose, M.; Heidenreich, A.; Knüchel, R.; Gaisa, N.T.; Dahl, E. Epigenetic inactivation of ST6GAL1 in human bladder cancer. *BMC Cancer* **2014**, *14*, 901. [CrossRef]

228. Zahnow, C.A. CCAAT/enhancer-binding protein beta: Its role in breast cancer and associations with receptor tyrosine kinases. *Expert Rev. Mol. Med.* **2009**, *11*, e12. [CrossRef]

229. Krumpel, M.; Reithmeier, A.; Senge, T.; Baeumler, T.A.; Frank, M.; Nyholm, P.G.; Ek-Rylander, B.; Andersson, G. The small chemical enzyme inhibitor 5-phenylnicotinic acid/CD13 inhibits cell migration and invasion of tartrate-resistant acid phosphatase/ACP5-overexpressing MDA-MB-231 breast cancer cells. *Exp. Cell Res.* **2015**, *339*, 154–162. [CrossRef]

230. Nagata, T.; Shimada, Y.; Sekine, S.; Hori, R.; Matsui, K.; Okumura, T.; Sawada, S.; Fukuoka, J.; Tsukada, K. Prognostic significance of NANOG and KLF4 for breast cancer. *Breast Cancer* **2014**, *21*, 96–101. [CrossRef]

231. Wang, Y.; Cai, X.; Zhang, S.; Cui, M.; Liu, F.; Sun, B.; Zhang, W.; Zhang, X.; Ye, L. HBXIP up-regulates ACSL1 through activating transcriptional factor Sp1 in breast cancer. *Biochem. Biophys. Res. Commun.* **2017**, *484*, 565–571. [CrossRef]

232. Luker, K.E.; Pica, C.M.; Schreiber, R.D.; Piwnica-Worms, D. Overexpression of IRF9 confers resistance to antimicrotubule agents in breast cancer cells. *Cancer Res.* **2001**, *61*, 6540–6547.

233. Chang, Y.W.; Tseng, C.F.; Wang, M.Y.; Chang, W.C.; Lee, C.C.; Chen, L.T.; Hung, M.C.; Su, J.L. Deacetylation of HSPA5 by HDAC6 leads to GP78-mediated HSPA5 ubiquitination at K447 and suppresses metastasis of breast cancer. *Oncogene* **2016**, *35*, 1517–1528. [CrossRef] [PubMed]

234. Rosette, C.; Roth, R.B.; Oeth, P.; Braun, A.; Kammerer, S.; Ekblom, J.; Denissenko, M.F. Role of ICAM1 in invasion of human breast cancer cells. *Carcinogenesis* **2005**, *26*, 943–950. [CrossRef] [PubMed]

235. Ogony, J.; Choi, H.J.; Lui, A.; Cristofanilli, M.; Lewis-Wambi, J. Interferon-induced transmembrane protein 1 (IFITM1) overexpression enhances the aggressive phenotype of SUM149 inflammatory breast cancer cells in a signal transducer and activator of transcription 2 (STAT2)-dependent manner. *Breast Cancer Res.* **2016**, *18*, 25. [CrossRef]

236. Danish, H.H.; Goyal, S.; Taunk, N.K.; Wu, H.; Moran, M.S.; Haffty, B.G. Interferon-induced protein with tetratricopeptide repeats 1 (IFIT1) as a prognostic marker for local control in T1-2 N0 breast cancer treated with breast-conserving surgery and radiation therapy (BCS + RT). *Breast J.* **2013**, *19*, 231–239. [CrossRef]

237. Bektas, N.; Noetzel, E.; Veeck, J.; Press, M.F.; Kristiansen, G.; Naami, A.; Hartmann, A.; Dimmler, A.; Beckmann, M.W.; Knüchel, R.; et al. The ubiquitin-like molecule interferon-stimulated gene 15 (ISG15) is a potential prognostic marker in human breast cancer. *Breast Cancer Res.* **2008**, *10*, R58. [CrossRef] [PubMed]

