

**Reactivation of Tumor Suppressor in Breast Cancer by Enhancer
Switching through NamiRNA Network**

Supplemental Materials

This file includes:

Supplemental Figure 1-5.

Supplemental Table 1-7.

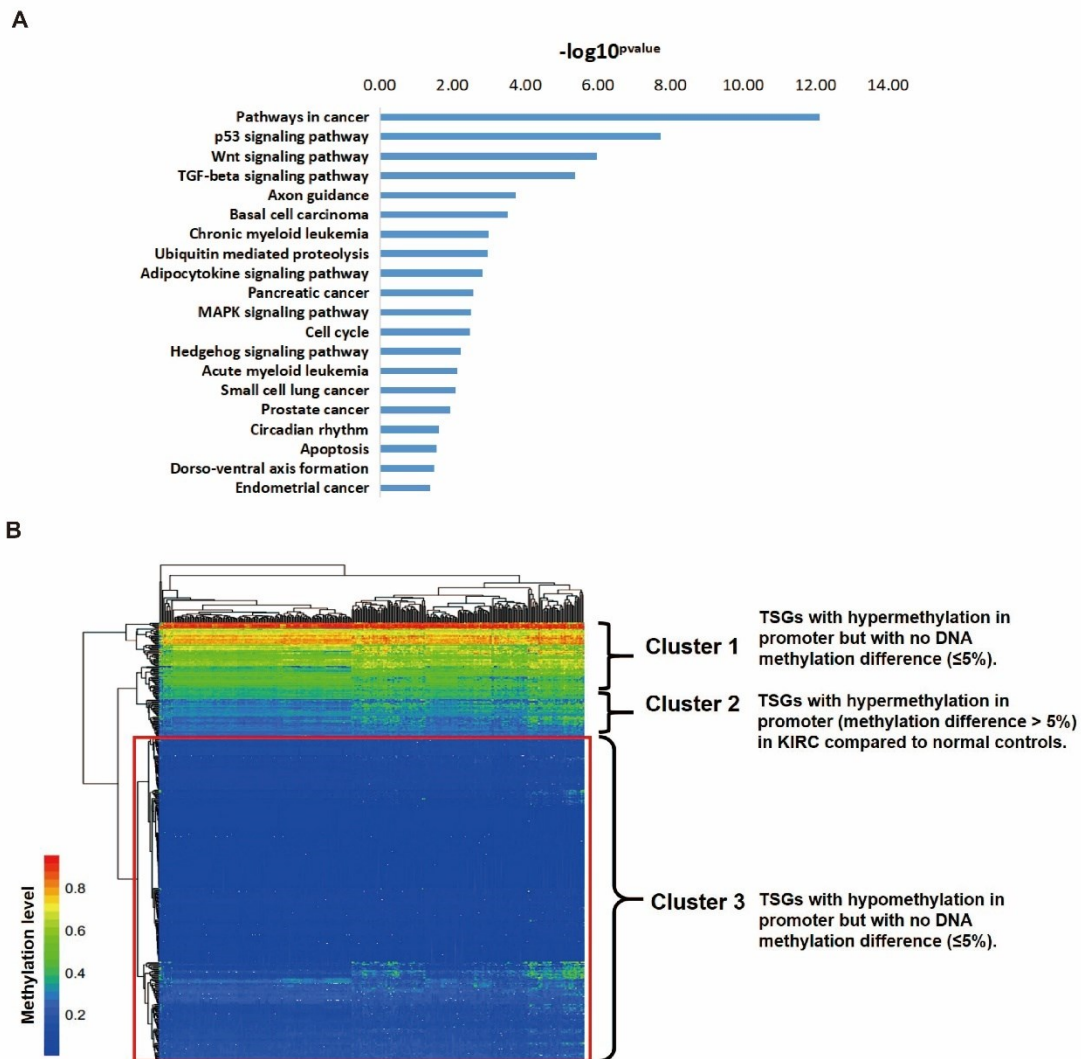


Figure S1. GO analyses of downregulated TSGs in breast cancer and DNA methylation analyses of downregulated TSGs in kidney renal clear cell carcinoma (KIRC). (A) TSGs in breast cancer are significantly linked to typically cancer-associated p53 and Wnt signaling pathways by GO analyses. The x-axis indicates the degree of GO pathway enrichment by P value. The y-axis indicates the name of the GO terms. $P < 0.05$ indicates a significant difference. (B) Heatmap of promoter methylation status of TSGs in 320 TCGA samples. The difference between the mean methylation level of paired samples $> 5\%$ followed by Wilcoxon Rank Sum Test was considered to be significant. Cluster 1 represents 64 TSGs (about 13.8%) are DNA hypermethylated in promoter regions in both cancer and normal controls but without methylation difference; Cluster 2 represents 42 TSGs (about 9.1%), exhibited relative DNA hypermethylation status in promoter regions; Cluster 3, as seen in red box, represents 358 downregulated TSGs (accounting for 77.1% of the total downregulated TSGs) showed hypomethylation but without methylation difference between breast cancer and normal controls.

