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Article

MicroRNA-Regulated Protein-Protein Interaction Networks and Their Functions in Breast Cancer

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Abstract: MicroRNAs, which are small endogenous RNA regulators, have been associated with various types of cancer. Breast cancer is a major health threat for women worldwide. Many miRNAs were reported to be associated with the progression and carcinogenesis of breast cancer. In this study, we aimed to discover novel breast cancer-related miRNAs and to elucidate their functions. First, we identified confident miRNA-target pairs by combining data from miRNA target prediction databases and expression profiles of miRNA and mRNA. Then, miRNA-regulated protein interaction networks (PINs) were constructed with confident pairs and known interaction data in the human protein reference database (HPRD). Finally, the functions of miRNA-regulated PINs were elucidated by functional enrichment analysis. From the results, we identified some previously reported breast cancer-related miRNAs and functions of the PINs, e.g., miR-125b, miR-125a,

miR-21, and miR-497. Some novel miRNAs without known association to breast cancer were also found, and the putative functions of their PINs were also elucidated. These include miR-139 and miR-383. Furthermore, we validated our results by receiver operating characteristic (ROC) curve analysis using our miRNA expression profile data, gene expression-based outcome for breast cancer online (GOBO) survival analysis, and a literature search. Our results may provide new insights for research in breast cancer-associated miRNAs.

Keywords: miRNA; breast cancer; protein interaction network; functional analysis

1. Introduction

Breast cancer is a global health threat for women. According to a 2008 survey [1], breast cancer was the leading cause of cancer deaths in women. Our knowledge of possible risk factors has led to developments in diagnostic methods, drugs, and surgery procedures for treatment [2,3]; however, the details of breast carcinoma progression, and perhaps most importantly, how to cure breast cancer, remain elusive.

Previous research has identified a number of risk factors for breast cancer. Early menarche, late menopause, obesity, late first full pregnancy, and hormone replacement therapy were considered as high risk factors for breast cancer [2]. Breast cancer risk has also been reported to be related to fat intake in diets rich in red meats and high-fat dairy foods [3].

MicroRNAs (miRNAs) [4], are short endogenous non-coding RNAs which are able to regulate gene expression. After miRNA precursors are transcribed from the genome or generated from spliceosomes, they are exported to the cytoplasm and further processed by the Dicer complex [5]. The mature miRNA is then bound to Argonaute protein, forming a miRNA-protein complex known as the RNA-induced silencing complex (RISC) [6], miRNP, or RNAi (RNA interference) enzyme complex [7,8]. The RISC has been reported to down-regulate target genes by translational repression [9] or mRNA cleavage [10].

Like other protein-based regulators, miRNAs have been associated with cancer. Calin *et al.*, reported that miR-15 and miR-16 were deleted in leukemia [11], which was believed to be one of the earliest reports associating miRNAs with cancer [12]. After this report, many miRNAs were found to act as tumor suppressors or oncogenes (also known as oncomirs). For example, miR-21 was identified as an oncomir in hepatocellular cancer [13], breast cancer [14], and kidney cancer [15]. On the other hand, let-7c was found to be a tumor suppressor in prostate cancer [16], and miR-181a was reported as a tumor suppressor in glioma [17]. Further, miR-125b [18], and miR-145 [19] were identified as tumor suppressors in breast cancer, and miR-125a was found to repress tumor growth in breast cancer [20]. Thus, it is highly likely that miRNAs play an important role in breast cancer.

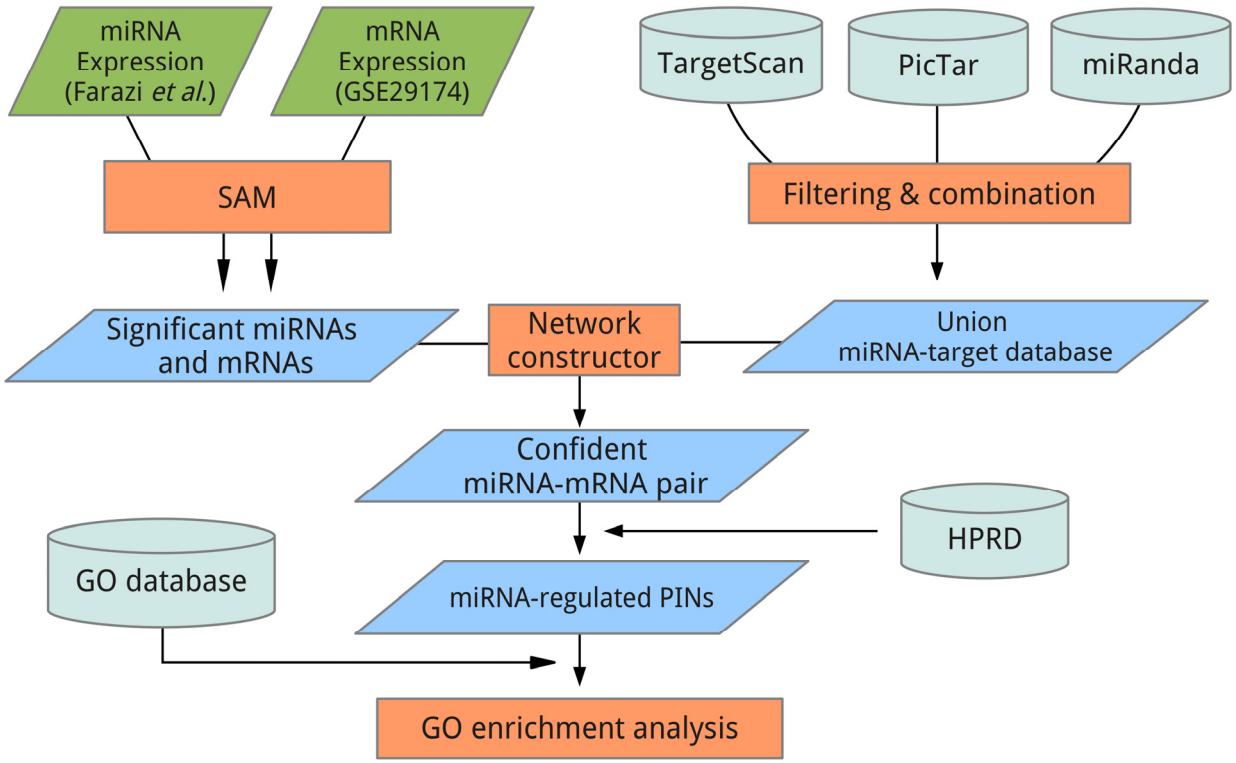
Since miRNA functions by regulating its target genes, we may deduce the effects of miRNAs by analyzing their regulated networks. To use such a method to elucidate miRNA functions, targets of miRNAs should be deduced. Currently, predictions in most target prediction database are based on sequence and statistical methods [21]. For example, in TargetScan, seed base pairing, target site context, conservation of target site and miRNA, and site accessibility are considered in the prediction process [22].

Another method to elucidate miRNA targets is to integrate expression profiles of miRNA and mRNA. In the work of Huang *et al.* [23], a Bayesian-based algorithm, GenMiR++, was developed to predict possible targets of 104 miRNAs in humans. They also verified their results by RT-PCR and microarray experiments. However, the power of other sequence-based target prediction algorithms was not utilized in their work.

It is also possible to combine sequence-based target prediction and expression-based target prediction methods. By integrating expression data into sequence-based predictions, possible false positives can be reduced. Previously, miRNA-mRNA interactions were explored with splitting-averaging Bayesian networks [24]. In that work, expression profiles of miRNA and mRNA from public databases, miRNA target prediction databases, and miRNA sequence information were integrated together to discover miRNA-mRNA interaction networks.

Here, we combined expression profiles of miRNA and mRNA, and three target prediction databases, TargetScan, PicTar and miRanda, to obtain confident miRNA-mRNA relationships and construct miRNA-regulated protein-protein networks for breast cancer. Furthermore, we explored the functions of the miRNAs by inspecting the underlying protein interaction networks (PINs) of the miRNAs with functional enrichment analysis. This method, as described in Figure 1, was used to elucidate the functions of gastric cancer-related miRNAs in our previous work [25]. In that study, a gastric cancer-associated miRNA, miR-148a, was identified and validated as being involved in tumor proliferation, invasion, migration, and the survival rate of the patients. By using a similar method, we aimed to elucidate breast cancer-related miRNA-regulated PINs and their functions.

Figure 1. Analysis flow chart used in this work. After expression profiles and target prediction databases were fetched and preprocessed, they were subjected to the analysis process described here and in the "Experimental Section".



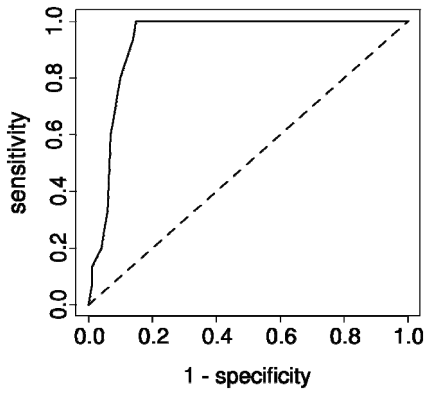
2. Results and Discussion

To construct miRNA-regulated PINs, differentially expressed miRNAs and genes from the dataset from Farazi *et al.* [26] were extracted following proper processing of the expression profiles. From our selected public miRNA dataset, we found 89 down-regulated miRNAs (93 prior to fold-change filtering) and only 1 up-regulated miRNA (Table S1). In gene expression dataset GSE29174, we found a total of 1268 down-regulated genes and 587 up-regulated genes before applying the fold change filter. There were 726 down-regulated genes (Table S2) and 437 up-regulated genes (Table S3) after significantly and differentially expressed genes were filtered by fold change (fold change >2).

From the results of SAM analysis, we identified some well-known breast cancer-related miRNAs (Table S1). For example, miR-214-3p [27] and miR-335-5p [28] have been previously reported to be down-regulated in breast cancer. Let-7c was found to be down-regulated in this work, while let-7a, another member of the let-7 family, was found to be down-regulated in another work [29]. MicroRNAs of the let-7 family were also reportedly down-regulated in several types of cancer [30]. We also found that miR-21-5p, the sole up-regulated miRNA in our list, was also previously found to be up-regulated [14,31]. However, changes in the expression of most of the miRNAs in our down-regulated list have not been reported in the literature. Therefore, we could not rule out the possibility that these miRNAs were novel breast cancer-related miRNAs. There are also some well-known miRNAs not presented in our list (for such a list, one may see [32–34]). The reason that some known miRNAs, for example, miR-19a, miR-155 and miR-205, did not show up in our result might be that we used a very stringent threshold (described in Experimental Section) when selecting differentially expressed miRNAs for PIN construction.

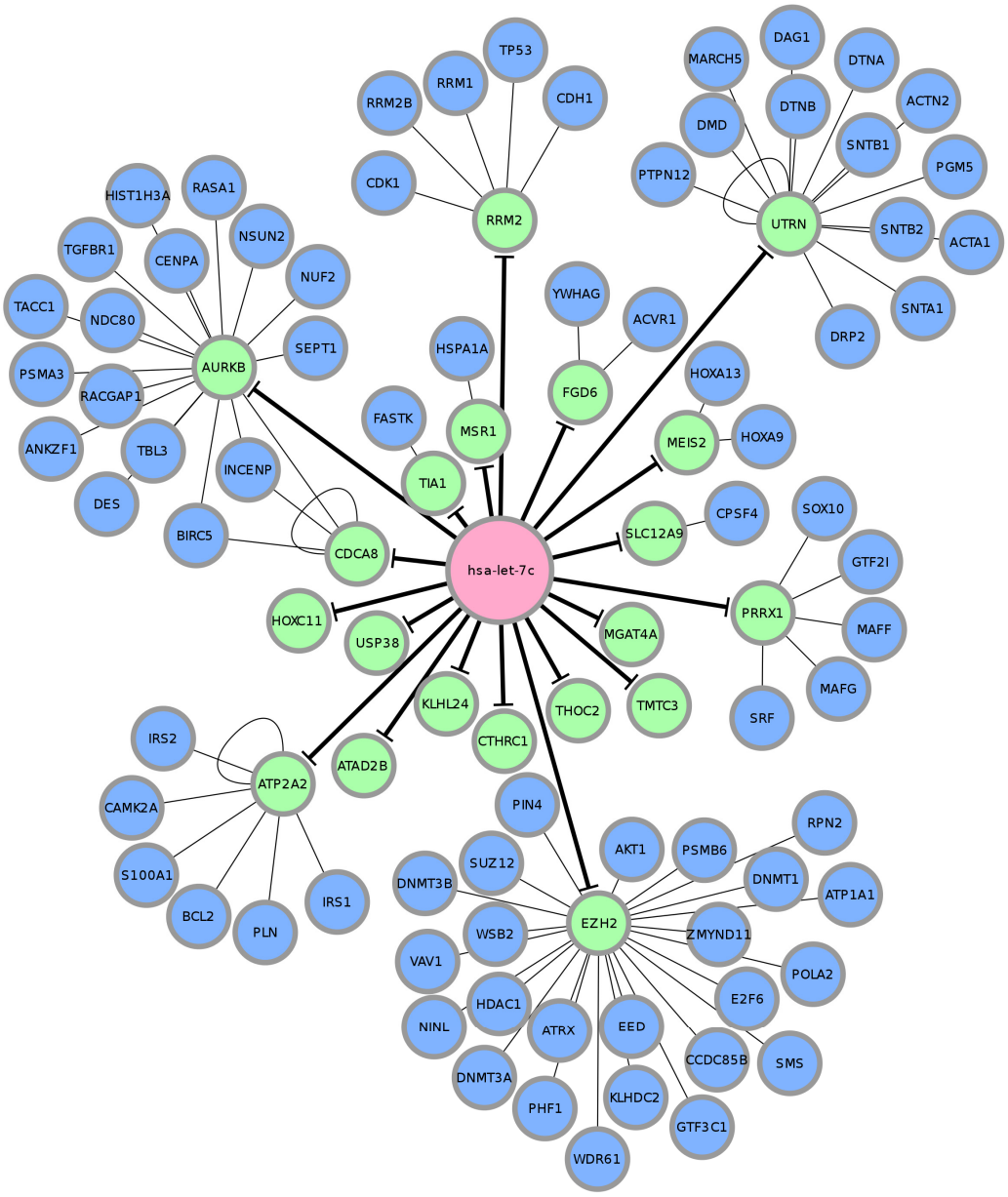
Since the miRNAs of the miRNA-regulated PINs were differentially expressed between normal and tumor tissues, and we identified some cancer-related functions in our functional enrichment analysis, the miRNAs may potentially be useful diagnostic markers for breast cancer. To verify this, we applied ROC curve analysis on the miRNA expression profile that was not used in constructing the miRNA-regulated PINs. Notably, our results (Figures 2 and S1 and Table S4) showed that let-7c (Figure 2), miR-497-5p, miR-125b-5p, and some other miRNAs of miRNA-regulated PINs, performed well when used as breast cancer diagnostic markers.

Figure 2. Receiver operating characteristic (ROC) curve of let-7c from our miRNA array dataset. For ROC curves of other miRNAs, see Figure S1.



Following elucidation of differentially expressed miRNAs and genes, miRNA-regulated PINs could then be constructed. We identified and constructed partial networks, containing the miRNA and its direct target, with the differentially expressed miRNAs and genes as described in the "Experimental Section". We then extended the network by appending known interactions from the HPRD database. Finally, 18 miRNA-regulated PINs were constructed by the steps described above (Figure 3, Figures S2–S13, and Table S5).

Figure 3. The let-7c-regulated protein interaction network (PIN). This is one of the 18 miRNA-regulated PINs constructed in this work. Figures of all other miRNA-regulated PINs are displayed in Supplementary Figures S2–S13.



After construction of the 18 PINs was completed, we observed that the sizes of the PINs were not similar: some of the miRNAs seemed to regulate larger sized PINs, while other miRNAs affected only a small number of genes. Small miRNA-regulated PINs may be caused by the strict *q*-value threshold

set during SAM analysis, the processing steps performed on the target prediction databases discussed previously, and possibly by lack of protein-protein interaction data for some proteins in the HPRD. Although the HPRD may be considered the most comprehensive source of protein-protein interaction data [35], some proteins may not have been considered and researched by other investigators, and therefore, interaction data for those proteins would not be included in the HPRD. However, it may be true that some of the miRNA-regulated PINs were small in breast cancer, since the construction of the PINs were based on differentially expressed miRNAs and genes between normal tissues and tumor samples, and those miRNAs with small PINs may not be as important as others with larger PINs.

To elucidate the functions of a miRNA with a regulated PIN, GO enrichment analysis was applied to the miRNA-regulated PINs. We did not consider the miRNAs with ≤5 genes in their regulated PINs, and some of the miRNA-regulated PINs had no enriched functions using the defined threshold, FDR < 0.0001. To exclude GO terms that describe a broad range of concepts, we only included high level GO terms, *i.e.*, larger than 5.