238. Nagelkerke, A.; Bussink, J.; Mujcic, H.; Wouters, B.G.; Lehmann, S.; Sweep, F.C.; Span, P.N. Hypoxia stimulates migration of breast cancer cells via the PERK/ATF4/LAMP3-arm of the unfolded protein response. *Breast Cancer Res.* **2013**, *15*, R2. [CrossRef] [PubMed]

239. Madeleine, M.M.; Johnson, L.G.; Malkki, M.; Resler, A.J.; Petersdorf, E.W.; McKnight, B.; Malone, K.E. Genetic variation in proinflammatory cytokines IL6, IL6R, TNF-region, and TNFRSF1A and risk of breast cancer. *Breast Cancer Res Treat.* **2011**, *129*, 887–899. [CrossRef] [PubMed]

240. Godoy, P.; Cadenas, C.; Hellwig, B.; Marchan, R.; Stewart, J.; Reif, R.; Lohr, M.; Gehrmann, M.; Rahnenführer, J.; Schmidt, M.; et al. Interferon-inducible guanylate binding protein (GBP2) is associated with better prognosis in breast cancer and indicates an efficient T cell response. *Breast Cancer* **2014**, *21*, 491–499. [CrossRef]

241. Bouker, K.B.; Skaar, T.C.; Riggins, R.B.; Harburger, D.S.; Fernandez, D.R.; Zwart, A.; Wang, A.; Clarke, R. Interferon regulatory factor-1 (IRF-1) exhibits tumor suppressor activities in breast cancer associated with caspase activation and induction of apoptosis. *Carcinogenesis* **2005**, *26*, 1527–1535. [CrossRef] [PubMed]

242. Gaur, S.; Shively, J.E.; Yen, Y.; Gaur, R.K. Altered splicing of CEACAM1 in breast cancer: Identification of regulatory sequences that control splicing of CEACAM1 into long or short cytoplasmic domain isoforms. *Mol. Cancer* **2008**, *7*, 46. [CrossRef] [PubMed]

243. Yu, S.E.; Park, S.H.; Jang, Y.K. Epigenetic silencing of TNFSF7 (CD70) by DNA methylation during progression to breast cancer. *Mol. Cells* **2010**, *29*, 217–221. [CrossRef] [PubMed]

244. Dong, C.; Yuan, L.; Dai, J.; Lai, L.; Mao, L.; Xiang, S.; Rowan, B.; Hill, S.M. Melatonin inhibits mitogenic cross-talk between retinoic acid-related orphan receptor alpha (RORalpha) and ERalpha in MCF-7 human breast cancer cells. *Steroids* **2010**, *75*, 944–951. [CrossRef] [PubMed]

245. Vendrell, J.A.; Ghayad, S.; Ben-Larbi, S.; Dumontet, C.; Mechti, N.; Cohen, P.A. A20/TNFAIP3, a new estrogen-regulated gene that confers tamoxifen resistance in breast cancer cells. *Oncogene* **2007**, *26*, 4656–4667. [CrossRef] [PubMed]

246. Shi, B.; Vinyals, A.; Alia, P.; Broceño, C.; Chen, F.; Adrover, M.; Gelpi, C.; Price, J.E.; Fabra, A. Differential expression of MHC class II molecules in highly metastatic breast cancer cells is mediated by the regulation of the CIITA transcription Implication of CIITA in tumor and metastasis development. *Int. J. Biochem. Cell Biol.* **2006**, *38*, 544–562. [CrossRef] [PubMed]

247. Liu, X.X.; Li, X.J.; Zhang, B.; Liang, Y.J.; Zhou, C.X.; Cao, D.X.; He, M.; Chen, G.Q.; He, J.R.; Zhao, Q. MicroRNA-26b is underexpressed in human breast cancer and induces cell apoptosis by targeting SLC7A11. *FEBS Lett.* **2011**, *585*, 1363–1367. [CrossRef] [PubMed]