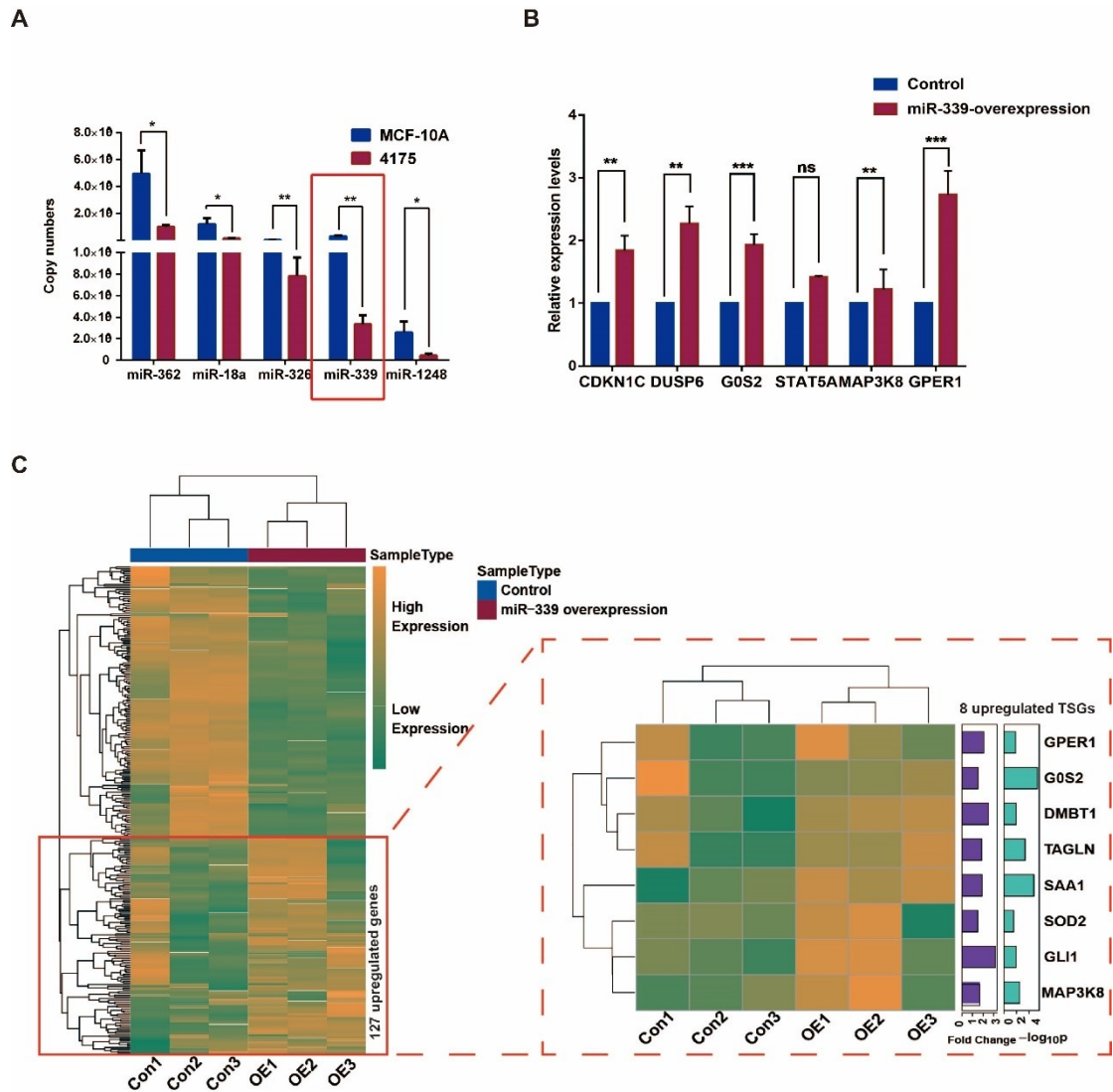


Figure S2. miRNA and its target genes in breast cancer. (A) The absolute copy numbers of 5 randomly selected NamiRNAs are fewer in breast cancer cell line 4175 than those in the normal breast cell line MCF-10A in absolute qPCR. **(B)** *GPER1* and another 5 selected target genes (*CDKN1C*, *DUSP6*, *G0S2*, *STAT5A*, *MAP3K8*) were upregulated when transfecting miR-339 in breast cancer cells by QPCR, while *GPER1* showed a highest expression level. **(C)** RNA-seq profiling of breast cancer cell 4175 compared to control group by high throughput sequencing in triplicate (fold change > 1.5, $P < 0.05$). A total of 127 genes are upregulated (Left panel) and 8 TSGs positively regulated by miR-339 through targeting enhancer (Right panel). Con1, 2, 3 represent control groups, and OE1, 2, 3 represent miR-339 overexpression groups. Data are presented as Mean \pm s.d. of experiments conducted in triplicate. *** $P < 0.001$. ** $P < 0.01$. * $P < 0.05$. "ns" is representative of no significance.