The results of the GO enrichment analysis for let-7c related to cancer are listed in Table 1. (Results of all miRNA-regulated PINs were in Table S6). We defined a GO term as cancer-related if a GO term contained "cell proliferation", "cell death", "apoptosis", "signaling", "microtubule", and "actin". We noted that 7 miRNAs had enriched GO terms related to apoptosis, cell death, and cell proliferation, *i.e.*, miR-520d-3p, miR-497-5p, miR-125b-5p, miR-21-5p, miR-31-5p, let-7c, and miR-125-5p. Further, some miRNA-regulated PINs may have functions other than cell survival. For example, the nerve growth factor receptor pathway was enriched in miR-regulated PINs of miR-520d-3p, miR-497-5p, miR-125a-5p, miR-125b-5p, and miR-31-5p, and the epidermal growth factor receptor pathway was enriched in miR-regulated PINs of miR-520d-3p, miR-21-5p, and miR-497-5p. Most of the miRNAs had been previously described and were known to be implicated in breast cancer. Let-7c was not only likely to be down-regulated in breast cancer [29], but was also found to be a tumor suppressor in prostate cancer [16]. Another reported tumor suppressor was miR-125b-5p, which was found to be down-regulated in breast tumor tissue [18], and this finding was consistent with our functional enrichment results. The miR-125a-5p-regulated PIN was found to be able to inhibit apoptosis and regulate epithelial cell proliferation, and has been reported to repress cell growth [36].

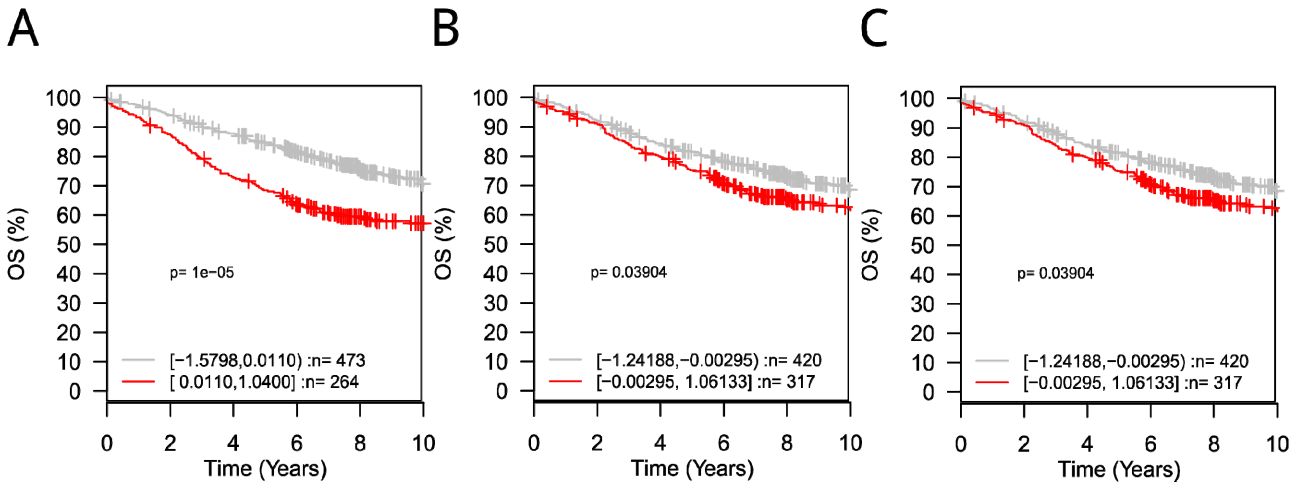
Table 1. Selected enriched functions of let-7c. Member genes of the let-7c-regulated network annotated with corresponding enriched functions are listed.

MIMAT0000064(hsa-let-7c)		
GO term	**Genes**	**Adj. *p*-value**
GO:0043067, Regulation of programmed cell death	RRM2B, ACVR1, TP53, RASA1, TGFBR1, PSMA3, BIRC5, ACTN2, HOXA13, IRS2, FASTK, VAV1, PSMB6, BCL2, CDK1, HDAC1, SOX10, TIA1, AKT1, AURKB	3.43×10^{-8}
GO:0043069, Negative regulation of programmed cell death	RRM2B, ACVR1, TP53, RASA1, TGFBR1, BIRC5, IRS2, BCL2, CDK1, HDAC1, SOX10, AKT1, AURKB	6.58×10^{-6}
GO:0060548, Negative regulation of cell death	RRM2B, ACVR1, TP53, RASA1, TGFBR1, BIRC5, IRS2, BCL2, CDK1, HDAC1, SOX10, AKT1, AURKB	8.92×10^{-6}
GO:0015630, Microtubule cytoskeleton	INCENP, SNTB2, SEPT1, TACC1, BIRC5, RACGAP1, PIN4, CDCA8, CDK1, PHF1, AKT1, AURKB, NINL, CCDC85B	5.15×10^{-5}

We also found that some breast cancer-specific functions were enriched in our results. For example, in the miR-497-5p-regulated PIN, the term "androgen receptor signaling pathway" was enriched. Although it is not clear whether androgens are related to breast cancer, androgen receptors are known to be up-regulated in breast cancer and related to node invasiveness [37].

To further verify the results of the enriched cancer-related functions, we used GOBO for survival analysis. Our hypothesis is that expression of genes annotated with enriched cancer-related terms may be related to survival outcome of patients. With exception to some cell death/proliferation-related terms, it is already known that some pathways or functions are also related to clinical outcomes. For example, cell proliferation-related GO terms have a high probability of affecting survival of cancer tissues, and patient outcome may worsen if cancer tissue survives. In addition, some signaling pathways were known to enhance invasiveness, migration abilities, or were associated with reduced patient survival. For example, the BMP signaling pathway is known to confer various tumor cells with enhanced migration and invasion abilities [38], and nerve growth factor receptor (NGFR) was found to be associated with overall survival of breast cancer [38]. Furthermore, Toll-like receptor 4 has been reported to promote adhesion and invasive migration in breast cancer [39]. Finally, the cytoskeleton plays an important role in regulating cell motility in all cells. Actin filaments are known to participate in the invasive migration of cancer cells [40]. Since some of these functions were present in our enriched terms, we wished to test if the expression of a gene set annotated to the cancer-related enriched terms in the PIN would be related to clinical outcome of patients.

Figure 4. Validation of let-7c result. Gene expression-based outcome for breast cancer online (GOBO) survival analysis of let-7c-regulated PIN members marked with the following functions: (**A**) Microtubule cytoskeleton; (**B**) Negative regulation of programmed cell death; and (**C**) negative regulation of cell death. **Red**: samples with high expression of selected gene set (PIN members); **grey**: samples with low expression of selected gene set (PIN members).



As shown in Figure 4, Figure S14 and Table S7, only some of the enriched terms were significantly associated with clinical outcome. This may be because the changes in these key genes occurred at the protein level, such as in protein expression or even post-translational modification; therefore, mRNA expression-centric tools like GOBO cannot explore association of such genes to clinical outcomes.

Alternatively, it is possible the miRNA did not regulate the whole pathway, or the miRNA did not target the key part of the pathway directly, and thus the clinical outcome of gene sets of the enriched GO terms in this condition cannot be determined. However, some functions associated with clinical outcomes were observed. For example, proteins annotated with the terms "microtubule cytoskeleton", "negative regulation of programmed cell death", and "negative regulation of cell death" in the let-7c-regulated PIN were related to 10 year survival rate of patients, as reported by GOBO (Figure 4). Also, the enriched term "regulation of epithelial cell proliferation" for both miR-125a-5p and miR-125b-5p were found to be associated with the 10-year survival rate of patients. Therefore, these results further supported the GO enrichment analysis discussed previously.

3. Experimental Section

3.1. miRNA Microarray Experiments

We performed a miRNA microarray to obtain the expression profiles for receiver operating characteristic (ROC) curve analysis. This dataset was deposited in Gene Expression Omnibus (GEO, http://www.ncbi.nlm.nih.gov/geo/, Series Accession: GSE45666). In total, there were 15 normal samples and 101 tumor samples in the expression profile. Detailed pathophysiogical characteistics of these samples were in Table S8 and GSE45666. All human tissue samples collected from breast cancer patients were approved and human subject confidentiality was protected by the Institute Review Board of National Taiwan University Hospital (IRB, 20071211R).

Total RNA was extracted from tissues collected from the patients using Trizol® Reagent (Invitrogen, Carlsbad, CA, USA, USA) according to the manufacturer's protocol. Purified RNA was quantified at OD260nm by using a ND-1000 spectrophotometer (Nanodrop Technology, Wilmington, DE, USA) and qualitated by using a Bioanalyzer 2100 with the RNA 6000 Nano LabChip kit (Agilent Technologies, Santa Clara, CA, USA).

After RNA extraction, 100 ng of total RNA was dephosphorylated and labeled with pCp-Cy3 using the Agilent miRNA Complete Labeling and Hyb Kit in conjunction with the microRNA Spike-In kit (Agilent Technologies, Santa Clara, CA, USA). Briefly, 2X hybridization buffer (Agilent Technologies) was added to the labeled mixture to a final volume of 45 μL. The mixture was heated for 5 min at 100 °C and immediately cooled to 0 °C. Each 45 μL sample was hybridized onto an Agilent human miRNA Microarray Release 12.0, 8 × 15 K (Agilent Technologies) at 55 °C for 20 h. After hybridization, slides were washed for 5 min in Gene Expression Wash Buffer 1 at room temperature, then for 5 min in Gene Expression Wash Buffer 2 at 37 °C. Slides were scanned on an Agilent microarray scanner (Agilent Technologies, model G2505C) at 100% and 5% sensitivity settings. Feature Extraction (Agilent Technologies) software version 10.7.3.1 (Agilent Technologies, Santa Clara, CA, USA) was used for image analysis.

3.2. mRNA Expression Profiles

For miRNA-regulated protein-protein interaction network construction, the mRNA expression profile was fetched from GEO (Series Accession: GSE29174). This dataset was produced by Farazi *et al*. [26], which was the only dataset publicly available with large size of tumor samples and

reasonably sized normal samples. In total, 161 clinical samples were collected from breast cancer patients by biopsy: 110 invasive ductal carcinoma (IDC), 11 normal, 17 ductal carcinoma *in situ* (DCIS), 1 mucinous A, 8 atypical medullary, 4 apocrine, 8 metaplastic, and 2 adenoid, as classified by Farazi *et al.* The110 IDC samples were classified as the tumor group and the 11 normal samples were classified as the normal group in this study.

3.3. miRNA Expression Profiles

The miRNA expression profile used in this work was fetched from Table S4A of the work of Farazi *et al*. [26]. There were 189 samples in this dataset, with 6 of them from cell lines, and another 183 samples from patient tissues. In the 183 clinical samples collected from breast cancer patients by biopsy in this dataset, there were 128 IDC, 11 normal, 18 DCIS, 1 mucinous A, 8 atypical medullary, 4 apocrine, 9 metaplastic, and 2 adenoid cases, as classified by Farazi *et al.* The 128 IDC samples were classified as the tumor group and the 11 normal samples as were classified as the normal group.

3.4. Data Analysis

The overall workflow design was similar to the previous work of Tseng *et al*. [25] (see Figure 1). However, we applied the workflow on breast cancer expression profiles instead of gastric cancer as in the work of Tseng *et al.* Additionally, we used 3 miRNA target prediction databases, TargetScan (v6.0) [22,41,42], PicTar [43,44], and miRanda (release August 2010) [45] here, while only TargetScan was used in the previous study.

To construct the networks, we first elucidated differentially expressed miRNAs and mRNAs from published datasets. Both of miRNA (generated with miRNA-Seq technique) and mRNA array expression data were produced by Farazi *et al.* [26] from the same batch of clinical tumor samples. To obtain a list of differentially expressed genes and miRNAs between normal and tumor groups, we used significance analysis of microarrays (SAM) [46] implemented in R package samr (version 2.0; Stanford University, Stanford, CA, USA). We set the false discovery rate (FDR) as ≤0.0001%, fold change as ≥2.5 for miRNA, and fold change as ≥1.9 for genes as thresholds to reduce false positives. If a gene/miRNA was expressed higher in the normal group compared to the tumor group, we defined that gene/miRNA as a down-regulated gene/miRNA, and *vice versa*.

Following this, we paired the miRNAs and mRNAs with different expression trends. For example, an up-regulated miRNA would be paired with a down-regulated mRNA. If such pairs could be found in 2 (or more) of the 3 miRNA target prediction databases, they were then added to their corresponding miRNA-regulated network. To further extend the coverage of our network, we incorporated the human protein reference database (HPRD) [47], which contains experimentally verified interaction data, into our miRNA-regulated PINs.

Finally, we used gene ontology (GO) enrichment analysis to explore the function of the miRNA-regulated PINs. Hypergeometric tests were used to determine if a GO term was enriched in a PIN. In this section, we excluded PINs with less than 5 proteins. We also excluded GO terms with levels of less than 5 to avoid non-specific GO terms. Since we tested multiple GO terms on each miRNA-regulated PIN, we adjusted the significance of the test with the FDR method developed by Benjamini *et al.* [48]. We used the adjusted p-value < 0.0001 as our threshold. A GO term would

be excluded if its *p*-value was larger than 0.0001. Therefore, for each network, we ran the GO enrichment analysis, collected the calculated *p*-values, and adjusted these values using the methods described above.

3.5. ROC and GOBO Survival Analysis

After the PINs were constructed, we attempted to verify our results by literature search, ROC, and GOBO survival analysis [49]. To determine if the miRNAs we found could serve as classification markers for discriminating between normal and tumor samples, we applied ROC analysis on our miRNA array data (described in Section 2.1). ROC analysis is usually used to evaluate the efficiency of a classifier or a biological marker. R package ROCR [50] (version 1.0.4) was used to plot the ROC curve and calculate the area under curve (AUC). The standard error of AUC was then calculated as described in the work of Hanlye and McNeil [51]. The *p*-value of AUC was thus calculated with standard error obtained in the previous step. To further validate if the PINs we found were related to cancer, we used survival analysis implemented in GOBO [49] (available at http://co.bmc.lu.se/gobo), which provides a large amount of breast cancer gene expression profiles collected from public databases with clinical outcome data. In both ROC analysis and GOBO survival analysis, we considered our results significant when the *p*-value was smaller than 0.05.

4. Conclusions

Using integrative analysis of miRNA and mRNA expression profiles, we have identified not only breast cancer-related miRNAs and genes, but also putative roles for miRNAs in cancer as elucidated from miRNA-regulated PINs constructed in this work. Here, some previously known functions of miRNAs were again presented in our results, e.g., the relationship between the miRNAs, let-7c, miR-125a-5p, miR-125b-5p, and miR-21-5p, and breast cancer were demonstrated in this research. Furthermore, we have identified additional miRNAs and their related functions that have not been previously reported or discussed, providing valuable resources for further research in breast cancer.

Acknowledgments

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Information

Table S1. Significantly differentially expressed miRNAs found in miRNA dataset in Farazi *et al*. [26]. There are 89 down-regulated miRNAs and 1 up-regulated miRNA in this list. *Q*-values reported by SAM were 0 for all miRNAs in this list.