248. Naderi, A. Coagulation factor VII is regulated by androgen receptor in breast cancer. *Exp. Cell Res.* **2015**, *331*, 239–250. [CrossRef]

249. Feng, Y.H.; Chen, W.Y.; Kuo, Y.H.; Tung, C.L.; Tsao, C.J.; Shiau, A.L.; Wu, C.L. Elovl6 is a poor prognostic predictor in breast cancer. *Oncol. Lett.* **2016**, *12*, 207–212. [CrossRef]

250. Zhao, X.; Liu, X.; Su, L. Parthenolide induces apoptosis via TNFRSF10B and PMAIP1 pathways in human lung cancer cells. *J. Exp. Clin. Cancer Res.* **2014**, *33*, 3. [CrossRef]

251. Qian, X.L.; Li, Y.Q.; Yu, B.; Gu, F.; Liu, F.F.; Li, W.D.; Zhang, X.M.; Fu, L. Syndecan binding protein (SDCBP) is overexpressed in estrogen receptor negative breast cancers, and is a potential promoter for tumor proliferation. *PLoS ONE* **2013**, *8*, e60046. [CrossRef] [PubMed]

252. Stojadinovic, A.; Hooke, J.A.; Shriver, C.D.; Nissan, A.; Kovatich, A.J.; Kao, T.C.; Ponniah, S.; Peoples, G.E.; Moroni, M. HYOU1/Orp150 expression in breast cancer. *Med. Sci. Monit.* **2007**, *13*, BR231–BR239.

253. Diarra-Mehrpour, M.; Arrabal, S.; Jalil, A.; Pinson, X.; Gaudin, C.; Piétu, G.; Pitaval, A.; Ripoche, H.; Eloit, M.; Dormont, D.; et al. Prion protein prevents human breast carcinoma cell line from tumor necrosis factor alpha-induced cell death. *Cancer Res.* **2004**, *64*, 719–727. [CrossRef] [PubMed]

254. Kotsopoulos, J.; Ghadirian, P.; El-Sohemy, A.; Lynch, H.T.; Snyder, C.; Daly, M.; Domchek, S.; Randall, S.; Karlan, B.; Zhang, P.; et al. The CYP1A2 genotype modifies the association between coffee consumption and breast cancer risk among BRCA1 mutation carriers. *Cancer Epidemiol. Biomark. Prev.* **2007**, *16*, 912–926. [CrossRef] [PubMed]

255. Thompson, H.G.; Harris, J.W.; Wold, B.J.; Lin, F.; Brody, J.P. p62 overexpression in breast tumors and regulation by prostate-derivedEts factor in breast cancer cells. *Oncogene* **2003**, *22*, 2322–2333. [CrossRef]

256. Suzuki, S.; Takagi, K.; Miki, Y.; Onodera, Y.; Akahira, J.; Ebata, A.; Ishida, T.; Watanabe, M.; Sasano, H.; Suzuki, T. Nucleobindin 2 in human breast carcinoma as a potent prognostic factor. *Cancer Sci.* **2012**, *103*, 136–143. [CrossRef]

257. Wang, S.; Chen, F.; Tang, L. IL-32 promotes breast cancer cell growth and invasiveness. *Oncol. Lett.* **2015**, *9*, 305–307. [CrossRef]

258. Roberti, M.P.; Rocca, Y.S.; Amat, M.; Pampena, M.B.; Loza, J.; Coló, F.; Fabiano, V.; Loza, C.M.; Arriaga, J.M.; Bianchini, M.; et al. IL-2- or IL-15-activated NK cells enhance Cetuximab-mediated activity against triple-negative breast cancer in xenografts and in breast cancer patients. *Breast Cancer Res. Treat.* **2012**, *136*, 659–671. [CrossRef]

259. Dalamaga, M. Nicotinamide phosphoribosyl-transferase/visfatin: A missing link between overweight/obesity and postmenopausal breast cancer? Potential preventive and therapeutic perspectives and challenges. *Med. Hypotheses* **2012**, *79*, 617–621. [CrossRef]