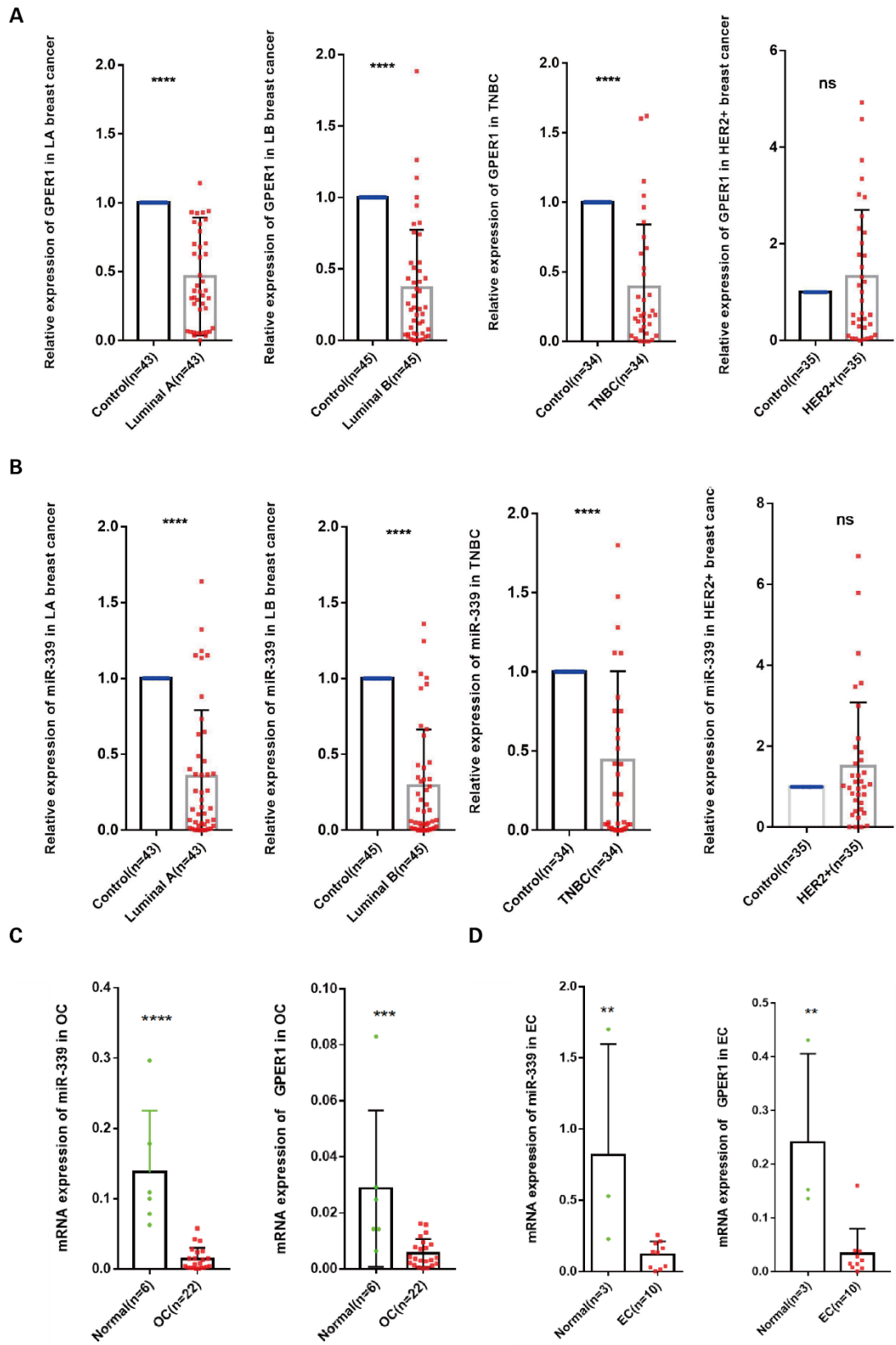


Figure S3. miR-339 and its targeted gene *GPER1* expression in female hormone-related cancers. (A-B) *GPER1*, and miR-339 were both down-regulated in Luminal A, Luminal B and

TNBC breast cancer subtypes compared to the corresponding adjacent control tissues except for the HER2-positive subgroup. LA, LB, and TNBC mean Luminal A, Luminal B, and TNBC breast cancer subtypes respectively. **(C)** Both miR-339 and *GPER1* were downregulated in ovarian cancer tissues compared to the normal controls. OC means ovarian cancer. **(D)** miR-339 and *GPER1* were similarly downregulated in endometrial cancer tissues compared to the normal controls. EC means endometrial cancer. Data are presented as Mean \pm s.d. of experiments conducted in triplicate. ****P < 0.0001. ***P < 0.001. **P < 0.01. "ns" is representative of no significance.