miRBase Accession	miRNA Name	Fold Change	miRBase Accession	miRNA Name	Fold Change
MIMAT0004761	hsa-miR-483-5p	0.01	**MIMAT0000077**	hsa-miR-22-3p	0.21
MIMAT0004552	hsa-miR-139-3p	0.01	**MIMAT0000089**	hsa-miR-31-5p	0.21
MIMAT0000738	hsa-miR-383	0.02	**MIMAT0004612**	hsa-miR-186-3p	0.21
MIMAT0002856	hsa-miR-520d-3p	0.02	**MIMAT0004592**	hsa-miR-125b-1-3p	0.22
MIMAT0002811	hsa-miR-202-3p	0.03	**MIMAT0001639**	hsa-miR-409-3p	0.22
MIMAT0002177	hsa-miR-486-5p	0.04	**MIMAT0015032**	hsa-miR-3158-3p	0.22
MIMAT0022721	hsa-miR-1247-3p	0.05	**MIMAT0004496**	hsa-miR-23a-5p	0.22
MIMAT0002175	hsa-miR-485-5p	0.06	**MIMAT0000690**	hsa-miR-296-5p	0.22
MIMAT0000265	hsa-miR-204-5p	0.07	**MIMAT0000731**	hsa-miR-378a-5p	0.23
MIMAT0000752	hsa-miR-328	0.07	**MIMAT0000448**	hsa-miR-136-5p	0.23
MIMAT0000421	hsa-miR-122-5p	0.07	**MIMAT0004796**	hsa-miR-576-3p	0.23
MIMAT0000447	hsa-miR-134	0.08	**MIMAT0010133**	hsa-miR-2110	0.23
MIMAT0000722	hsa-miR-370	0.09	**MIMAT0004951**	hsa-miR-887	0.23
MIMAT0004513	hsa-miR-101-5p	0.09	**MIMAT0003239**	hsa-miR-574-3p	0.25
MIMAT0000446	hsa-miR-127-3p	0.10	**MIMAT0005901**	hsa-miR-1249	0.25
MIMAT0000097	hsa-miR-99a-5p	0.10	**MIMAT0000510**	hsa-miR-320a	0.26
MIMAT0004566	hsa-miR-218-2-3p	0.10	**MIMAT0002172**	hsa-miR-376b	0.26
MIMAT0000729	hsa-miR-376a-3p	0.11	**MIMAT0000250**	hsa-miR-139-5p	0.27
MIMAT0009197	hsa-miR-205-3p	0.11	**MIMAT0005825**	hsa-miR-1180	0.27
MIMAT0004615	hsa-miR-195-3p	0.11	**MIMAT0000437**	hsa-miR-145-5p	0.28
MIMAT0005899	hsa-miR-1247-5p	0.11	**MIMAT0004601**	hsa-miR-145-3p	0.28
MIMAT0000720	hsa-miR-376c	0.12	**MIMAT0003322**	hsa-miR-652-3p	0.28
MIMAT0000762	hsa-miR-324-3p	0.12	**MIMAT0000756**	hsa-miR-326	0.28
MIMAT0004679	hsa-miR-296-3p	0.12	**MIMAT0000098**	hsa-miR-100-5p	0.29
MIMAT0004614	hsa-miR-193a-5p	0.12	**MIMAT0003296**	hsa-miR-627	0.29
MIMAT0003880	hsa-miR-671-5p	0.12	**MIMAT0002820**	hsa-miR-497-5p	0.31
MIMAT0004795	hsa-miR-574-5p	0.12	**MIMAT0004507**	hsa-miR-92a-1-5p	0.31
MIMAT0004599	hsa-miR-143-5p	0.13	**MIMAT0000271**	hsa-miR-214-3p	0.32
MIMAT0000423	hsa-miR-125b-5p	0.13	**MIMAT0004702**	hsa-miR-339-3p	0.33
MIMAT0004957	hsa-miR-760	0.13	**MIMAT0004611**	hsa-miR-185-3p	0.33
MIMAT0004911	hsa-miR-874	0.14	**MIMAT0000064**	hsa-let-7c	0.34
MIMAT0004603	hsa-miR-125b-2-3p	0.15	**MIMAT0004673**	hsa-miR-29c-5p	0.35
MIMAT0004952	hsa-miR-665	0.15	**MIMAT0000733**	hsa-miR-379-5p	0.35
MIMAT0018205	hsa-miR-3928	0.15	**MIMAT0004594**	hsa-miR-132-5p	0.35
MIMAT0004767	hsa-miR-193b-5p	0.15	**MIMAT0000765**	hsa-miR-335-5p	0.35
MIMAT0002861	hsa-miR-518e-3p	0.15	**MIMAT0002819**	hsa-miR-193b-3p	0.36
MIMAT0004604	hsa-miR-127-5p	0.16	**MIMAT0000088**	hsa-miR-30a-3p	0.36
MIMAT0002807	hsa-miR-491-5p	0.16	**MIMAT0005951**	hsa-miR-1307-3p	0.36
MIMAT0004689	hsa-miR-377-5p	0.16	**MIMAT0004597**	hsa-miR-140-3p	0.37
MIMAT0004762	hsa-miR-486-3p	0.16	**MIMAT0004556**	hsa-miR-10b-3p	0.37
MIMAT0000732	hsa-miR-378a-3p	0.17	**MIMAT0000272**	hsa-miR-215	0.37
MIMAT0017981	hsa-miR-3605-5p	0.18	**MIMAT0004511**	hsa-miR-99a-3p	0.37
MIMAT0004605	hsa-miR-129-2-3p	0.19	**MIMAT0000443**	hsa-miR-125a-5p	0.38
MIMAT0006789	hsa-miR-1468	0.20	**MIMAT0004482**	hsa-let-7b-3p	0.38
MIMAT0000737	hsa-miR-382-5p	0.21	**MIMAT0000076**	hsa-miR-21-5p	6.58

Table S2. Down-regulated genes found in dataset GSE29174. There are 726 down-regulated genes in this list. *Q*-values reported by SAM were 0 for all genes in this list.

NCBI gene ID	Gene Symbol	Fold Change	NCBI gene ID	Gene Symbol	Fold Change
2949	GSTM5	0.06	**619373**	MBOAT4	0.17
10894	LYVE1	0.06	**130399**	ACVR1C	0.17
5950	RBP4	0.07	**1646**	AKR1C2	0.17
762	CA4	0.09	**80763**	C12orf39	0.17
54997	TESC	0.09	**2159**	F10	0.18
3489	IGFBP6	0.09	**84889**	SLC7A3	0.18
3952	LEP	0.09	**1308**	COL17A1	0.18
213	ALB	0.09	**83699**	SH3BGRL2	0.18
3131	HLF	0.10	**84417**	C2orf40	0.18
4023	LPL	0.10	**4081**	MAB21L1	0.18
10633	RASL10A	0.11	**3484**	IGFBP1	0.18
364	AQP7	0.11	**5239**	PGM5	0.19
1908	EDN3	0.11	**4969**	OGN	0.19
1811	SLC26A3	0.11	**2719**	GPC3	0.19
91851	CHRDL1	0.11	**116362**	RBP7	0.19
729359	PLIN4	0.13	**948**	CD36	0.19
1149	CIDEA	0.13	**5764**	PTN	0.19
5959	RDH5	0.13	**3043**	HBB	0.19
5348	FXYD1	0.14	**56920**	SEMA3G	0.20
5346	PLIN1	0.14	**94274**	PPP1R14A	0.20
10249	GLYAT	0.14	**57447**	NDRG2	0.20
158800	RHOXF1	0.14	**84795**	PYROXD2	0.20
221476	PI16	0.14	**84649**	DGAT2	0.20
3040	HBA2	0.14	**2690**	GHR	0.20
6939	TCF15	0.14	**22802**	CLCA4	0.20
79645	EFCAB1	0.14	**5179**	PENK	0.20
80343	SEL1L2	0.14	**6663**	SOX10	0.20
9413	FAM189A2	0.15	**6649**	SOD3	0.21
26289	AK5	0.15	**54922**	RASIP1	0.21
25891	PAMR1	0.15	**8406**	SRPX	0.21
3679	ITGA7	0.15	**1446**	CSN1S1	0.21
1264	CNN1	0.15	**7123**	CLEC3B	0.22
92304	SCGB3A1	0.15	**9647**	PPM1F	0.22
2167	FABP4	0.15	**1842**	ECM2	0.22
23285	KIAA1107	0.15	**3909**	LAMA3	0.22
7145	TNS1	0.16	**8639**	AOC3	0.23
4881	NPR1	0.16	**2934**	GSN	0.23
1028	CDKN1C	0.16	**9370**	ADIPOQ	0.23
1036	CDO1	0.16	**3202**	HOXA5	0.23
130271	PLEKHH2	0.16	**9452**	ITM2A	0.23
8736	MYOM1	0.16	**6290**	SAA3P	0.23
8908	GYG2	0.16	**4604**	MYBPC1	0.23

Table S2. *Cont.*

NCBI gene ID	Gene Symbol	Fold Change	NCBI gene ID	Gene Symbol	Fold Change
79785	RERGL	0.16	**1128**	CHRM1	0.23
221091	LRRN4CL	0.17	**83878**	USHBP1	0.24
3991	LIPE	0.17	**63970**	TP53AIP1	0.24
27175	TUBG2	0.24	**79192**	IRX1	0.28
1346	COX7A1	0.24	**3400**	ID4	0.28
6376	CX3CL1	0.24	**57519**	STARD9	0.29
50486	G0S2	0.24	**57666**	FBRSL1	0.29
6285	S100B	0.24	**3590**	IL11RA	0.29
443	ASPA	0.24	**57664**	PLEKHA4	0.29
947	CD34	0.25	**197257**	LDHD	0.29
84632	AFAP1L2	0.25	**66036**	MTMR9	0.29
3866	KRT15	0.25	**2321**	FLT1	0.29
147463	ANKRD29	0.25	**126**	ADH1C	0.29
2878	GPX3	0.25	**1363**	CPE	0.29
7079	TIMP4	0.25	**56131**	PCDHB4	0.29
54345	SOX18	0.25	**22915**	MMRN1	0.29
51277	DNAJC27	0.25	**7069**	THRSP	0.29
84870	RSPO3	0.25	**57161**	PELI2	0.30
55323	LARP6	0.25	**770**	CA11	0.30
6387	CXCL12	0.25	**53342**	IL17D	0.30
137835	TMEM71	0.25	**79987**	SVEP1	0.30
5212	VIT	0.25	**857**	CAV1	0.30
26577	PCOLCE2	0.25	**222166**	C7orf41	0.30
845	CASQ2	0.25	**27190**	IL17B	0.30
6422	SFRP1	0.25	**116159**	CYYR1	0.30
10351	ABCA8	0.26	**4487**	MSX1	0.30
10840	ALDH1L1	0.26	**9068**	ANGPTL1	0.30
65983	GRAMD3	0.26	**10411**	RAPGEF3	0.30
84327	ZBED3	0.26	**3199**	HOXA2	0.30
57124	CD248	0.26	**2944**	GSTM1	0.30
3235	HOXD9	0.26	**2920**	CXCL2	0.30
2192	FBLN1	0.26	**201134**	CEP112	0.31
91653	BOC	0.26	**220001**	VWCE	0.31
4147	MATN2	0.26	**83888**	FGFBP2	0.31
126669	SHE	0.27	**6366**	CCL21	0.31
2788	GNG7	0.27	**6711**	SPTBN1	0.31
129804	FBLN7	0.27	**85378**	TUBGCP6	0.31
270	AMPD1	0.27	**26040**	SETBP1	0.31
79656	BEND5	0.27	**4692**	NDN	0.31
58503	PROL1	0.27	**25890**	ABI3BP	0.31
3316	HSPB2	0.27	**23531**	MMD	0.31
729440	CCDC61	0.27	**30846**	EHD2	0.31
54438	GFOD1	0.27	**6196**	RPS6KA2	0.31
5243	ABCB1	0.27	**2009**	EML1	0.31

Table S2. *Cont.*

NCBI gene ID	Gene Symbol	Fold Change	NCBI gene ID	Gene Symbol	Fold Change
810	CALML3	0.27	**6289**	SAA2	0.31
6898	TAT	0.27	**345275**	HSD17B13	0.31
5648	MASP1	0.28	**2701**	GJA4	0.32
25999	CLIP3	0.28	**112609**	MRAP2	0.32
125875	CLDND2	0.28	**727**	C5	0.32
7102	TSPAN7	0.28	**477**	ATP1A2	0.32
1879	EBF1	0.28	**9627**	SNCAIP	0.32
23252	OTUD3	0.28	**4435**	CITED1	0.32
5493	PPL	0.28	**10974**	C10orf116	0.32
83987	CCDC8	0.28	**11005**	SPINK5	0.32
9073	CLDN8	0.28	**80325**	ABTB1	0.33
221981	THSD7A	0.28	**221395**	GPR116	0.33
64102	TNMD	0.28	**10014**	HDAC5	0.33
137872	ADHFE1	0.33	**1489**	CTF1	0.37
27151	CPAMD8	0.33	**35**	ACADS	0.37
387923	SERP2	0.33	**3749**	KCNC4	0.37
145581	LRFN5	0.33	**140738**	TMEM37	0.37
6263	RYR3	0.33	**2791**	GNG11	0.37
2354	FOSB	0.33	**23604**	DAPK2	0.37
51302	CYP39A1	0.33	**10217**	CTDSPL	0.37
4128	MAOA	0.34	**23550**	PSD4	0.37
117248	GALNTL2	0.34	**4306**	NR3C2	0.37
10268	RAMP3	0.34	**119587**	CPXM2	0.37
7730	ZNF177	0.34	**7942**	TFEB	0.37
10873	ME3	0.34	**3815**	KIT	0.37
7461	CLIP2	0.34	**1805**	DPT	0.37
7049	TGFBR3	0.34	**23242**	COBL	0.37
79901	CYBRD1	0.34	**4313**	MMP2	0.37
5152	PDE9A	0.34	**4139**	MARK1	0.37
50805	IRX4	0.34	**9104**	RGN	0.37
8644	AKR1C3	0.34	**2329**	FMO4	0.37
5915	RARB	0.34	**25802**	LMOD1	0.38
2770	GNAI1	0.34	**4239**	MFAP4	0.38
54996	2-Mar	0.35	**10392**	NOD1	0.38
79791	FBXO31	0.35	**6794**	STK11	0.38
54776	PPP1R12C	0.35	**85458**	DIXDC1	0.38
9079	LDB2	0.35	**4123**	MAN2C1	0.38
57104	PNPLA2	0.35	**54476**	RNF216	0.38
30008	EFEMP2	0.35	**9920**	KBTBD11	0.38
91461	PKDCC	0.35	**6329**	SCN4A	0.38
23368	PPP1R13B	0.35	**10253**	SPRY2	0.38
23461	ABCA5	0.35	**1910**	EDNRB	0.38
9572	NR1D1	0.35	**9249**	DHRS3	0.38
23338	PHF15	0.35	**22869**	ZNF510	0.38

Table S2. *Cont.*

NCBI gene ID	Gene Symbol	Fold Change	NCBI gene ID	Gene Symbol	Fold Change
114800	CCDC85A	0.35	**3384**	ICAM2	0.38
2550	GABBR1	0.35	**8613**	PPAP2B	0.38
4638	MYLK	0.35	**1950**	EGF	0.38
2327	FMO2	0.35	**55273**	TMEM100	0.38
139411	PTCHD1	0.35	**6297**	SALL2	0.38
10391	CORO2B	0.35	**9365**	KL	0.38
25854	FAM149A	0.35	**8863**	PER3	0.38
55701	ARHGEF40	0.36	**8404**	SPARCL1	0.38
1759	DNM1	0.36	**2202**	EFEMP1	0.38
22849	CPEB3	0.36	**8369**	HIST1H4G	0.38
57716	PRX	0.36	**5187**	PER1	0.39
1628	DBP	0.36	**30815**	ST6GALNAC6	0.39
80031	SEMA6D	0.36	**256364**	EML3	0.39
259217	HSPA12A	0.36	**57381**	RHOJ	0.39
6909	TBX2	0.36	**761**	CA3	0.39
1511	CTSG	0.36	**83989**	FAM172A	0.39
79971	WLS	0.36	**1408**	CRY2	0.39
90865	IL33	0.36	**2281**	FKBP1B	0.39
11343	MGLL	0.36	**51222**	ZNF219	0.39
55800	SCN3B	0.36	**54540**	FAM193B	0.39
1949	EFNB3	0.36	**4053**	LTBP2	0.39
284217	LAMA1	0.36	**55184**	DZANK1	0.39
22927	HABP4	0.37	**5740**	PTGIS	0.39
23645	PPP1R15A	0.39	**84814**	PPAPDC3	0.42
342574	KRT27	0.39	**79365**	BHLHE41	0.42
83543	AIF1L	0.39	**316**	AOX1	0.42
624	BDKRB2	0.39	**23380**	SRGAP2	0.42
347	APOD	0.39	**84033**	OBSCN	0.42
84935	C13orf33	0.39	**90353**	CTU1	0.42
858	CAV2	0.39	**9013**	TAF1C	0.42
5138	PDE2A	0.40	**474344**	GIMAP6	0.42
114928	GPRASP2	0.40	**84883**	AIFM2	0.42
58190	CTDSP1	0.40	**58480**	RHOU	0.42
513	ATP5D	0.40	**65982**	ZSCAN18	0.42
57684	ZBTB26	0.40	**666**	BOK	0.42
7041	TGFB1I1	0.40	**79762**	C1orf115	0.42
5787	PTPRB	0.40	**525**	ATP6V1B1	0.42
7294	TXK	0.40	**4675**	NAP1L3	0.42
56301	SLC7A10	0.40	**3257**	HPS1	0.43
55937	APOM	0.40	**55781**	RIOK2	0.43
6368	CCL23	0.40	**63947**	DMRTC1	0.43
55020	TTC38	0.40	**1969**	EPHA2	0.43
134265	AFAP1L1	0.40	**25927**	CNRIP1	0.43
4485	MST1	0.40	**57685**	CACHD1	0.43

Table S2. *Cont.*

NCBI gene ID	Gene Symbol	Fold Change	NCBI gene ID	Gene Symbol	Fold Change
51559	NT5DC3	0.40	**29997**	GLTSCR2	0.43
7169	TPM2	0.40	**26051**	PPP1R16B	0.43
51705	EMCN	0.40	**83604**	TMEM47	0.43
8938	BAIAP3	0.40	**2308**	FOXO1	0.43
10365	KLF2	0.40	**55225**	RAVER2	0.43
59	ACTA2	0.40	**54839**	LRRC49	0.43
80309	SPHKAP	0.40	**122953**	JDP2	0.43
3779	KCNMB1	0.41	**29775**	CARD10	0.43
10826	C5orf4	0.41	**166**	AES	0.43
219654	ZCCHC24	0.41	**25924**	MYRIP	0.43
92162	TMEM88	0.41	**2852**	GPER	0.43
7450	VWF	0.41	**51421**	AMOTL2	0.43
10266	RAMP2	0.41	**124936**	CYB5D2	0.43
25875	LETMD1	0.41	**1294**	COL7A1	0.43
1938	EEF2	0.41	**127435**	PODN	0.43
121551	BTBD11	0.41	**84952**	CGNL1	0.43
2119	ETV5	0.41	**83483**	PLVAP	0.43
9696	CROCC	0.41	**1958**	EGR1	0.43
1031	CDKN2C	0.41	**230**	ALDOC	0.43
9037	SEMA5A	0.41	**65987**	KCTD14	0.43
3397	ID1	0.41	**4804**	NGFR	0.44
84707	BEX2	0.41	**64852**	TUT1	0.44
57616	TSHZ3	0.41	**84253**	GARNL3	0.44
1471	CST3	0.41	**5866**	RAB3IL1	0.44
55214	LEPREL1	0.41	**10608**	MXD4	0.44
3914	LAMB3	0.41	**4211**	MEIS1	0.44
57478	USP31	0.41	**83547**	RILP	0.44
3783	KCNN4	0.41	**9172**	MYOM2	0.44
8839	WISP2	0.41	**57192**	MCOLN1	0.44
1583	CYP11A1	0.42	**255877**	BCL6B	0.44
10124	ARL4A	0.42	**56904**	SH3GLB2	0.44
738	C11orf2	0.42	**51285**	RASL12	0.44
29800	ZDHHC1	0.42	**3425**	IDUA	0.44
23135	KDM6B	0.44	**402117**	VWC2L	0.46
171024	SYNPO2	0.44	**81490**	PTDSS2	0.46
10350	ABCA9	0.44	**283748**	PLA2G4D	0.46
3691	ITGB4	0.44	**23523**	CABIN1	0.46
2348	FOLR1	0.44	**6146**	RPL22	0.46
11145	PLA2G16	0.44	**85360**	SYDE1	0.46
554	AVPR2	0.45	**60468**	BACH2	0.46
64072	CDH23	0.45	**57451**	ODZ2	0.46
80177	MYCT1	0.45	**4013**	VWA5A	0.46
5957	RCVRN	0.45	**339768**	ESPNL	0.46
408	ARRB1	0.45	**3860**	KRT13	0.46