260. Puvirajesinghe, T.M.; Bertucci, F.; Jain, A.; Scerbo, P.; Belotti, E.; Audebert, S.; Sebbagh, M.; Lopez, M.; Brech, A.; Finetti, P.; et al. Identification of p62/SQSTM1 as a component of non-canonical Wnt VANGL2-JNK signaling in breast cancer. *Nat. Commun.* **2016**, *7*, 10318. [CrossRef]

261. Ajona, D.; Castaño, Z.; Garayoa, M.; Zudaire, E.; Pajares, M.J.; Martinez, A.; Cuttitta, F.; Montuenga, L.M.; Pio, R. Expression of complement factor H by lung cancer cells: Effects on the activation of the alternative pathway of complement. *Cancer Res.* **2004**, *64*, 6310–6318. [CrossRef] [PubMed]

262. Othman, E.Q.; Kaur, G.; Mutee, A.F.; Muhammad, T.S.; Tan, M.L. Immunohistochemical expression of MAP1LC3A and MAP1LC3B protein in breast carcinoma tissues. *J. Clin. Lab. Anal.* **2009**, *23*, 249–258. [CrossRef] [PubMed]

263. Lv, P.; Qiu, X.; Gu, Y.; Yang, X.; Xu, X.; Yang, Y. Long non-coding RNA SNHG6 enhances cell proliferation, migration and invasion by regulating miR-26a-5p/MAPK6 in breast cancer. *Biomed. Pharmacother.* **2018**, *110*, 294–301. [CrossRef] [PubMed]

264. Nagai, M.A.; Gerhard, R.; Fregnani, J.H.; Nonogaki, S.; Rierger, R.B.; Netto, M.M.; Soares, F.A. Prognostic value of NDRG1 and SPARC protein expression in breast cancer patients. *Breast Cancer Res. Treat.* **2011**, *126*, 1–14. [CrossRef] [PubMed]

265. Shima, N.; Buske, T.R.; Schimenti, J.C. Genetic screen for chromosome instability in mice: Mcm4 and breast cancer. *Cell Cycle* **2007**, *6*, 1135–1140. [CrossRef] [PubMed]

266. McCaig, C.; Perks, C.M.; Holly, J.M. Intrinsic actions of IGFBP-3 and IGFBP-5 on Hs578T breast cancer epithelial cells: Inhibition or accentuation of attachment and survival is dependent upon the presence of fibronectin. *J. Cell Sci.* **2002**, *115*, 4293–4303. [CrossRef] [PubMed]

267. Knight, J.A.; Onay, U.V.; Wells, S.; Li, H.; Shi, E.J.; Andrulis, I.L.; Ozcelik, H. Genetic variants of GPX1 and SOD2 and breast cancer risk at the Ontario site of the Breast Cancer Family Registry. *Cancer Epidemiol. Biomark. Prev.* **2004**, *13*, 146–149. [CrossRef]

268. Li, X.; Xiao, R.; Tembo, K.; Hao, L.; Xiong, M.; Pan, S.; Yang, X.; Yuan, W.; Xiong, J.; Zhang, Q. PEG10 promotes human breast cancer cell proliferation, migration and invasion. *Int. J. Oncol.* **2016**, *48*, 1933–1942. [CrossRef]

269. Chen, Y.; Hughes-Fulford, M. Human prostate cancer cells lack feedback regulation of low-density lipoprotein receptor and its regulator, SREBP2. *Int. J. Cancer* **2001**, *91*, 41–45. [CrossRef]

270. Watkins, G.; Douglas-Jones, A.; Mansel, R.E.; Jiang, W.G. Expression of thromboxane synthase, TBXAS1 and the thromboxane A2 receptor, TBXA2R, in human breast cancer. *Int. Semin. Surg. Oncol.* **2005**, *2*, 23. [CrossRef]