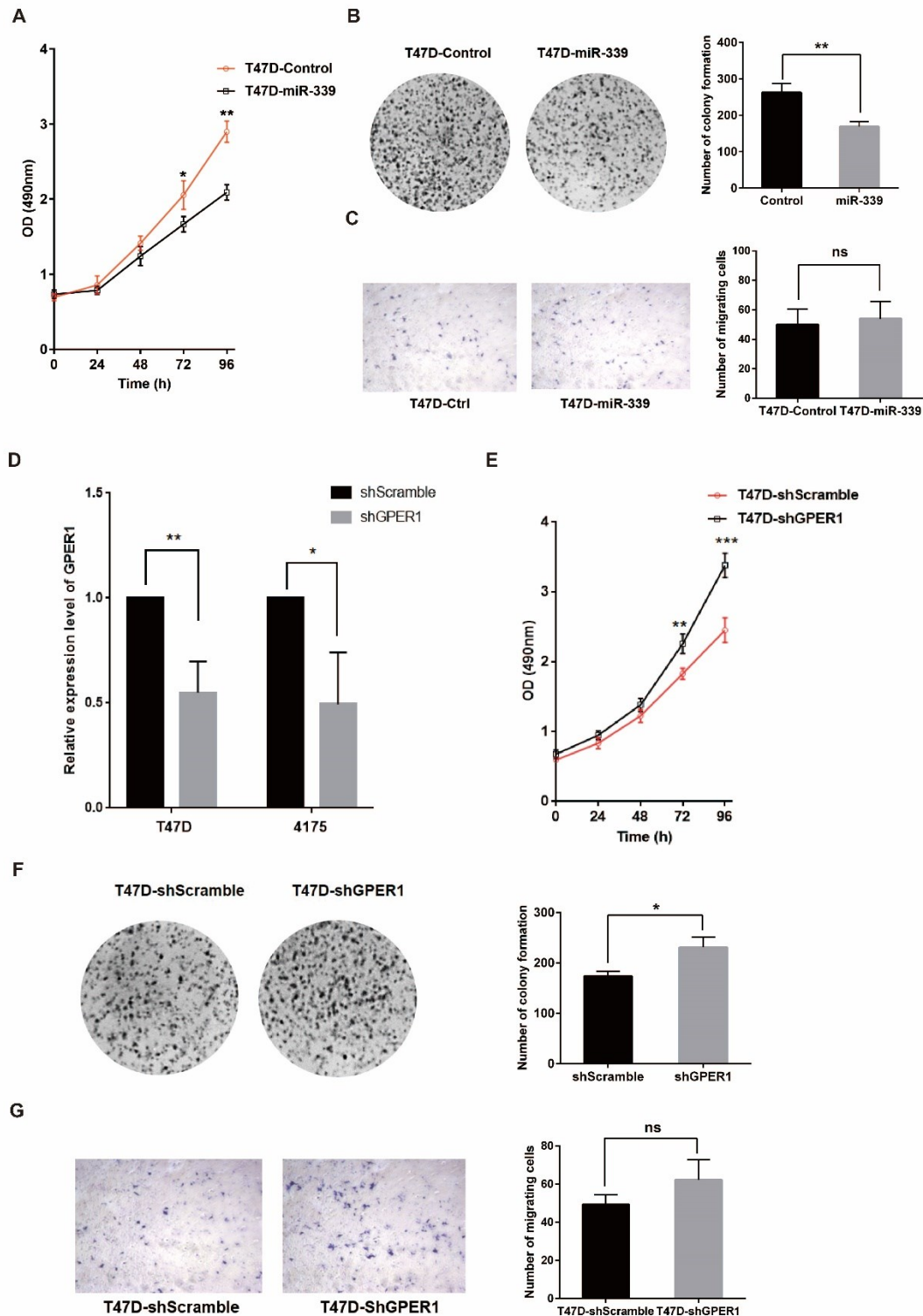


Figure S4. miR-339 and *GPER1* inhibit the proliferation but not migration of breast cancer cell. (A-B) miR-339 can repress breast cancer cell proliferation in T47D cells at 72 hours and 96 hours through CCK8 assay and colony forming assay. **(C)** No difference of migration ability between miR-339 transfected cells and control cells for T47D cells. **(D)** *GPER1* was successfully downregulated after transfecting shGPER1 lentivirus in 4175 and T47D breast cells by QPCR assay. **(E)** Knock-down *GPER1* by transfecting shGPER1 increased the

proliferation ability at 72 hours and 96 hours. **(F)** Knock-down *GPER1* by transfecting shGPER1 increased colony numbers in T47D cells. **(G)** No difference for migration ability after knocking down *GPER1* for T47D cells in transwell assay. ***P < 0.001. **P < 0.01. *P < 0.05. "ns" is representative of no significance.