Table S2. *Cont.*

NCBI gene ID	Gene Symbol	Fold Change	NCBI gene ID	Gene Symbol	Fold Change
144699	FBXL14	0.45	**7094**	TLN1	0.46
83719	YPEL3	0.45	**4232**	MEST	0.46
22841	RAB11FIP2	0.45	**1410**	CRYAB	0.46
283927	NUDT7	0.45	**57452**	GALNTL1	0.47
293	SLC25A6	0.45	**63935**	PCIF1	0.47
90507	SCRN2	0.45	**25873**	RPL36	0.47
37	ACADVL	0.45	**9812**	KIAA0141	0.47
112744	IL17F	0.45	**51665**	ASB1	0.47
6709	SPTAN1	0.45	**64123**	ELTD1	0.47
8086	AAAS	0.45	**6122**	RPL3	0.47
7423	VEGFB	0.45	**222962**	SLC29A4	0.47
64221	ROBO3	0.45	**23102**	TBC1D2B	0.47
7273	TTN	0.45	**3476**	IGBP1	0.47
2657	GDF1	0.45	**93408**	MYL10	0.47
59271	C21orf63	0.45	**5310**	PKD1	0.47
132160	PPM1M	0.45	**4628**	MYH10	0.47
27244	SESN1	0.45	**221935**	SDK1	0.47
51310	SLC22A17	0.45	**23328**	SASH1	0.47
4828	NMB	0.45	**8522**	GAS7	0.47
54360	CYTL1	0.45	**10023**	FRAT1	0.47
203245	NAIF1	0.45	**7301**	TYRO3	0.47
23166	STAB1	0.45	**2767**	GNA11	0.47
2121	EVC	0.45	**9457**	FHL5	0.47
116496	FAM129A	0.45	**4094**	MAF	0.47
23239	PHLPP1	0.45	**65268**	WNK2	0.47
51673	TPPP3	0.45	**54585**	LZTFL1	0.47
64094	SMOC2	0.45	**375449**	MAST4	0.47
6383	SDC2	0.45	**138311**	FAM69B	0.47
2180	ACSL1	0.45	**160622**	GRASP	0.47
23770	FKBP8	0.45	**22837**	COBLL1	0.47
55901	THSD1	0.46	**51435**	SCARA3	0.47
25895	METTL21B	0.46	**217**	ALDH2	0.47
23731	C9orf5	0.46	**6236**	RRAD	0.47
126393	HSPB6	0.46	**8322**	FZD4	0.47
4056	LTC4S	0.46	**653275**	CFC1B	0.47
79825	CCDC48	0.46	**10908**	PNPLA6	0.47
10810	WASF3	0.46	**57526**	PCDH19	0.47
29911	HOOK2	0.46	**8424**	BBOX1	0.47
583	BBS2	0.46	**9905**	SGSM2	0.48
28984	C13orf15	0.46	**10435**	CDC42EP2	0.48
1465	CSRP1	0.46	**23087**	TRIM35	0.48
55258	THNSL2	0.46	**60314**	C12orf10	0.48
161198	CLEC14A	0.46	**1073**	CFL2	0.48
3699	ITIH3	0.48	**5256**	PHKA2	0.49

Table S2. *Cont.*

NCBI gene ID	Gene Symbol	Fold Change	NCBI gene ID	Gene Symbol	Fold Change
92922	CCDC102A	0.48	**6237**	RRAS	0.49
65057	ACD	0.48	**5288**	PIK3C2G	0.49
9095	TBX19	0.48	**10252**	SPRY1	0.49
6441	SFTPD	0.48	**79026**	AHNAK	0.49
22846	VASH1	0.48	**9693**	RAPGEF2	0.49
51066	C3orf32	0.48	**51226**	COPZ2	0.49
23179	RGL1	0.48	**158326**	FREM1	0.49
4664	NAB1	0.48	**1956**	EGFR	0.49
50511	SYCP3	0.48	**5360**	PLTP	0.49
6430	SRSF5	0.48	**290**	ANPEP	0.49
11078	TRIOBP	0.48	**1756**	DMD	0.49
78991	PCYOX1L	0.48	**5118**	PCOLCE	0.49
6623	SNCG	0.48	**56654**	NPDC1	0.49
23384	SPECC1L	0.48	**9254**	CACNA2D2	0.49
53826	FXYD6	0.48	**55536**	CDCA7L	0.49
9397	NMT2	0.48	**124975**	GGT6	0.49
6041	RNASEL	0.48	**1906**	EDN1	0.49
113510	HELQ	0.48	**81029**	WNT5B	0.49
64788	LMF1	0.48	**2646**	GCKR	0.49
2217	FCGRT	0.48	**9811**	CTIF	0.50
79720	VPS37B	0.48	**145376**	PPP1R36	0.50
6764	ST5	0.48	**222865**	TMEM130	0.50
252969	NEIL2	0.48	**92999**	ZBTB47	0.50
8987	STBD1	0.48	**168002**	DACT2	0.50
41	ACCN2	0.48	**6829**	SUPT5H	0.50
7905	REEP5	0.48	**9992**	KCNE2	0.50
5919	RARRES2	0.48	**58509**	C19orf29	0.50
10544	PROCR	0.48	**79706**	PRKRIP1	0.50
6876	TAGLN	0.48	**1153**	CIRBP	0.50
8436	SDPR	0.49	**9639**	ARHGEF10	0.50
23500	DAAM2	0.49	**4054**	LTBP3	0.50
130132	RFTN2	0.49	**1120**	CHKB	0.50
80310	PDGFD	0.49	**286046**	XKR6	0.50
4215	MAP3K3	0.49	**9590**	AKAP12	0.50
282775	OR5J2	0.49	**64115**	C10orf54	0.50
51161	C3orf18	0.49	**2067**	ERCC1	0.50
29098	RANGRF	0.49	**7507**	XPA	0.50
53336	CPXCR1	0.49	**22897**	CEP164	0.50
9081	PRY	0.49	**652**	BMP4	0.50
9459	ARHGEF6	0.49	**55702**	CCDC94	0.50
2995	GYPC	0.49	**57613**	KIAA1467	0.50
23057	NMNAT2	0.49	**28514**	DLL1	0.50
4669	NAGLU	0.49	**169270**	ZNF596	0.50
6452	SH3BP2	0.49	**83982**	IFI27L2	0.50

Table S2. *Cont.*

NCBI gene ID	Gene Symbol	Fold Change	NCBI gene ID	Gene Symbol	Fold Change
51458	RHCG	0.49	**2247**	FGF2	0.50
1112	FOXN3	0.49	**26248**	OR2K2	0.50
29954	POMT2	0.49	**84303**	CHCHD6	0.50
9612	NCOR2	0.49	**3615**	IMPDH2	0.50
3198	HOXA1	0.49	**1813**	DRD2	0.50
5311	PKD2	0.49	**80148**	PQLC1	0.50
2946	GSTM2	0.49	**390081**	OR52E4	0.50
2109	ETFB	0.49	**352954**	GATS	0.50
56062	KLHL4	0.49	**90871**	C9orf123	0.50
6915	TBXA2R	0.50	**50945**	TBX22	0.52
64288	ZNF323	0.50	**5204**	PFDN5	0.52
5195	PEX14	0.50	**5338**	PLD2	0.52
84557	MAP1LC3A	0.50	**94**	ACVRL1	0.52
6164	RPL34	0.50	**54039**	PCBP3	0.52
8835	SOCS2	0.50	**7691**	ZNF132	0.52
2735	GLI1	0.50	**338**	APOB	0.52
26022	TMEM98	0.50	**84658**	EMR3	0.52
3908	LAMA2	0.50	**283232**	TMEM80	0.52
1825	DSC3	0.50	**5430**	POLR2A	0.52
5730	PTGDS	0.50	**54623**	PAF1	0.52
162515	SLC16A11	0.51	**11070**	TMEM115	0.52
274	BIN1	0.51	**10395**	DLC1	0.52
79654	HECTD3	0.51	**57140**	RNPEPL1	0.52
22863	ATG14	0.51	**79781**	IQCA1	0.52
25949	SYF2	0.51	**1838**	DTNB	0.52
84872	ZC3H10	0.51	**51386**	EIF3L	0.52
23187	PHLDB1	0.51	**56919**	DHX33	0.52
5434	POLR2E	0.51	**57542**	KLHDC5	0.52
6181	RPLP2	0.51	**3628**	INPP1	0.52
6141	RPL18	0.51	**4520**	MTF1	0.52
84747	UNC119B	0.51	**8547**	FCN3	0.52
23399	CTDNEP1	0.51	**60401**	EDA2R	0.52
599	BCL2L2	0.51	**8082**	SSPN	0.52
197258	FUK	0.51	**80755**	AARSD1	0.52
5207	PFKFB1	0.51	**710**	SERPING1	0.52
8131	NPRL3	0.51	**56246**	MRAP	0.52
25839	COG4	0.51	**10555**	AGPAT2	0.52
10816	SPINT3	0.51	**949**	SCARB1	0.52
60485	SAV1	0.51	**23743**	BHMT2	0.52
5681	PSKH1	0.51	**3910**	LAMA4	0.52
80318	GKAP1	0.51	**60370**	AVPI1	0.52
57088	PLSCR4	0.51	**5021**	OXTR	0.52
93129	ORAI3	0.51	**55997**	CFC1	0.52
5829	PXN	0.51	**23144**	ZC3H3	0.52

Table S2. *Cont.*

NCBI gene ID	Gene Symbol	Fold Change	NCBI gene ID	Gene Symbol	Fold Change
56776	FMN2	0.51	**150709**	ANKAR	0.52
85456	TNKS1BP1	0.51	**6591**	SNAI2	0.52
283	ANG	0.51	**10129**	FRY	0.52
7035	TFPI	0.51	**5166**	PDK4	0.52
51232	CRIM1	0.51	**146433**	IL34	0.52
112616	CMTM7	0.51	**118812**	MORN4	0.53
22981	NINL	0.51	**10516**	FBLN5	0.53
8727	CTNNAL1	0.51	**9463**	PICK1	0.53
9902	MRC2	0.51	**127495**	LRRC39	0.53
10900	RUNDC3A	0.51	**7753**	ZNF202	0.53
51299	NRN1	0.51	**79827**	CLMP	0.53
79632	FAM184A	0.52	**203260**	CCDC107	0.53
80820	EEPD1	0.52	**83657**	DYNLRB2	0.53

Table S1. Up-regulated genes found in dataset GSE29174. There are 437 up-regulated genes in this list. *Q*-values reported by SAM were 0 for all genes in this list.

NCBI gene ID	Gene Symbol	Fold Change	NCBI gene ID	Gene Symbol	Fold Change
1300	COL10A1	42.74	**54443**	ANLN	5.79
3007	HIST1H1D	29.72	**6710**	SPTB	5.71
8366	HIST1H4B	25.58	**7272**	TTK	5.64
6286	S100P	25.19	**10635**	RAD51AP1	5.49
1301	COL11A1	24.72	**4069**	LYZ	5.37
3627	CXCL10	17.83	**55183**	RIF1	5.34
4283	CXCL9	15.88	**891**	CCNB1	5.34
1387	CREBBP	12.83	**91543**	RSAD2	5.31
27299	ADAMDEC1	12.78	**81610**	FAM83D	5.24
54986	ULK4	12.46	**64581**	CLEC7A	5.10
55771	PRR11	12.02	**10051**	SMC4	5.02
54790	TET2	11.25	**4085**	MAD2L1	4.96
6241	RRM2	10.60	**55872**	PBK	4.83
3433	IFIT2	10.49	**991**	CDC20	4.82
6999	TDO2	9.73	**9221**	NOLC1	4.74
1656	DDX6	9.72	**2124**	EVI2B	4.66
55088	C10orf118	9.37	**375248**	ANKRD36	4.66
9648	GCC2	9.24	**1164**	CKS2	4.64
6696	SPP1	8.92	**1230**	CCR1	4.62
2803	GOLGA4	8.57	**890**	CCNA2	4.56
83540	NUF2	7.73	**127933**	UHMK1	4.49
10112	KIF20A	7.66	**10274**	STAG1	4.45
9833	MELK	7.59	**597**	BCL2A1	4.43
55165	CEP55	7.50	**55355**	HJURP	4.41
10142	AKAP9	7.44	**54210**	TREM1	4.36
9447	AIM2	7.42	**253558**	LCLAT1	4.26

Table S3. *Cont.*

NCBI gene ID	Gene Symbol	Fold Change	NCBI gene ID	Gene Symbol	Fold Change
2706	GJB2	7.33	**1033**	CDKN3	4.24
6498	SKIL	7.13	**79801**	SHCBP1	4.23
219285	SAMD9L	7.06	**126731**	C1orf96	4.21
10261	IGSF6	7.01	**6772**	STAT1	4.20
2335	FN1	6.95	**55729**	ATF7IP	4.14
699	BUB1	6.75	**6713**	SQLE	4.14
1058	CENPA	6.75	**157570**	ESCO2	4.10
332	BIRC5	6.73	**79871**	RPAP2	4.09
51203	NUSAP1	6.59	**9493**	KIF23	4.09
259266	ASPM	6.54	**4751**	NEK2	4.05
1063	CENPF	6.49	**10631**	POSTN	4.03
165918	RNF168	6.44	**23515**	MORC3	4.02
9232	PTTG1	6.34	**7153**	TOP2A	4.02
5996	RGS1	6.07	**10403**	NDC80	4.00
29089	UBE2T	5.96	**10915**	TCERG1	3.99
22974	TPX2	5.94	**57650**	KIAA1524	3.99
4321	MMP12	5.91	**23049**	SMG1	3.93
983	CDK1	5.89	**80231**	CXorf21	3.87
85444	LRRCC1	5.87	**5111**	PCNA	3.86
29121	CLEC2D	3.83	**79682**	MLF1IP	3.11
4090	SMAD5	3.80	**29123**	ANKRD11	3.09
2123	EVI2A	3.80	**5429**	POLH	3.09
57695	USP37	3.79	**701**	BUB1B	3.07
133418	EMB	3.76	**200030**	NBPF11	3.06
4131	MAP1B	3.76	**55677**	IWS1	3.06
9787	DLGAP5	3.75	**160418**	TMTC3	3.04
9768	KIAA0101	3.74	**9147**	NEMF	3.04
54625	PARP14	3.73	**11320**	MGAT4A	3.04
2215	FCGR3B	3.71	**5238**	PGM3	3.03
9134	CCNE2	3.70	**2820**	GPD2	3.02
3117	HLA-DQA1	3.68	**388886**	FAM211B	3.01
10380	BPNT1	3.67	**7852**	CXCR4	3.00
79056	PRRG4	3.63	**57082**	CASC5	2.99
10673	TNFSF13B	3.63	**22926**	ATF6	2.98
8467	SMARCA5	3.61	**7594**	ZNF43	2.98
115908	CTHRC1	3.61	**968**	CD68	2.97
3428	IFI16	3.61	**7171**	TPM4	2.96
1520	CTSS	3.61	**11004**	KIF2C	2.96
10797	MTHFD2	3.57	**10808**	HSPH1	2.95
55681	SCYL2	3.57	**84909**	C9orf3	2.94
9749	PHACTR2	3.57	**1894**	ECT2	2.93
94240	EPSTI1	3.56	**1629**	DBT	2.92
64151	NCAPG	3.51	**116969**	ART5	2.90
25879	DCAF13	3.51	**3227**	HOXC11	2.88