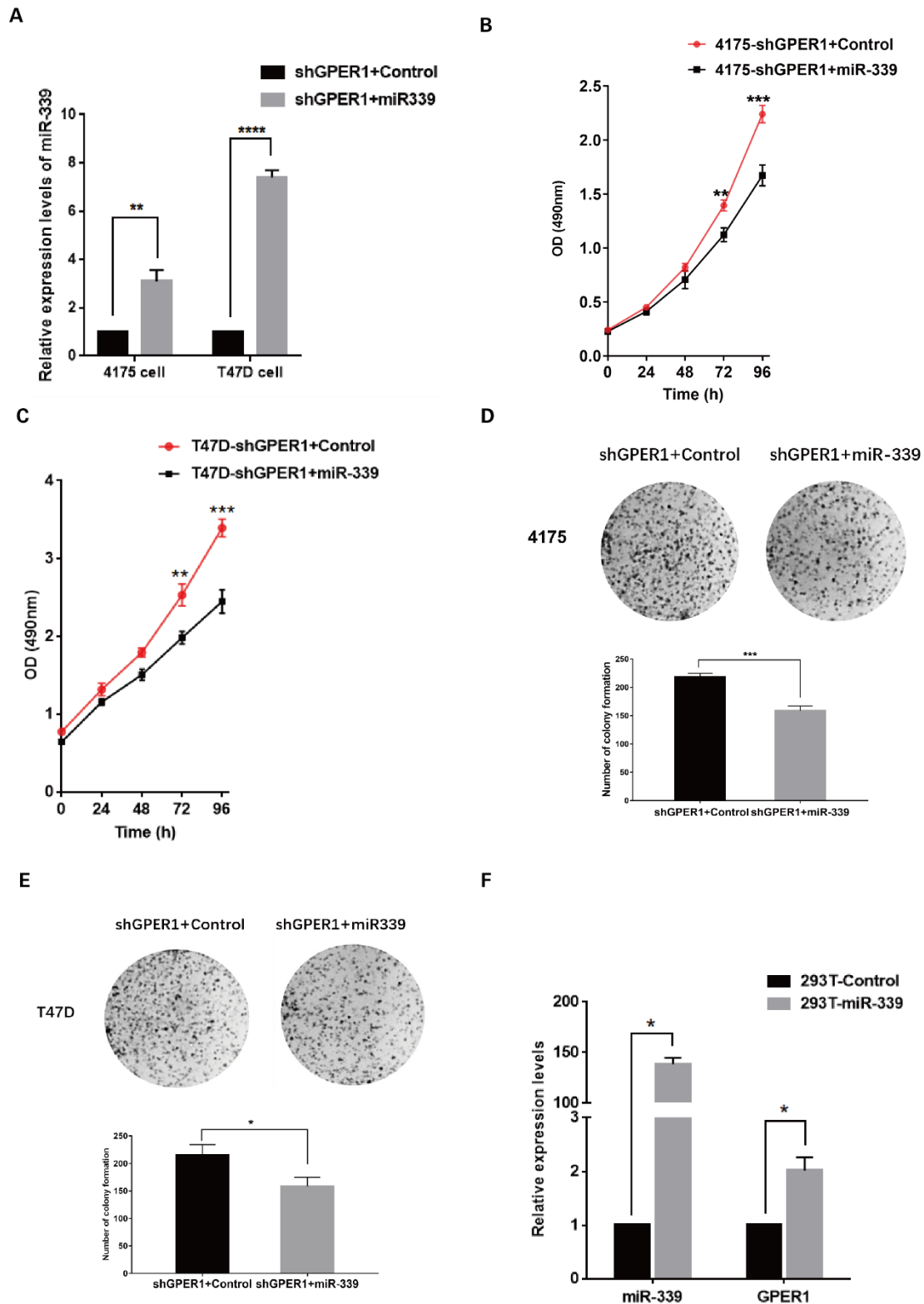


Figure S5. Reactivation of *GPER1* by overexpressing miR-339 can inhibit the proliferation and growth of breast cancer cell. (A) miR-339 expression after transfecting miR-339 lentivirus in 4175 and T47D breast cancer cells by QPCR assay. **(B-C)** The proliferation ability was repressed when transfected miR-339 in *GPER1* knock-down group for both 4175 **(B)** and T47D **(C)** breast cancer cells by CCK8 assays. **(D-E)** Colony numbers

decreased in *GPER1* knock-down group when transfected miR-339 in both 4175 **(D)** and T47D **(E)** breast cancer cells. **(F)** Transfecting miR-339 can activate *GPER1* expression in 293T cells. Data are presented as Mean \pm s.d. of experiments conducted in triplicate. ****P < 0.0001. ***P < 0.001. **P < 0.01. *P < 0.05.

Supplemental Table 1. The primer sequences used for RT-PCR and ChIP-qPCR assays.

Primer Names	Sequence (5'→3')
miR-1248-F	CGTCAGCTGTCCGAGTAGAGGACCTTCTTGTATAAGC