Table S3. *Cont.*

NCBI gene ID	Gene Symbol	Fold Change	NCBI gene ID	Gene Symbol	Fold Change
116064	LRRC58	3.47	**3149**	HMGB3	2.87
29899	GPSM2	3.47	**10437**	IFI30	2.87
135114	HINT3	3.45	**57489**	ODF2L	2.87
27333	GOLIM4	3.43	**2151**	F2RL2	2.86
55839	CENPN	3.43	**23215**	PRRC2C	2.85
23213	SULF1	3.41	**128710**	C20orf94	2.85
81671	VMP1	3.39	**23594**	ORC6	2.84
9889	ZBED4	3.36	**5205**	ATP8B1	2.83
3092	HIP1	3.34	**51430**	C1orf9	2.80
51512	GTSE1	3.34	**57405**	SPC25	2.80
92797	HELB	3.34	**112401**	BIRC8	2.80
51426	POLK	3.30	**3606**	IL18	2.80
5611	DNAJC3	3.30	**115362**	GBP5	2.80
6596	HLTF	3.28	**50515**	CHST11	2.79
9910	RABGAP1L	3.25	**83461**	CDCA3	2.79
528	ATP6V1C1	3.23	**10744**	PTTG2	2.78
3833	KIFC1	3.23	**51765**	MST4	2.77
197131	UBR1	3.20	**10926**	DBF4	2.76
29923	HILPDA	3.20	**27125**	AFF4	2.75
28998	MRPL13	3.19	**10615**	SPAG5	2.75
58527	C6orf115	3.19	**55143**	CDCA8	2.74
79000	C1orf135	3.19	**51602**	NOP58	2.74
9857	CEP350	3.18	**51478**	HSD17B7	2.73
84296	GINS4	3.18	**2209**	FCGR1A	2.73
81034	SLC25A32	3.15	**9958**	USP15	2.72
55723	ASF1B	3.14	**5469**	MED1	2.72
7110	TMF1	3.14	**8813**	DPM1	2.70
84081	NSRP1	3.14	**6731**	SRP72	2.70
23075	SWAP70	3.12	**9991**	PTBP3	2.70
6726	SRP9	2.69	**79866**	BORA	2.41
55215	FANCI	2.68	**7072**	TIA1	2.40
57590	WDFY1	2.67	**55632**	G2E3	2.40
55142	HAUS2	2.66	**2213**	FCGR2B	2.40
23047	PDS5B	2.66	**3987**	LIMS1	2.39
5373	PMM2	2.66	**829**	CAPZA1	2.39
11065	UBE2C	2.66	**26973**	CHORDC1	2.38
23085	ERC1	2.66	**435**	ASL	2.38
389197	C4orf50	2.65	**29979**	UBQLN1	2.38
11260	XPOT	2.65	**8548**	BLZF1	2.37
29980	DONSON	2.65	**9694**	TTC35	2.37
64399	HHIP	2.64	**55055**	ZWILCH	2.36
6453	ITSN1	2.63	**4481**	MSR1	2.36
29108	PYCARD	2.63	**10213**	PSMD14	2.35
9877	ZC3H11A	2.62	**9966**	TNFSF15	2.35

Table S3. *Cont.*

NCBI gene ID	Gene Symbol	Fold Change	NCBI gene ID	Gene Symbol	Fold Change
81624	DIAPH3	2.62	**51582**	AZIN1	2.35
79723	SUV39H2	2.61	**54843**	SYTL2	2.34
55789	DEPDC1B	2.61	**9039**	UBA3	2.33
10097	ACTR2	2.59	**933**	CD22	2.33
23036	ZNF292	2.58	**5685**	PSMA4	2.33
22936	ELL2	2.57	**9885**	OSBPL2	2.33
8477	GPR65	2.57	**9262**	STK17B	2.33
23397	NCAPH	2.57	**56942**	C16orf61	2.32
3015	H2AFZ	2.54	**10767**	HBS1L	2.32
55749	CCAR1	2.53	**87178**	PNPT1	2.32
25937	WWTR1	2.52	**6303**	SAT1	2.32
360023	ZBTB41	2.51	**7316**	UBC	2.32
5080	PAX6	2.51	**4205**	MEF2A	2.32
4193	MDM2	2.51	**85465**	EPT1	2.31
24137	KIF4A	2.51	**84640**	USP38	2.31
9212	AURKB	2.51	**5810**	RAD1	2.30
168850	ZNF800	2.50	**64397**	ZFP106	2.29
55109	AGGF1	2.49	**5706**	PSMC6	2.29
23185	LARP4B	2.49	**22948**	CCT5	2.29
51571	FAM49B	2.49	**10672**	GNA13	2.29
51077	FCF1	2.49	**339344**	MYPOP	2.28
23167	EFR3A	2.49	**7292**	TNFSF4	2.28
23468	CBX5	2.48	**57103**	C12orf5	2.28
5396	PRRX1	2.48	**388403**	YPEL2	2.28
10096	ACTR3	2.47	**54876**	DCAF16	2.27
10308	ZNF267	2.47	**113235**	SLC46A1	2.27
6782	HSPA13	2.47	**11177**	BAZ1A	2.27
3832	KIF11	2.47	**339175**	METTL2A	2.26
917	CD3G	2.47	**26586**	CKAP2	2.26
80821	DDHD1	2.46	**55785**	FGD6	2.26
52	ACP1	2.46	**24145**	PANX1	2.25
4179	CD46	2.46	**253461**	ZBTB38	2.25
10499	NCOA2	2.44	**23232**	TBC1D12	2.25
60558	GUF1	2.44	**995**	CDC25C	2.25
55676	SLC30A6	2.43	**55974**	SLC50A1	2.25
6646	SOAT1	2.43	**472**	ATM	2.25
5440	POLR2K	2.43	**23008**	KLHDC10	2.24
84955	NUDCD1	2.42	**10024**	TROAP	2.24
54739	XAF1	2.42	**9521**	EEF1E1	2.24
84295	PHF6	2.23	**7402**	UTRN	2.09
7295	TXN	2.23	**55589**	BMP2K	2.08
2710	GK	2.23	**158747**	MOSPD2	2.08
10905	MAN1A2	2.22	**56886**	UGGT1	2.07
6780	STAU1	2.22	**203100**	HTRA4	2.07

Table S3. *Cont.*

NCBI gene ID	Gene Symbol	Fold Change	NCBI gene ID	Gene Symbol	Fold Change
10282	BET1	2.22	**55279**	ZNF654	2.07
134430	WDR36	2.21	**54499**	TMCO1	2.07
4299	AFF1	2.21	**81930**	KIF18A	2.07
6747	SSR3	2.21	**142686**	ASB14	2.06
7334	UBE2N	2.21	**55209**	SETD5	2.06
5965	RECQL	2.21	**9736**	USP34	2.04
4605	MYBL2	2.2	**116285**	ACSM1	2.04
6093	ROCK1	2.19	**2201**	FBN2	2.04
161725	OTUD7A	2.19	**963**	CD53	2.04
23518	R3HDM1	2.18	**55159**	RFWD3	2.03
2239	GPC4	2.18	**9871**	SEC24D	2.03
28977	MRPL42	2.18	**9887**	SMG7	2.02
64859	OBFC2A	2.18	**23376**	UFL1	2.02
3845	KRAS	2.18	**79646**	PANK3	2.01
51388	NIP7	2.18	**50613**	UBQLN3	2.00
7586	ZKSCAN1	2.18	**201595**	STT3B	2.00
10762	NUP50	2.17	**59345**	GNB4	1.99
7328	UBE2H	2.17	**5876**	RABGGTB	1.99
10730	YME1L1	2.17	**79820**	CATSPERB	1.99
23093	TTLL5	2.17	**6637**	SNRPG	1.99
6790	AURKA	2.17	**51330**	TNFRSF12A	1.99
22889	KIAA0907	2.17	**9928**	KIF14	1.99
10875	FGL2	2.17	**286097**	EFHA2	1.98
23161	SNX13	2.17	**9131**	AIFM1	1.98
9169	SCAF11	2.16	**488**	ATP2A2	1.98
1788	DNMT3A	2.15	**23042**	PDXDC1	1.98
9088	PKMYT1	2.15	**7114**	TMSB4X	1.98
23033	DOPEY1	2.13	**9123**	SLC16A3	1.98
89882	TPD52L3	2.13	**54454**	ATAD2B	1.97
6556	SLC11A1	2.13	**23143**	LRCH1	1.97
64216	TFB2M	2.13	**4212**	MEIS2	1.97
3071	NCKAP1L	2.13	**1457**	CSNK2A1	1.97
51068	NMD3	2.13	**80012**	PHC3	1.97
509	ATP5C1	2.13	**128497**	SPATA25	1.96
953	ENTPD1	2.13	**186**	AGTR2	1.96
51105	PHF20L1	2.13	**53981**	CPSF2	1.96
5062	PAK2	2.13	**56996**	SLC12A9	1.96
9205	ZMYM5	2.12	**1584**	CYP11B1	1.96
55157	DARS2	2.12	**133619**	PRRC1	1.96
8520	HAT1	2.11	**4288**	MKI67	1.96
79739	TTLL7	2.11	**9014**	TAF1B	1.96
9495	AKAP5	2.10	**55858**	TMEM165	1.96
3181	HNRNPA2B1	2.10	**2212**	FCGR2A	1.96

Table S3. *Cont.*

NCBI gene ID	Gene Symbol	Fold Change	NCBI gene ID	Gene Symbol	Fold Change
389898	UBE2NL	2.10	**10075**	HUWE1	1.96
29850	TRPM5	2.10	**220988**	HNRNPA3	1.96
3070	HELLS	2.10	**80146**	UXS1	1.95
331	XIAP	2.09	**122011**	CSNK1A1L	1.95
55751	TMEM184C	2.09	**150468**	CKAP2L	1.95
2146	EZH2	2.09	**84624**	FNDC1	1.95
26057	ANKRD17	1.95	**7332**	UBE2L3	1.92
128061	C1orf131	1.95	**3336**	HSPE1	1.92
64090	GAL3ST2	1.94	**54800**	KLHL24	1.92
130507	UBR3	1.93	**2290**	FOXG1	1.91
2298	FOXD4	1.93	**50848**	F11R	1.91
123169	LEO1	1.93	**10627**	MYL12A	1.91
57187	THOC2	1.93	**5074**	PAWR	1.91
148789	B3GALNT2	1.93	**6476**	SI	1.91
58508	MLL3	1.92	**1009**	CDH11	1.90
5701	PSMC2	1.92	**29066**	ZC3H7A	1.90
148066	ZNRF4	1.92	**51319**	RSRC1	1.90
6670	SP3	1.92			

Table S4. Result of ROC curve analysis on our miRNA array data. ROC analysis was done to validate the diagnostic value of the miRNA in the miRNA-regulated PINs. AUC: area under (ROC) curve; * p-value < 0.05; *** p-value < 0.001.

miRBase Accession	miRNA name	AUC	p-value
MIMAT0002856	hsa-miR-520d-3p	0.49	0.549112
MIMAT0000265	hsa-miR-204-5p	0.98	6.47×10^{-10} ***
MIMAT0000272	hsa-miR-215	0.21	0.999782
MIMAT0000271	hsa-miR-214-3p	0.68	0.010387 *
MIMAT0002820	hsa-miR-497-5p	0.99	2.75×10^{-10} ***
MIMAT0000076	hsa-miR-21-5p	0.78	0.000184 ***
MIMAT0000738	hsa-miR-383	0.60	0.106284
MIMAT0000423	hsa-miR-125b-5p	0.99	2.48×10^{-10} ***
MIMAT0000064	hsa-let-7c	0.93	3.79×10^{-8} ***
MIMAT0000089	hsa-miR-31-5p	0.80	8.63×10^{-5} ***
MIMAT0000077	hsa-miR-22-3p	0.27	0.99749
MIMAT0000098	hsa-miR-100-5p	0.98	5.55×10^{-10} ***
MIMAT0000097	hsa-miR-99a-5p	0.99	2.55×10^{-10} ***
MIMAT0000443	hsa-miR-125a-5p	0.31	0.990694
MIMAT0002819	hsa-miR-193b-3p	0.41	0.86128
MIMAT0000250	hsa-miR-139-5p	0.99	2.42×10^{-10} ***
MIMAT0000437	hsa-miR-145-5p	0.96	3.14×10^{-9} ***
MIMAT0000421	hsa-miR-122-5p	0.48	0.597483

Table S5. Summary of constructed miRNA-regulated networks. L0 gene: genes connected directly to the miRNA (*i.e.*, direct target of miRNA); L1 gene: genes not connected directly to the miRNA.

miRBase Accession	miR name	Total gene count	L0 count	L1 count
MIMAT0002819	hsa-miR-193b-3p	16	1	15
MIMAT0000250	hsa-miR-139-5p	28	10	18
MIMAT0000437	hsa-miR-145-5p	86	22	64
MIMAT0000423	hsa-miR-125b-5p	211	16	195
MIMAT0000443	hsa-miR-125a-5p	206	14	192
MIMAT0000097	hsa-miR-99a-5p	14	1	13
MIMAT0000265	hsa-miR-204-5p	64	18	46
MIMAT0000076	hsa-miR-21-5p	91	16	75
MIMAT0000064	hsa-let-7c	96	20	76
MIMAT0000421	hsa-miR-122-5p	5	3	2
MIMAT0000098	hsa-miR-100-5p	14	1	13
MIMAT0000272	hsa-miR-215	3	3	0
MIMAT0000271	hsa-miR-214-3p	14	8	6
MIMAT0000738	hsa-miR-383	34	3	31
MIMAT0002856	hsa-miR-520d-3p	146	23	123
MIMAT0000077	hsa-miR-22-3p	46	11	35
MIMAT0002820	hsa-miR-497-5p	267	32	235
MIMAT0000089	hsa-miR-31-5p	34	3	31

Table S6. Specific enriched GO terms of each miRNA-regulated PINs. Genes annotated with the specific GO term in the PIN were also listed in this table. Adj. *p*-value: multiple-test adjusted p-value calculated by the method described in the work of Benjamini and Yekutieli [48].

MIMAT0002856(hsa-miR-520d-3p)		
GO term	**Genes**	**Adj. *p*-value**
GO:0007169, Transmembrane receptor protein tyrosine kinase signaling pathway	SH3KBP1, HDAC2, RET, ABI1, LYN, GRB2, SORBS1, CLTC, CLTA, CDC42, CASP9, RAF1, SRC, AP2A1, AP2B1, MAPK3, ARHGEF7, PRKCA, RPS6, PRKAR2B, MAPK1, ARHGEF6, CDK1, SH3GL2, EIF4G1, HDAC1, ECT2, MKNK1, CASP3, PRKACA, ADRB2, PRKAR2A, EIF4B, SHC1, RAC1	2.77×10^{-29}
GO:0048011, Nerve growth factor receptor signaling pathway	HDAC2, GRB2, CLTC, CLTA, CASP9, RAF1, SRC, AP2A1, AP2B1, MAPK3, ARHGEF7, PRKCA, PRKAR2B, MAPK1, ARHGEF6, CDK1, SH3GL2, HDAC1, ECT2, CASP3, PRKACA, PRKAR2A, SHC1, RAC1	5.09×10^{-24}
GO:0007173, Epidermal growth factor receptor signaling pathway	SH3KBP1, GRB2, CLTC, CLTA, CDC42, CASP9, RAF1, SRC, AP2A1, AP2B1, MAPK3, ARHGEF7, PRKCA, PRKAR2B, MAPK1, CDK1, SH3GL2, PRKACA, PRKAR2A, SHC1	2.96×10^{-22}
GO:0043067, Regulation of programmed cell death	HDAC2, STK17B, ESR1, ABL1, LYN, TP53, GABRB3, PAK2, LCK, CASP9, RAF1, PLK1, ARHGEF7, PRKCA, RPS6, SH3RF1, MAPK1, IFT57, ARHGAP10, ARHGEF6, CDK1, APAF1, HDAC1, ECT2, CASP3, SOX10, EP300, ARAF, TFAP2A, ADRB2, HCK, KLHL20, CASP8, HIP1, RAC1	4.76×10^{-19}
GO:0042058, Regulation of epidermal growth factor receptor signaling pathway	SH3KBP1, ESR1, GRB2, CLTC, CLTA, CDC42, AP2A1, AP2B1, ARHGEF7, SH3GL2, SHC1	2.36×10^{-12}
GO:0008543, Fibroblast growth factor receptor signaling pathway	GRB2, CASP9, RAF1, SRC, MAPK3, PRKCA, PRKAR2B, MAPK1, CDK1, MKNK1, PRKACA, PRKAR2A, SHC1	2.39×10^{-12}
GO:0043068, Positive regulation of programmed cell death	STK17B, ABL1, LYN, TP53, LCK, CASP9, ARHGEF7, PRKCA, RPS6, SH3RF1, MAPK1, ARHGEF6, APAF1, ECT2, CASP3, EP300, TFAP2A, ADRB2, CASP8, HIP1, RAC1	3.09×10^{-12}
GO:0010942, Positive regulation of cell death	STK17B, ABL1, LYN, TP53, LCK, CASP9, ARHGEF7, PRKCA, RPS6, SH3RF1, MAPK1, ARHGEF6, APAF1, ECT2, CASP3, EP300, TFAP2A, ADRB2, CASP8, HIP1, RAC1	4.49×10^{-12}
GO:0006917, Induction of apoptosis	STK17B, ABL1, TP53, LCK, CASP9, ARHGEF7, PRKCA, SH3RF1, MAPK1, ARHGEF6, APAF1, ECT2, CASP3, EP300, CASP8, HIP1, RAC1	6.91×10^{-11}
GO:0012502, Induction of programmed cell death	STK17B, ABL1, TP53, LCK, CASP9, ARHGEF7, PRKCA, SH3RF1, MAPK1, ARHGEF6, APAF1, ECT2, CASP3, EP300, CASP8, HIP1, RAC1	7.42×10^{-11}