miR-1248-R	TGTCAGGCAACCGTATTCACCTTTAGCACAGT
miR-326-F	CGTCAGCTGTCCGAGTAGAGGCCTCTGGGCCCTT
miR-326-R	TGTCAGGCAACCGTATTCACCCTGGAGG
miR-18a-F	CGTCAGCTGTCCGAGTAGAGGTAAGGTGCATCTAGTG
miR-18a-R	TGTCAGGCAACCGTATTCACCCTATCTG
miR-339-F	CGTCAGCTGTCCGAGTAGAGGTCCCTGTCCTCCAGGA
miR-339-R	TGTCAGGCAACCGTATTCACCCGTGAGC
miR-362-F	CGTCAGCTGTCCGAGTAGAGGAATCCTTGGAACCTAGG
miR-362-R	TGTCAGGCAACCGTATTCACCACTCACA
GP1B-F	TGTAATTCATCAACCTGGC
GP1B-R	AGGAAGAAGACGCTGCTGTA
CDKN1C-F	GCGATCAAGAAGCTGTCCGG
CDKN1C-R	TCGCCCCGACGACTTCTCA
DUSP6-F	CGGGCGTTCTACCTGGAAGGTG
DUSP6-R	TCCGAGGAAGAGTCAGAGC
G0S2-F	GCCGTGCCACTAAGGTCATTCC
G0S2-R	ATCAGCTCCTGGACCGTTT
STAT5A-F	CGTGCTACAGTCCTGGTGTGAG
STAT5A-R	GGCCAGCATCTCCTCCACT
MAP3K8-F	ATGGCGTGTAACCTGATCCCAG
MAP3K8-R	CTCCAGAACAGACCCTCCC
GAPDH-F	ACCGTCAAGGCTGAGAAC
GAPDH-R	GCCTTCTCCATGGTGGTGA
AGO2-F	AGGCGTGAACAACATCCTG
AGO2-R	AGAAAGATGACGGGCTGCT
miR-339- ChIP -F	ATACGAGTCCAGGGGCTGCTAC
miR-339- ChIP -R	TGAGCGCCTCGACGACAGA

Supplemental Table 2. 383 downregulated TSGs in breast cancer.

Gene	P-value	Log2(Fold change)	Gene	P-value	Log2(Fold change)
ADIPOQ	2.31E-67	-6.77	PPARG	3.50E-113	-3.24
TUSC5	6.85E-81	-6.47	SCGB3A1	8.87E-26	-3.17
CD300LG	2.58E-131	-6.46	ID4	2.70E-59	-3.13
CIDEC	4.54E-89	-6.45	EGR1	4.10E-77	-3.12
FABP4	6.69E-80	-6.18	IRX1	9.62E-37	-3.11
CIDEA	3.75E-84	-5.73	CSN1S1	2.94E-72	-3.08
HEPACAM	7.62E-141	-5.17	KL	6.37E-101	-3
C2orf40	9.08E-88	-5.1	LIFR	6.89E-106	-2.99
WIF1	4.69E-60	-4.95	EBF3	1.78E-102	-2.95
ACVR1C	1.71E-132	-4.91	SEMA3G	3.97E-94	-2.94
CD36	2.59E-99	-4.82	SYNPO2	1.25E-79	-2.9
SFRP1	7.17E-60	-4.82	PROX1	9.62E-63	-2.89
SAA1	6.19E-67	-4.79	SPRY2	4.61E-124	-2.89
TAT	3.18E-31	-4.49	IGF1	5.90E-55	-2.87
ZBTB16	7.45E-75	-4.44	SRPX	9.47E-88	-2.87
HSPB7	2.78E-121	-4.42	NTRK3	3.66E-35	-2.86
BTNL9	4.17E-129	-4.35	NGFR	2.36E-43	-2.82
FHL1	8.64E-143	-4.34	KRT17	7.73E-17	-2.8
OXTR	1.93E-100	-4.29	MT1M	7.62E-60	-2.8
STAC2	3.62E-32	-4.29	DEFB1	9.83E-30	-2.79
DLK1	5.82E-50	-4.27	AKAP12	1.54E-82	-2.75
SYNM	4.17E-104	-4.25	ADAMTS18	1.09E-39	-2.73
MME	4.56E-106	-4.24	DSC3	1.18E-19	-2.72
G0S2	3.25E-86	-4.11	UGT2B11	2.13E-12	-2.72
GPIHBP1	1.73E-104	-4.04	KLK6	2.14E-17	-2.71
CDO1	4.90E-95	-3.98	MIA	1.15E-19	-2.71
TSLP	5.25E-124	-3.98	CMTM5	9.55E-64	-2.7
OLFM4	5.93E-31	-3.91	NDRG2	2.05E-91	-2.68
ALDH1A2	1.01E-96	-3.88	RBMS3	7.32E-81	-2.66
DMD	1.06E-117	-3.81	BMP2	1.01E-67	-2.65
LRRC3B	8.08E-173	-3.79	TFPI2	2.82E-24	-2.65