Table S6. *Cont.*

MIMAT0002856(hsa-miR-520d-3p)		
GO term	**Genes**	**Adj. *p*-value**
GO:0042059, Negative regulation of epidermal growth factor receptor signaling pathway	SH3KBP1, GRB2, CLTC, CLTA, CDC42, AP2A1, AP2B1, ARHGEF7, SH3GL2	8.63×10^{-11}
GO:0015630, Microtubule cytoskeleton	STMN1, SORBS1, SMAD4, CLTC, CDC42, LCK, RACGAP1, PLK1, PRKAR2B, YES1, MAPK1, IFT57, CDK1, ECT2, PRKACA, RB1, EP300, CCNB1, CHAF1B, TFAP2A, CASP8, PRKAR2A	4.75×10^{-10}
GO:0060548, Negative regulation of cell death	HDAC2, ESR1, TP53, SMAD4, RAF1, PLK1, PRKCA, RPS6, SH3RF1, CDK1, HDAC1, CASP3, SOX10, ARAF, TFAP2A, HCK, KLHL20	6.27×10^{-8}
GO:0008286, Insulin receptor signaling pathway	GRB2, SORBS1, RAF1, MAPK3, RPS6, MAPK1, CDK1, EIF4G1, EIF4B, SHC1	2.15×10^{-7}
GO:0043069, Negative regulation of programmed cell death	HDAC2, ESR1, TP53, RAF1, PLK1, PRKCA, RPS6, SH3RF1, CDK1, HDAC1, CASP3, SOX10, ARAF, TFAP2A, HCK, KLHL20	3.13×10^{-7}
GO:0008284, Positive regulation of cell proliferation	HDAC2, ESR1, LYN, CDC42, E2F1, PRKCA, MAPK1, CDK1, RHOG, HDAC1, NCK1, SOX10, CCNB1, ADRB2, HCK, SHC1	8.34×10^{-7}
GO:0051988, Regulation of attachment of spindle microtubules to kinetochore	CDC42, RACGAP1, ECT2, CCNB1	3.27×10^{-5}
GO:0008629, Induction of apoptosis by intracellular signals	ABL1, TP53, CASP9, APAF1, CASP3, EP300, CASP8	5.83×10^{-5}
MIMAT0002820(hsa-miR-497-5p)		
GO term	**Genes**	**Adj. *p*-value**
GO:0043067, Regulation of programmed cell death	ESR1, MEN1, ABL1, HIPK3, PPARGC1A, SIAH1, SH3RF1, PAK2, LCK, MED1, PPARG, CBX4, ARHGEF7, YWHAB, RXRA, ACVR1, MAPK1, CASP3, CASP6, AR, PTPRF, MDM2, BRCA1, MLH1, RAB27A, PIAS4, FAF1, RAC1, VHL, SKI, NR4A1, LYN, TP53, PSMC2, GATA1, GATA6, GATA3, RAF1, CDKN1B, PLK1, PSMD11, HOXA13, RPS6, ESR2, ARHGAP10, ARHGEF6, SMAD3, SKIL, RYR2, PSEN1, HCK, TRAF2	2.67×10^{-25}
GO:0043068, Positive regulation of programmed cell death	MEN1, ABL1, SIAH1, SH3RF1, LCK, PPARG, ARHGEF7, YWHAB, RXRA, MAPK1, CASP3, CASP6, PTPRF, BRCA1, MLH1, RAB27A, PIAS4, FAF1, RAC1, NR4A1, LYN, TP53, GATA6, CDKN1B, HOXA13, RPS6, ESR2, ARHGEF6, SMAD3, RYR2, PSEN1, TRAF2	1.74×10^{-17}
GO:0010942, Positive regulation of cell death	MEN1, ABL1, SIAH1, SH3RF1, LCK, PPARG, ARHGEF7, YWHAB, RXRA, MAPK1, CASP3, CASP6, PTPRF, BRCA1, MLH1, RAB27A, PIAS4, FAF1, RAC1, NR4A1, LYN, TP53, GATA6, CDKN1B, HOXA13, RPS6, ESR2, ARHGEF6, SMAD3, RYR2, PSEN1, TRAF2	3.08×10^{-17}

Table S6. *Cont.*

MIMAT0002820(hsa-miR-497-5p)		
GO term	**Genes**	**Adj. *p*-value**
GO:0008285, Negative regulation of cell proliferation	MEN1, MED1, PPARG, RXRA, CASP3, AR, PTPRF, VDR, VHL, SKI, LYN, TP53, TOB1, GATA1, GATA3, RAF1, HNF4A, CDKN1B, BRD7, MED25, ESR2, ABI1, SMAD1, SMAD2, SMAD3, SMAD4, SOX7	3.85×10^{-14}
GO:0015629, Actin cytoskeleton	ABL1, SORBS1, FLNA, SEPT7, ANLN, MACF1, HAP1, SH3PXD2A, IQGAP2, BRCA1, ACTC1, ACTA1, MYL2, MYLK, SORBS2, ARPC4, ARPC5, ACTR2, ACTR3, ARPC1B, WASF1, WASF2, HCK	2.52×10^{-13}
GO:0006917, Induction of apoptosis	ABL1, SH3RF1, LCK, PPARG, ARHGEF7, YWHAB, MAPK1, CASP3, CASP6, BRCA1, MLH1, RAB27A, RAC1, NR4A1, TP53, CDKN1B, ARHGEF6, SMAD3, RYR2, PSEN1, TRAF2	9.69×10^{-11}
GO:0012502, Induction of programmed cell death	ABL1, SH3RF1, LCK, PPARG, ARHGEF7, YWHAB, MAPK1, CASP3, CASP6, BRCA1, MLH1, RAB27A, RAC1, NR4A1, TP53, CDKN1B, ARHGEF6, SMAD3, RYR2, PSEN1, TRAF2	1.06×10^{-10}
GO:0007178, Transmembrane receptor protein serine/threonine kinase signaling pathway	ACVR1, SMURF2, SKI, GDF6, BMP6, ZNF8, GATA4, HNF4A, SMAD1, SMAD2, SMAD3, SMAD4, SMAD5, RYR2	1.22×10^{-10}
GO:0007169, Transmembrane receptor protein tyrosine kinase signaling pathway	SORBS1, CDC42, SRC, MAPK3, ARHGEF7, YWHAB, MAPK1, SH3GL2, CASP3, MDM2, EIF4G1, RAC1, SH3KBP1, NR4A1, LYN, GRB2, RAF1, CDKN1B, RPS6, ABI1, ARHGEF6, MKNK1, PSEN1, EIF4B	1.67×10^{-10}
GO:0090092, Regulation of transmembrane receptor protein serine/threonine kinase signaling pathway	MEN1, ACVR1, SMURF2, SKI, GDF6, TP53, BMP6, GATA4, GATA6, HOXA13, SMAD2, SMAD3, SMAD4, SKIL	7.51×10^{-10}
GO:0030509, BMP signaling pathway	ACVR1, SMURF2, SKI, GDF6, BMP6, ZNF8, SMAD1, SMAD4, SMAD5, RYR2	3.25×10^{-9}
GO:0060548, Negative regulation of cell death	ESR1, HIPK3, PPARGC1A, SH3RF1, MED1, CBX4, ACVR1, CASP3, AR, MDM2, VHL, TP53, GATA1, GATA6, GATA3, RAF1, CDKN1B, PLK1, RPS6, SMAD3, SMAD4, PSEN1, HCK	7.88×10^{-9}
GO:0007173, Epidermal growth factor receptor signaling pathway	CDC42, SRC, MAPK3, ARHGEF7, YWHAB, MAPK1, SH3GL2, MDM2, SH3KBP1, NR4A1, GRB2, RAF1, CDKN1B	9.22×10^{-9}
GO:0030521, Androgen receptor signaling pathway	PPARGC1A, MED14, MED1, AR, BRCA1, MED12, PIAS1, RAN, NR1I3	1.42×10^{-8}
GO:0043069, Negative regulation of programmed cell death	ESR1, HIPK3, PPARGC1A, SH3RF1, MED1, CBX4, ACVR1, CASP3, AR, MDM2, VHL, TP53, GATA1, GATA6, GATA3, RAF1, CDKN1B, PLK1, RPS6, SMAD3, PSEN1, HCK	2.44×10^{-8}
GO:0048011, Nerve growth factor receptor signaling pathway	SRC, MAPK3, ARHGEF7, YWHAB, MAPK1, SH3GL2, CASP3, MDM2, RAC1, NR4A1, GRB2, RAF1, CDKN1B, ARHGEF6, PSEN1	2.64×10^{-8}
GO:0032956, Regulation of actin cytoskeleton organization	ABL1, LRP1, ARPC4, ARPC5, ACTR3, ARPC1B, SMAD3, NCK1, SORBS3, HCK, LIMK1	6.42×10^{-6}

Table S6. *Cont.*

MIMAT0002820(hsa-miR-497-5p)		
GO term	**Genes**	**Adj. *p*-value**
GO:0008543, Fibroblast growth factor receptor signaling pathway	SRC, MAPK3, YWHAB, MAPK1, MDM2, NR4A1, GRB2, RAF1, CDKN1B, MKNK1	9.06×10^{-6}
GO:0042059, Negative regulation of epidermal growth factor receptor signaling pathway	CDC42, ARHGEF7, SH3GL2, PTPRF, SH3KBP1, GRB2, PSEN1	1.11×10^{-5}
GO:0042058, Regulation of epidermal growth factor receptor signaling pathway	ESR1, CDC42, ARHGEF7, SH3GL2, PTPRF, SH3KBP1, GRB2, PSEN1	1.17×10^{-5}
GO:0007179, Transforming growth factor beta receptor signaling pathway	ACVR1, SMURF2, SKI, SMAD1, SMAD2, SMAD3, SMAD4, SMAD5	1.67×10^{-5}
GO:0015630, Microtubule cytoskeleton	STMN1, RIF1, SORBS1, CDC42, LCK, RACGAP1, YES1, YWHAB, MAPK1, SEPT7, KIF23, CDC16, MACF1, BRCA1, FEZ1, NCOR1, PLK1, CHD3, SMAD4, CEP350, CDC27, PSEN1	2.14×10^{-5}
GO:0017015, Regulation of transforming growth factor beta receptor signaling pathway	MEN1, SMURF2, SKI, TP53, SMAD2, SMAD3, SMAD4, SKIL	2.30×10^{-5}
GO:0070302, Regulation of stress-activated protein kinase signaling cascade	MEN1, ZEB2, HIPK3, SH3RF1, CDC42, MAPK3, MAPK1, LYN, NCOR1, TRAF2	2.74×10^{-5}
GO:0001959, Regulation of cytokine-mediated signaling pathway	HSP90AB1, MED1, PPARG, PTPRF, NR1H2, PIAS1, IL36RN, HIPK1	6.35×10^{-5}
GO:0008284, Positive regulation of cell proliferation	ESR1, CDC42, MED1, RARA, MAPK1, AR, MDM2, NR4A1, LYN, FZR1, BMP6, GATA1, GATA4, GATA6, CDKN1B, NCK1, HCLS1, HCK	7.29×10^{-5}

Table S6. *Cont.*

MIMAT0000423(hsa-miR-125b-5p)		
GO term	**Genes**	**Adj. *p*-value**
GO:0043067, Regulation of programmed cell death	HMGA2, PML, PRNP, FGF2, XRCC4, BRCA1, IGFBP3, HDAC3, CTNNB1, CD5, CDK1, NKX2-5, MEF2C, PRKCI, CASP2, PSMA4, PSMA3, CFDP1, CAV1, FAF1, YWHAB, HIF1A, RELA, TCF7L2, TNFSF12, PSEN2, TP53, TOP2A, TNFRSF4, BID, MYC, JUN, OGT, CDKN1A, HOXA13, RNF7, PPP2R4, HDAC2, HDAC1, SNCA, PTEN, NFKBIA, IFI16, NOL3, TRAF2, HSP90B1	4.56×10^{-24}
GO:0060548, Negative regulation of cell death	HMGA2, PRNP, FGF2, XRCC4, HDAC3, CTNNB1, CDK1, NKX2-5, MEF2C, PRKCI, CFDP1, HIF1A, RELA, TCF7L2, PSEN2, TP53, TNFRSF4, MYC, JUN, CDKN1A, RNF7, HDAC2, HDAC1, SNCA, PTEN, MGMT, NFKBIA, NOL3, HSP90B1	8.04×10^{-17}
GO:0008284, Positive regulation of cell proliferation	HMGA2, FGF2, XRCC4, CDC25B, CTNNB1, EGR1, AGGF1, CDK1, NKX2-5, MEF2C, PRKCI, IRS1, HIF1A, RELA, HCLS1, TNFSF12, ARNT, PTPRC, TNFSF4, TNFRSF4, MYC, JUN, FGF1, CDKN1A, HDAC2, HDAC1, NOLC1, PTEN	2.20×10^{-15}
GO:0043069, Negative regulation of programmed cell death	HMGA2, PRNP, XRCC4, HDAC3, CTNNB1, CDK1, NKX2-5, MEF2C, PRKCI, CFDP1, HIF1A, RELA, TCF7L2, PSEN2, TP53, TNFRSF4, MYC, JUN, CDKN1A, RNF7, HDAC2, HDAC1, SNCA, PTEN, NFKBIA, NOL3, HSP90B1	3.62×10^{-15}
GO:0043068, Positive regulation of programmed cell death	HMGA2, PML, BRCA1, IGFBP3, CTNNB1, CD5, MEF2C, PRKCI, CASP2, CAV1, FAF1, YWHAB, TNFSF12, PSEN2, TP53, TOP2A, BID, JUN, OGT, CDKN1A, HOXA13, RNF7, PPP2R4, PTEN, IFI16, TRAF2	4.51×10^{-14}
GO:0010942, Positive regulation of cell death	HMGA2, PML, BRCA1, IGFBP3, CTNNB1, CD5, MEF2C, PRKCI, CASP2, CAV1, FAF1, YWHAB, TNFSF12, PSEN2, TP53, TOP2A, BID, JUN, OGT, CDKN1A, HOXA13, RNF7, PPP2R4, PTEN, IFI16, TRAF2	7.15×10^{-14}
GO:0006916, Anti-apoptosis	PRNP, HDAC3, CDK1, NKX2-5, MEF2C, PRKCI, CFDP1, RELA, TCF7L2, PSEN2, RNF7, HDAC1, SNCA, NFKBIA, NOL3, HSP90B1	1.25×10^{-10}
GO:0008285, Negative regulation of cell proliferation	SERPINF1, SRF, PML, PRNP, FGF2, CSNK2B, IGFBP3, CTNNB1, CAV1, HMGA1, VDR, CDH5, HSF1, COL18A1, TP53, MYC, JUN, CDKN1A, PAK1, PTEN	2.08×10^{-9}
GO:0015630, Microtubule cytoskeleton	STMN1, KIF1C, RANGAP1, CDC25B, BRCA1, HDAC3, CTNNB1, PIN4, HSPH1, RANBP9, CDK1, SPTAN1, YWHAQ, DVL1, FKBP4, YWHAB, CCDC85B, MAPT, PSEN2, TOP2A, SPIB, MYC, OGT, APEX1, PAFAH1B1	2.24×10^{-9}
GO:0048011, Nerve growth factor receptor signaling pathway	HDAC3, CDK1, MEF2C, PRKCI, CASP2, IRS1, YWHAB, RELA, PSEN2, HDAC2, HDAC1, PTEN, ATF1, NFKBIA	1.99×10^{-8}
GO:0050678, Regulation of epithelial cell proliferation	SERPINF1, PGR, FGF2, CTNNB1, AGGF1, CAV1, HIF1A, TNFSF12, ARNT, MYC, JUN, FGF1, PTEN	3.41×10^{-8}
GO:0007169, Transmembrane receptor protein tyrosine kinase signaling pathway	FGF2, HDAC3, CDK1, MEF2C, PRKCI, CASP2, IRS1, FIBP, PTPN1, YWHAB, RELA, PSEN2, FGF1, HDAC2, HDAC1, PTEN, ATF1, NFKBIA, EIF4EBP1	6.39×10^{-8}

Table S6. *Cont.*

MIMAT0000423(hsa-miR-125b-5p)		
GO term	**Genes**	**Adj. *p*-value**
GO:0006917, Induction of apoptosis	PML, BRCA1, CD5, CASP2, CAV1, YWHAB, TNFSF12, PSEN2, TP53, BID, OGT, CDKN1A, RNF7, PTEN, IFI16, TRAF2	1.68×10^{-7}
GO:0012502, Induction of programmed cell death	PML, BRCA1, CD5, CASP2, CAV1, YWHAB, TNFSF12, PSEN2, TP53, BID, OGT, CDKN1A, RNF7, PTEN, IFI16, TRAF2	1.81×10^{-7}
GO:0035666, TRIF-dependent toll-like receptor signaling pathway	ATF2, CDK1, MEF2C, FOS, RELA, JUN, ATF1, NFKBIA	2.40×10^{-6}
GO:0034138, Toll-like receptor 3 signaling pathway	ATF2, CDK1, MEF2C, FOS, RELA, JUN, ATF1, NFKBIA	2.71×10^{-6}
GO:0051693, Actin filament capping	SPTB, SPTBN1, SPTAN1, SPTA1, ADD1, EPB49	3.43×10^{-6}
GO:0002756, MyD88-independent toll-like receptor signaling pathway	ATF2, CDK1, MEF2C, FOS, RELA, JUN, ATF1, NFKBIA	3.82×10^{-6}
GO:0034134, Toll-like receptor 2 signaling pathway	ATF2, CDK1, MEF2C, FOS, RELA, JUN, ATF1, NFKBIA	5.33×10^{-6}
GO:0034130, Toll-like receptor 1 signaling pathway	ATF2, CDK1, MEF2C, FOS, RELA, JUN, ATF1, NFKBIA	5.33×10^{-6}
GO:0030835, Negative regulation of actin filament depolymerization	SPTB, SPTBN1, SPTAN1, SPTA1, ADD1, EPB49	5.58×10^{-6}
GO:0015629, Actin cytoskeleton	WAS, CDH1, BRCA1, SPTB, SPTBN1, SPTAN1, CTDP1, STX1A, SPTA1, PAK1, SNCA, ADD1, EPB41, EPB49	5.58×10^{-6}
GO:0002755, MyD88-dependent toll-like receptor signaling pathway	ATF2, CDK1, MEF2C, FOS, RELA, JUN, ATF1, NFKBIA	7.66×10^{-6}
GO:0034142, Toll-like receptor 4 signaling pathway	ATF2, CDK1, MEF2C, FOS, RELA, JUN, ATF1, NFKBIA	1.14×10^{-5}
GO:0050679, Positive regulation of epithelial cell proliferation	FGF2, CTNNB1, AGGF1, HIF1A, TNFSF12, ARNT, MYC, JUN, FGF1	1.14×10^{-5}

Table S6. *Cont.*

MIMAT0000076(hsa-miR-21-5p)		
GO term	**Genes**	**Adj. *p*-value**
GO:0030834, Regulation of actin filament depolymerization	SPTB, SPTBN1, SPTAN1, SPTA1, ADD1, EPB49	1.27×10^{-5}
GO:0030837, Negative regulation of actin filament polymerization	SPTB, SPTBN1, SPTAN1, SPTA1, ADD1, EPB49	2.71×10^{-5}
GO:0002224, Toll-like receptor signaling pathway	ATF2, CDK1, MEF2C, FOS, RELA, JUN, ATF1, NFKBIA	2.96×10^{-5}
GO:0008629, Induction of apoptosis by intracellular signals	PML, BRCA1, YWHAB, TP53, BID, CDKN1A, RNF7, IFI16	3.52×10^{-5}
GO:0043067, Regulation of programmed cell death	SPRY2, TP53, ADAMTSL4, ETS1, TDGF1, RAF1, HOXA5, HOXA13, MSX1, MSX2, NKX2-5, CBL, INHBB, COL4A3, ACVR1C, TRAF2	1.92×10^{-5}
GO:0007173, Epidermal growth factor receptor signaling pathway	SPRY2, SPRY1, GRB2, PTPN11, TDGF1, RAF1, CBL	9.44×10^{-5}
MIMAT0000250(hsa-miR-139-5p)		
GO term	**Genes**	**Adj. *p*-value**
GO:0035583, Negative regulation of transforming growth factor beta receptor signaling pathway by extracellular sequestering of TGFbeta	LTBP1, FBN1, FBN2	2.61×10^{-5}
MIMAT0000089(hsa-miR-31-5p)		
GO term	**Genes**	**Adj. *p*-value**
GO:0007187, G-protein signaling, coupled to cyclic nucleotide second messenger	GNA12, GNA13, DRD5, MTNR1A, S1PR3, TSHR, S1PR4	8.74×10^{-7}
GO:0019935, Cyclic-nucleotide-mediated signaling	GNA12, GNA13, DRD5, MTNR1A, S1PR3, TSHR, S1PR4	1.60×10^{-6}
GO:0007188, G-protein signaling, coupled to cAMP nucleotide second messenger	GNA12, GNA13, DRD5, S1PR3, TSHR, S1PR4	6.82×10^{-6}

Table S6. *Cont.*

MIMAT0000089(hsa-miR-31-5p)		
GO term	**Genes**	**Adj. *p*-value**
GO:0048011, Nerve growth factor receptor signaling pathway	ARHGEF1, PRKCD, ARHGEF12, PRKACA, PRKCE, MCF2, ARHGEF11	6.93×10^{-6}
GO:0019933, CAMP-mediated signaling	GNA12, GNA13, DRD5, S1PR3, TSHR, S1PR4	1.05×10^{-5}
GO:0043067, Regulation of programmed cell death	PTK2B, PRKCD, TGFBR1, ARHGEF12, CTNNB1, PRKCE, TIA1, MCF2, FASTK, ARHGEF11, F2R	1.25×10^{-5}
GO:0003376, Sphingosine-1-phosphate signaling pathway	S1PR3, S1PR2, S1PR4	3.22×10^{-5}
GO:0007169, Transmembrane receptor protein tyrosine kinase signaling pathway	PTK2B, ARHGEF1, PRKCD, ARHGEF12, PRKACA, PRKCE, MCF2, ARHGEF11	5.20×10^{-5}
GO:0043068, Positive regulation of programmed cell death	TGFBR1, ARHGEF12, CTNNB1, PRKCE, TIA1, MCF2, FASTK, ARHGEF11	7.67×10^{-5}
GO:0010942, Positive regulation of cell death	TGFBR1, ARHGEF12, CTNNB1, PRKCE, TIA1, MCF2, FASTK, ARHGEF11	8.78×10^{-5}
GO:0006917, Induction of apoptosis	TGFBR1, ARHGEF12, PRKCE, TIA1, MCF2, FASTK, ARHGEF11	9.32×10^{-5}
GO:0012502, Induction of programmed cell death	TGFBR1, ARHGEF12, PRKCE, TIA1, MCF2, FASTK, ARHGEF11	9.51×10^{-5}
MIMAT0000437(hsa-miR-145-5p)		
GO term	**Genes**	**Adj. *p*-value**
GO:0030509, BMP signaling pathway	BMP6, ZNF8, ACVR1, SMAD1, SMAD4, RYR2, SMAD5, SMURF2, GDF6	1.37×10^{-11}
GO:0007178, Transmembrane receptor protein serine/threonine kinase signaling pathway	BMP6, ZNF8, ACVR1, SMAD1, SMAD4, RYR2, SMAD5, SMURF2, GDF6	2.56×10^{-8}
GO:0090092, Regulation of transmembrane receptor protein serine/threonine kinase signaling pathway	MEN1, TP53, BMP6, HOXA13, ACVR1, SMAD4, SULF1, SMURF2, GDF6	8.22×10^{-8}

Table S6. *Cont.*

MIMAT0000064(hsa-let-7c)		
GO term	**Genes**	**Adj. *p*-value**
GO:0043067, Regulation of programmed cell death	RRM2B, ACVR1, TP53, RASA1, TGFBR1, PSMA3, BIRC5, ACTN2, HOXA13, IRS2, FASTK, VAV1, PSMB6, BCL2, CDK1, HDAC1, SOX10, TIA1, AKT1, AURKB	3.43×10^{-8}
GO:0043069, Negative regulation of programmed cell death	RRM2B, ACVR1, TP53, RASA1, TGFBR1, BIRC5, IRS2, BCL2, CDK1, HDAC1, SOX10, AKT1, AURKB	6.58×10^{-6}
GO:0060548, Negative regulation of cell death	RRM2B, ACVR1, TP53, RASA1, TGFBR1, BIRC5, IRS2, BCL2, CDK1, HDAC1, SOX10, AKT1, AURKB	8.92×10^{-6}
GO:0015630, Microtubule cytoskeleton	INCENP, SNTB2, SEPT1, TACC1, BIRC5, RACGAP1, PIN4, CDCA8, CDK1, PHF1, AKT1, AURKB, NINL, CCDC85B	5.15×10^{-5}
GO:0043067, Regulation of programmed cell death	HMGA2, PML, PRNP, FGF2, XRCC4, BRCA1, IGFBP3, HDAC3, CTNNB1, CD5, CDK1, NKX2-5, MEF2C, PRKCI, CASP2, PSMA4, PSMA3, CFDP1, CAV1, FAF1, YWHAB, HIF1A, RELA, TCF7L2, TNFSF12, PSEN2, TP53, TOP2A, TNFRSF4, BID, MYC, JUN, OGT, CDKN1A, RNF7, PPP2R4, HDAC2, HDAC1, SNCA, PTEN, NFKBIA, IFI16, NOL3, TRAF2, HSP90B1	1.62×10^{-23}
GO:0060548, Negative regulation of cell death	HMGA2, PRNP, FGF2, XRCC4, HDAC3, CTNNB1, CDK1, NKX2-5, MEF2C, PRKCI, CFDP1, HIF1A, RELA, TCF7L2, PSEN2, TP53, TNFRSF4, MYC, JUN, CDKN1A, RNF7, HDAC2, HDAC1, SNCA, PTEN, MGMT, NFKBIA, NOL3, HSP90B1	4.53×10^{-17}
GO:0008284, Positive regulation of cell proliferation	HMGA2, FGF2, XRCC4, CDC25B, CTNNB1, EGR1, AGGF1, CDK1, NKX2-5, MEF2C, PRKCI, IRS1, HIF1A, RELA, HCLS1, TNFSF12, ARNT, PTPRC, TNFSF4, TNFRSF4, MYC, JUN, FGF1, CDKN1A, HDAC2, HDAC1, NOLC1, PTEN	1.23×10^{-15}
MIMAT0000443(hsa-miR-125a-5p)		
GO term	**Genes**	**Adj. *p*-value**
GO:0043069, Negative regulation of programmed cell death	HMGA2, PRNP, XRCC4, HDAC3, CTNNB1, CDK1, NKX2-5, MEF2C, PRKCI, CFDP1, HIF1A, RELA, TCF7L2, PSEN2, TP53, TNFRSF4, MYC, JUN, CDKN1A, RNF7, HDAC2, HDAC1, SNCA, PTEN, NFKBIA, NOL3, HSP90B1	2.02×10^{-15}
GO:0043068, Positive regulation of programmed cell death	HMGA2, PML, BRCA1, IGFBP3, CTNNB1, CD5, MEF2C, PRKCI, CASP2, CAV1, FAF1, YWHAB, TNFSF12, PSEN2, TP53, TOP2A, BID, JUN, OGT, CDKN1A, RNF7, PPP2R4, PTEN, IFI16, TRAF2	2.80×10^{-13}
GO:0010942, Positive regulation of cell death	HMGA2, PML, BRCA1, IGFBP3, CTNNB1, CD5, MEF2C, PRKCI, CASP2, CAV1, FAF1, YWHAB, TNFSF12, PSEN2, TP53, TOP2A, BID, JUN, OGT, CDKN1A, RNF7, PPP2R4, PTEN, IFI16, TRAF2	4.35×10^{-13}
GO:0006916, Anti-apoptosis	PRNP, HDAC3, CDK1, NKX2-5, MEF2C, PRKCI, CFDP1, RELA, TCF7L2, PSEN2, RNF7, HDAC1, SNCA, NFKBIA, NOL3, HSP90B1	9.04×10^{-11}
GO:0008285, Negative regulation of cell proliferation	SERPINF1, SRF, PML, PRNP, FGF2, CSNK2B, IGFBP3, CTNNB1, CAV1, HMGA1, VDR, CDH5, HSF1, COL18A1, TP53, MYC, JUN, CDKN1A, PAK1, PTEN	1.32×10^{-9}

Table S6. *Cont.*

MIMAT0000443(hsa-miR-125a-5p)		
GO term	**Genes**	**Adj. *p*-value**
GO:0015630, Microtubule cytoskeleton	STMN1, KIF1C, RANGAP1, CDC25B, BRCA1, HDAC3, CTNNB1, PIN4, HSPH1, RANBP9, CDK1, SPTAN1, YWHAQ, DVL1, FKBP4, YWHAB, CCDC85B, MAPT, PSEN2, TOP2A, SPIB, MYC, OGT, APEX1, PAFAH1B1	1.32×10^{-9}
GO:0048011, Nerve growth factor receptor signaling pathway	HDAC3, CDK1, MEF2C, PRKCI, CASP2, IRS1, YWHAB, RELA, PSEN2, HDAC2, HDAC1, PTEN, ATF1, NFKBIA	1.50×10^{-8}
GO:0050678, Regulation of epithelial cell proliferation	SERPINF1, PGR, FGF2, CTNNB1, AGGF1, CAV1, HIF1A, TNFSF12, ARNT, MYC, JUN, FGF1, PTEN	2.66×10^{-8}
GO:0007169, Transmembrane receptor protein tyrosine kinase signaling pathway	FGF2, HDAC3, CDK1, MEF2C, PRKCI, CASP2, IRS1, FIBP, PTPN1, YWHAB, RELA, PSEN2, FGF1, HDAC2, HDAC1, PTEN, ATF1, NFKBIA, EIF4EBP1	4.37×10^{-8}
GO:0006917, Induction of apoptosis	PML, BRCA1, CD5, CASP2, CAV1, YWHAB, TNFSF12, PSEN2, TP53, BID, OGT, CDKN1A, RNF7, PTEN, IFI16, TRAF2	1.22×10^{-7}
GO:0012502, Induction of programmed cell death	PML, BRCA1, CD5, CASP2, CAV1, YWHAB, TNFSF12, PSEN2, TP53, BID, OGT, CDKN1A, RNF7, PTEN, IFI16, TRAF2	1.31×10^{-7}
GO:0035666, TRIF-dependent toll-like receptor signaling pathway	ATF2, CDK1, MEF2C, FOS, RELA, JUN, ATF1, NFKBIA	2.01×10^{-6}
GO:0034138, Toll-like receptor 3 signaling pathway	ATF2, CDK1, MEF2C, FOS, RELA, JUN, ATF1, NFKBIA	2.27×10^{-6}
GO:0051693, Actin filament capping	SPTB, SPTBN1, SPTAN1, SPTA1, ADD1, EPB49	2.97×10^{-6}
GO:0002756, MyD88-independent toll-like receptor signaling pathway	ATF2, CDK1, MEF2C, FOS, RELA, JUN, ATF1, NFKBIA	3.20×10^{-6}
GO:0015629, Actin cytoskeleton	WAS, CDH1, BRCA1, SPTB, SPTBN1, SPTAN1, CTDP1, STX1A, SPTA1, PAK1, SNCA, ADD1, EPB41, EPB49	4.25×10^{-6}
GO:0034134, Toll-like receptor 2 signaling pathway	ATF2, CDK1, MEF2C, FOS, RELA, JUN, ATF1, NFKBIA	4.43×10^{-6}
GO:0034130, Toll-like receptor 1 signaling pathway	ATF2, CDK1, MEF2C, FOS, RELA, JUN, ATF1, NFKBIA	4.43×10^{-6}
GO:0030835, Negative regulation of actin filament depolymerization	SPTB, SPTBN1, SPTAN1, SPTA1, ADD1, EPB49	4.72×10^{-6}

Table S6. *Cont.*

MIMAT0000443(hsa-miR-125a-5p)		
GO term	**Genes**	**Adj. *p*-value**
GO:0002755, MyD88-dependent toll-like receptor signaling pathway	ATF2, CDK1, MEF2C, FOS, RELA, JUN, ATF1, NFKBIA	6.41×10^{-6}
GO:0050679, Positive regulation of epithelial cell proliferation	FGF2, CTNNB1, AGGF1, HIF1A, TNFSF12, ARNT, MYC, JUN, FGF1	9.31×10^{-6}
GO:0034142, Toll-like receptor 4 signaling pathway	ATF2, CDK1, MEF2C, FOS, RELA, JUN, ATF1, NFKBIA	9.31×10^{-6}
GO:0030834, Regulation of actin filament depolymerization	SPTB, SPTBN1, SPTAN1, SPTA1, ADD1, EPB49	1.09×10^{-5}
GO:0030837, Negative regulation of actin filament polymerization	SPTB, SPTBN1, SPTAN1, SPTA1, ADD1, EPB49	2.37×10^{-5}
GO:0002224, Toll-like receptor signaling pathway	ATF2, CDK1, MEF2C, FOS, RELA, JUN, ATF1, NFKBIA	2.48×10^{-5}
GO:0008629, Induction of apoptosis by intracellular signals	PML, BRCA1, YWHAB, TP53, BID, CDKN1A, RNF7, IFI16	2.92×10^{-5}
GO:0050851, Antigen receptor-mediated signaling pathway	WAS, MEF2C, RELA, PSEN2, PTPRC, PAK1, PTEN, NFKBIA	8.55×10^{-5}
GO:0002221, Pattern recognition receptor signaling pathway	ATF2, CDK1, MEF2C, FOS, RELA, JUN, ATF1, NFKBIA	9.15×10^{-5}
GO:0001936, Regulation of endothelial cell proliferation	FGF2, AGGF1, CAV1, HIF1A, TNFSF12, ARNT, JUN	9.47×10^{-5}
MIMAT0000077(hsa-miR-22-3p)		
GO term	**Genes**	**Adj. *p*-value**
GO:0035583, Negative regulation of transforming growth factor beta receptor signaling pathway by extracellular sequestering of TGFbeta	FBN2, FBN1, LTBP1	1.45×10^{-5}
MIMAT0000265(hsa-miR-204-5p)		
GO term	**Genes**	**Adj. *p*-value**
GO:0035583, Negative regulation of transforming growth factor beta receptor signaling pathway by extracellular sequestering of TGFbeta	FBN1, FBN2, LTBP1	6.31×10^{-5}

Table S7. GOBO survival analysis results. Genes which was annotated with the specified GO term of proteins in the PIN would be used as input gene set for GOBO analysis. * $p < 0.05$, ** $p < 0.01$; *** $p < 0.001$.

miRNA	GO term	*p*-value
MIMAT0000064(hsa-let-7c)	**GO:0015630, Microtubule cytoskeleton**	**9.97×10^{-6} *** **
	GO:0043067, Regulation of programmed cell death	0.268067
	GO:0043069, Negative regulation of programmed cell death	**0.0390439 ***
	GO:0060548, Negative regulation of cell death	**0.0390439 ***
MIMAT0000076(hsa-miR-21-5p)	GO:0007173, Epidermal growth factor receptor signaling pathway	0.721139
	GO:0043067, Regulation of programmed cell death	0.266312
MIMAT0000077(hsa-miR-22-3p)	GO:0035583, Negative regulation of transforming growth factor beta receptor signaling pathway by extracellular sequestering of TGFbeta	0.940727
MIMAT0000089(hsa-miR-31-5p)	GO:0003376, Sphingosine-1-phosphate signaling pathway	0.062202
	GO:0006917, Induction of apoptosis	**0.048584 ***
	GO:0007169, Transmembrane receptor protein tyrosine kinase signaling pathway	0.050408
	GO:0007187, G-protein signaling, coupled to cyclic nucleotide second messenger	0.289466
	GO:0007188, G-protein signaling, coupled to cAMP nucleotide second messenger	0.687572
	GO:0010942, Positive regulation of cell death	0.356228
	GO:0012502, Induction of programmed cell death	**0.048584 ***
	GO:0019933, CAMP-mediated signaling	0.687572
	GO:0019935, Cyclic-nucleotide-mediated signaling	0.289466
	GO:0043067, Regulation of programmed cell death	0.694486
	GO:0043068, Positive regulation of programmed cell death	0.356228
	GO:0048011, Nerve growth factor receptor signaling pathway	0.154543
MIMAT0000250(hsa-miR-139-5p)	GO:0035583, Negative regulation of transforming growth factor beta receptor signaling pathway by extracellular sequestering of TGFbeta	0.940727
MIMAT0000265(hsa-miR-204-5p)	GO:0035583, Negative regulation of transforming growth factor beta receptor signaling pathway by extracellular sequestering of TGFbeta	0.940727
MIMAT0000423(hsa-miR-125b-5p)	GO:0002224, Toll-like receptor signaling pathway	0.380928
	GO:0002755, MyD88-dependent toll-like receptor signaling pathway	0.380928
	GO:0002756, MyD88-independent toll-like receptor signaling pathway	0.380928
	GO:0006916, Anti-apoptosis	0.0593
	GO:0006917, Induction of apoptosis	0.618064
	GO:0007169, Transmembrane receptor protein tyrosine kinase signaling pathway	0.776269
	GO:0008284, Positive regulation of cell proliferation	0.882324
	GO:0008285, Negative regulation of cell proliferation	0.883393
	GO:0008629, Induction of apoptosis by intracellular signals	0.073118
	GO:0010942, Positive regulation of cell death	0.972892
	GO:0012502, Induction of programmed cell death	0.618064
	GO:0015629, Actin cytoskeleton	0.596528

Table S7. *Cont.*

miRNA	GO term	*p*-value
MIMAT0000423(hsa-miR-125b-5p)	**GO:0015630, Microtubule cytoskeleton**	**0.028245 ***
	GO:0030834, Regulation of actin filament depolymerization	0.654383
	GO:0030835, Negative regulation of actin filament depolymerization	0.654383
	GO:0030837, Negative regulation of actin filament polymerization	0.654383
	GO:0034130, Toll-like receptor 1 signaling pathway	0.380928
	GO:0034134, Toll-like receptor 2 signaling pathway	0.380928
	GO:0034138, Toll-like receptor 3 signaling pathway	0.380928
	GO:0034142, Toll-like receptor 4 signaling pathway	0.380928
	GO:0035666, TRIF-dependent toll-like receptor signaling pathway	0.380928
	GO:0043067, Regulation of programmed cell death	0.643418
	GO:0043068, Positive regulation of programmed cell death	0.972892
	GO:0043069, Negative regulation of programmed cell death	0.492576
	GO:0048011, Nerve growth factor receptor signaling pathway	0.171634
	GO:0050678, Regulation of epithelial cell proliferation	**0.002205 ****
	GO:0050679, Positive regulation of epithelial cell proliferation	0.205483
	GO:0051693, Actin filament capping	0.654383
	GO:0060548, Negative regulation of cell death	0.413665
MIMAT0000437(hsa-miR-145-5p)	GO:0007178, Transmembrane receptor protein serine/threonine kinase signaling pathway	0.196953
	GO:0030509, BMP signaling pathway	0.196953
	GO:0090092, Regulation of transmembrane receptor protein serine/threonine kinase signaling pathway	0.843529
MIMAT0000443(hsa-miR-125a-5p)	GO:0001936, Regulation of endothelial cell proliferation	0.115146
	GO:0002221, Pattern recognition receptor signaling pathway	0.380928
	GO:0002224, Toll-like receptor signaling pathway	0.380928
	GO:0002755, MyD88-dependent toll-like receptor signaling pathway	0.380928
	GO:0002756, MyD88-independent toll-like receptor signaling pathway	0.380928
	GO:0006916, Anti-apoptosis	0.0593
	GO:0006917, Induction of apoptosis	0.618064
	GO:0007169, Transmembrane receptor protein tyrosine kinase signaling pathway	0.776269
	GO:0008284, Positive regulation of cell proliferation	0.882324
	GO:0008285, Negative regulation of cell proliferation	0.883393
	GO:0008629, Induction of apoptosis by intracellular signals	0.073118
	GO:0010942, Positive regulation of cell death	0.972892
	GO:0012502, Induction of programmed cell death	0.618064

Table S7. *Cont.*

miRNA	GO term	*p*-value
MIMAT0000443(hsa-miR-125a-5p)	GO:0015629, Actin cytoskeleton	0.596528
	GO:0015630, Microtubule cytoskeleton	**0.028245 ***
	GO:0030834, Regulation of actin filament depolymerization	0.654383
	GO:0030835, Negative regulation of actin filament depolymerization	0.654383
	GO:0030837, Negative regulation of actin filament polymerization	0.654383
	GO:0034130, Toll-like receptor 1 signaling pathway	0.380928
	GO:0034134, Toll-like receptor 2 signaling pathway	0.380928
	GO:0034138, Toll-like receptor 3 signaling pathway	0.380928
	GO:0034142, Toll-like receptor 4 signaling pathway	0.380928
	GO:0035666, TRIF-dependent toll-like receptor signaling pathway	0.380928
	GO:0043067, Regulation of programmed cell death	0.643418
	GO:0043068, Positive regulation of programmed cell death	0.972892
	GO:0043069, Negative regulation of programmed cell death	0.492576
	GO:0048011, Nerve growth factor receptor signaling pathway	0.171634
	GO:0050678, Regulation of epithelial cell proliferation	**0.002205 ****
	GO:0050679, Positive regulation of epithelial cell proliferation	0.205483
	GO:0050851, Antigen receptor-mediated signaling pathway	0.103325
	GO:0051693, Actin filament capping	0.654383
	GO:0060548, Negative regulation of cell death	0.413665
MIMAT0002820(hsa-miR-497-5p)	GO:0001959, Regulation of cytokine-mediated signaling pathway	0.06699
	GO:0006917, Induction of apoptosis	0.142401
	GO:0007169, Transmembrane receptor protein tyrosine kinase signaling pathway	0.837635
	GO:0007173, Epidermal growth factor receptor signaling pathway	0.387447
	GO:0007178, Transmembrane receptor protein serine/threonine kinase signaling pathway	0.240167
	GO:0007179, Transforming growth factor beta receptor signaling pathway	**0.017876 ***
	GO:0008284, Positive regulation of cell proliferation	0.430255
	GO:0008285, Negative regulation of cell proliferation	0.149994
	GO:0008543, Fibroblast growth factor receptor signaling pathway	0.521978
	GO:0010942, Positive regulation of cell death	0.237692
	GO:0012502, Induction of programmed cell death	0.142401
	GO:0015629, Actin cytoskeleton	0.228804
	GO:0015630, Microtubule cytoskeleton	0.18331
	GO:0017015, Regulation of transforming growth factor beta receptor signaling pathway	0.128773

Table S7. *Cont.*

miRNA	GO term	*p*-value
MIMAT0002820(hsa-miR-497-5p)	GO:0030509, BMP signaling pathway	0.39837
	GO:0030521, Androgen receptor signaling pathway	0.383811
	GO:0032956, Regulation of actin cytoskeleton organization	0.91762
	GO:0042058, Regulation of epidermal growth factor receptor signaling pathway	0.934045
	GO:0042059, Negative regulation of epidermal growth factor receptor signaling pathway	0.789492
	GO:0043067, Regulation of programmed cell death	0.111544
	GO:0043068, Positive regulation of programmed cell death	0.237692
	GO:0043069, Negative regulation of programmed cell death	0.856892
	GO:0048011, Nerve growth factor receptor signaling pathway	0.471986
	GO:0060548, Negative regulation of cell death	0.667437
	GO:0070302, Regulation of stress-activated protein kinase signaling cascade	0.561032
	GO:0090092, Regulation of transmembrane receptor protein serine/threonine kinase signaling pathway	0.182314
MIMAT0002856(hsa-miR-520d-3p)	GO:0006917, Induction of apoptosis	0.489781
	GO:0007169, Transmembrane receptor protein tyrosine kinase signaling pathway	0.171689
	GO:0007173, Epidermal growth factor receptor signaling pathway	0.449696
	GO:0008284, Positive regulation of cell proliferation	0.05916
	GO:0008286, Insulin receptor signaling pathway	0.237933
	GO:0008543, Fibroblast growth factor receptor signaling pathway	0.159318
	GO:0008629, Induction of apoptosis by intracellular signals	0.502822
	GO:0010942, Positive regulation of cell death	0.076906
	GO:0012502, Induction of programmed cell death	0.489781
	GO:0015630, Microtubule cytoskeleton	**0.000292 *****
	GO:0042058, Regulation of epidermal growth factor receptor signaling pathway	0.762633
	GO:0042059, Negative regulation of epidermal growth factor receptor signaling pathway	0.826854
	GO:0043067, Regulation of programmed cell death	0.740092
	GO:0043068, Positive regulation of programmed cell death	0.076906
	GO:0043069, Negative regulation of programmed cell death	0.067499
	GO:0048011, Nerve growth factor receptor signaling pathway	**0.014926 ***
	GO:0051988, Regulation of attachment of spindle microtubules to kinetochore	**7.48×10^{-6} *****
	GO:0060548, Negative regulation of cell death	0.213035

Table S8. Pathophysiogical characteristics of miRNA array data used in ROC curve analysis.

Sample Name	ER	PR	HER	TNM	Stage	Grade
S621T1	0	0	0	pT1N0M0	I	2
S434T1	1	0	1	T2N1M0	IIB	3
S403T1	0	1	0	T2N1M0	IIB	2
S459T1	1	0	0	T4N0M1	IV	1
S455N1	1	0	0	T3N3M1	IV	3
S545T1	0	0	0	pT2N0M0	IIA	3
S173N1	0	0	1	T2N3M0	IIIC	3
S363T1	1	1	0	T2N1M0	IIB	1
S909T1	1	1	1	pT3N3aM0	IIIC	(Unknown)
S645T1	0	1	1	pT1bN0M0	I	3
S898T1	1	0	0	pT2N0(i-)M0	IIA	(Unknown)
S201T1	1	0	0	T1N1M0	IIA	2
S631T1	1	1	1	T2N3aM1	IV	2
S303T1	0	0	1	T2N0M0	IIA	2
S502T1	0	0	0	pT3N0M0	IIB	3
S498N1	1	1	1	pT1cN1aM0	IIA	2
S536T1	1	0	1	T1cN1miM0	IIA	2
S660T1	0	0	1	T1N0M0	I	3
S358N1	0	0	1	T2pN2M0	IIIA	2
S665T1	0	0	0	T2N3M0	IIIC	3
S475T1	0	0	1	pT1cN0M0	I	3
S423T1	1	1	0	T2N3M0	IIIC	1
S507T1	0	0	0	pT1cN1aM0	IIA	3
S891T1	1	0	0	pT2NxM0	IIA	2
S422T1	1	1	0	T2N0M0	IIA	1
S961T1	0	0	1	T2N2aM0	IIIA	2
S622T1	0	0	0	pT2N0M0	IIA	2
S454T1	0	0	0	T1cN0M0	I	2
S433T1	1	0	0	T2N0M0	IIA	1
S673T1	0	0	0	pT2N0M0	IIA	2
S450T1	0	0	1	T2N1M0	IIB	3
S430T1	1	1	0	T2N3M0	IIIC	2
S437T1	1	0	0	T3N1M0	IIIA	3
S574T1	0	0	0	T2N0M0	IIA	2
S401T1	1	1	0	T1N0M0	I	1
S427N1	0	0	0	T3N1M0	IIIA	2
S894T1	0	0	0	pT1cN0M0	I	2
S929T1	1	0	0	pT2N0M0	IIA	2
S173T1	0	0	1	T2N3M0	IIIC	3
S622N1	0	0	0	pT2N0M0	IIA	2
S562T1	1	1	1	pT1aN0M0	I	3
S602T1	0	0	0	pT1cN0M0	I	3
S490T1	1	1	1	pT2N0M0	IIA	2
S677T1	0	0	0	pT2N1M0	IIB	3
S881T1	0	0	0	pT2N1aM0	IIB	3
S619T1	0	0	0	pT2N0M0	IIA	3
S446T1	0	0	0	T2N2M0	IIIA	3
S446T2	0	0	0	T2N2M0	IIIA	3
S453T1	1	1	1	T2N1M0	IIB	2
S562N1	1	1	1	pT1aN0M0	I	3
S557T1	0	0	0	pT2N0M0	IIA	3

Table S8. *Cont.*

Sample Name	ER	PR	HER	TNM	Stage	Grade
S594T1	1	1	1	pT2N3aM0	IIIC	3
S582T1	0	0	0	pT2N0M0	IIA	3
S358T1	0	0	1	T2pN2M0	IIIA	2
S368T1	0	0	1	T3N3M0	IIIC	2
S175T1	1	1	0	T3N3Mx	IIIC	3
S357T1	0	0	0	T2pN1M0	IIIC	3
S653T1	0	0	0	pT3N3aM0	IIIC	2
S722T1	1	1	1	pT1N0M0	I	3
S593T1	0	0	0	pT1N0M0	I	3
S543T1	1	1	1	pT2N1M0	IIB	2
S498T1	1	1	1	pT1cN1aM0	IIA	2
S389T1	1	0	0	T2N1M0	IIB	3
S614T1	0	1	1	TxN0M1	IIIA	(Unknown)
S536N1	1	0	1	T1cN1miM0	IIA	2
S462T1	1	1	0	T3N3M0	IIIC	2
S477T1	0	0	0	pT1cN0M0	I	3
S917T1	0	0	0	T2N0M0	IIA	(Unknown)
S213T1	0	0	1	T1cN1M0	IIA	3
S628T1	0	0	0	T1N0M0	I	2
S291T1	0	0	0	T3pN2M0	IIIA	3
S593N1	0	0	0	pT1N0M0	I	3
S418T1	1	1	0	T2N3M0	IIIC	2
S420T1	1	1	0	T1N0M0	I	2
S363N1	1	1	0	T2N1M0	IIB	1
S629T1	1	0	1	pT1N0M0	I	2
S586T1	1	1	1	pT2N3aM0	IIIC	2
S415T1	0	1	0	T2N2M0	IIIA	2
S439T1	1	1	0	T2N2M0	IIIA	2
S941N1	0	0	0	pT1cN1aM0	IIA	3
S893T1	0	0	0	pT2N1micM0	IIB	3
S380T1	1	0	0	T2N1M0	IIB	2
S906N1	1	1	1	pT3N3aM0	IIIC	2
S918T1	0	0	0	pT2N0M0	IIA	3
S400T1	0	0	1	T2N0M0	IIA	2
S328T1	0	0	0	T1cpN0M0	I	3
S367T1	1	0	0	T1N1M0	IIIA	1
S420N1	1	1	0	T1N0M0	I	2
S922T1	0	0	0	pT1cN0(i-)M0	I	3
S896T1	0	0	1	pT2N1aM0	IIB	2
S410T1	0	1	1	T1N0M0	I	3
S572T1	0	0	1	T4N1aM0	IIIC	3
S448T1	0	0	0	T1N0M0	I	3
S207T1	0	0	1	T2N0M0	IIA	3
S604T1	0	0	1	pT2N1M0	IIB	3
S379T1	0	0	1	T2N2M0	IIIA	2
S906T1	1	1	1	pT3N3aM0	IIIC	2
S941T2	0	0	0	pT1cN1aM0	IIA	3
S941T1	0	0	0	pT1cN1aM0	IIA	3
S375T1	1	1	0	T1N0M0	I	2
S427T1	0	0	0	T3N1M0	IIIA	2
S417T1	0	0	0	pT2N0M0	IIA	3

Table S8. *Cont.*

Sample Name	ER	PR	HER	TNM	Stage
S180T1	1	0	0	T4NxM0	IIIC
S455T1	1	0	0	T3N3M1	IV
S887T1	0	0	0	pT2N0M0	IIA
S445T1	1	0	1	T2N1M0	IIB
S469T1	1	1	0	T2N0M0	IIA
S469T2	1	1	0	T2N0M0	IIA
S483T1	1	1	0	T2N3M0	IIIC
S444T1	1	1	0	T1NxM0	(Unknown)
S909N1	1	1	1	pT3N3aM0	IIIC
S464T1	1	1	0	T1N0M0	I
S894N1	0	0	0	pT1cN0M0	I
S698T1	1	1	1	pT1cN0M0	I
S452T1	0	0	0	T1N0M0	I
S474T1	(Unknown)	(Unknown)	(Unknown)	(Unknown)	(Unknown)

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