MUCL1	5.44E-19	-3.78	ANXA1	6.59E-101	-2.61
GPC3	7.51E-75	-3.74	DDR2	1.86E-58	-2.61
NNAT	2.14E-87	-3.72	KLF4	2.82E-87	-2.6
KIT	7.80E-74	-3.6	EDNRB	1.78E-86	-2.57
PCDH9	2.03E-87	-3.57	TCEAL7	8.19E-90	-2.57
CNN1	8.90E-91	-3.54	RBP7	1.29E-66	-2.56
CADM3	5.82E-53	-3.51	ANGPTL4	3.55E-40	-2.55
ITGA7	3.86E-104	-3.51	SHISA3	3.94E-61	-2.54
GPX3	9.75E-101	-3.48	PLA2G2A	3.30E-17	-2.51
TP63	7.65E-45	-3.41	LALBA	2.50E-34	-2.45
CAV1	2.63E-154	-3.38	KLK10	7.87E-15	-2.44
TGFBR3	6.42E-79	-3.34	EGR2	2.02E-61	-2.43
PPP1R1B	5.27E-15	-2.42	PTCH2	8.86E-46	-1.96
ATF3	1.43E-54	-2.41	LRIG3	1.02E-55	-1.95
TGFBR2	2.17E-104	-2.41	ALPL	2.71E-40	-1.94
GSN	3.10E-129	-2.38	CADM2	9.65E-22	-1.94
SERPINB5	1.07E-15	-2.38	EPAS1	2.02E-91	-1.93
WNT11	1.18E-32	-2.38	SLIT2	5.82E-31	-1.93
MAPK10	2.71E-40	-2.37	LEFTY2	6.52E-20	-1.9
DCN	2.21E-47	-2.34	PEG3	4.23E-16	-1.9
DUSP1	3.70E-60	-2.34	RASL10A	9.16E-44	-1.9
LRP1B	4.95E-16	-2.34	SPTBN1	1.37E-131	-1.89
CDKN1C	8.66E-76	-2.29	THRB	3.95E-52	-1.89
FAT4	2.23E-57	-2.28	NOV	5.98E-41	-1.88
LTF	6.8E-11	-2.28	CXCR2	2.56E-57	-1.86
WISP3	3.39E-25	-2.28	DLC1	1.52E-64	-1.86
CSN3	7.54E-23	-2.27	EMP1	1.42E-68	-1.86
ZFP36	1.38E-65	-2.27	ADAMTS8	1.01E-22	-1.85
AGTR1	5.56E-17	-2.26	ESR2	2.97E-74	-1.85
PIWIL2	2.24E-48	-2.25	RNF180	7.29E-54	-1.85
PARK2	4.12E-74	-2.24	CAT	3.01E-124	-1.83
CXCL12	4.76E-69	-2.23	IL17RD	5.18E-46	-1.83
MEG3	6.33E-42	-2.23	RND3	2.16E-50	-1.83
PACRG	1.51E-55	-2.21	DUSP6	2.15E-61	-1.82
TWIST2	1.23E-49	-2.21	GRIN2A	4.13E-25	-1.81

PLAGL1	4.53E-64	-2.2	CSRNP1	2.51E-81	-1.79
L3MBTL4	3.87E-39	-2.17	GAS1	2.97E-37	-1.78
TXNIP	5.02E-99	-2.17	PRDM5	3.09E-52	-1.78
CXCL14	4.01E-18	-2.13	PLA2R1	1.97E-61	-1.77
NR4A1	1.52E-40	-2.11	AHNAK	2.27E-66	-1.73
SPARCL1	1.12E-68	-2.11	SCGB2A2	0.000388691	-1.73
KANK1	1.07E-90	-2.07	DIRAS3	4.32E-20	-1.72
EPHB6	4.48E-32	-2.05	HPGD	1.44E-13	-1.72
CDH4	4.70E-47	-2.04	FOXC1	3.12E-19	-1.68
NR4A3	2.79E-34	-2.04	THSD1	3.52E-77	-1.68
NDN	4.13E-66	-2.03	PPARA	2.72E-57	-1.67
SOX7	1.94E-73	-2.03	CDH5	3.31E-66	-1.66
ABCG2	1.85E-47	-2.02	CCDC136	4.53E-41	-1.65
ZNF366	3.68E-47	-2.02	SASH1	1.66E-47	-1.64
LHX6	9.35E-57	-2	AKR1B15	2.42E-12	-1.63
PTCH1	4.69E-51	-2	BHLHE41	8.56E-39	-1.62
RECK	1.56E-66	-2	CEBPA	1.30E-47	-1.62
CSMD1	1.54E-22	-1.98	ADAMTS9	3.45E-43	-1.61
FOXO1	4.58E-96	-1.98	CDH13	1.93E-65	-1.61
DCDC2	2.17E-14	-1.97	CFTR	1.48E-18	-1.61
DPP4	1.75E-35	-1.97	DNAJB4	1.21E-83	-1.61
DLEC1	3.95E-30	-1.6	KLF10	1.50E-60	-1.24
PLD1	5.73E-47	-1.58	THBD	8.21E-32	-1.24
TAGLN	2.84E-36	-1.56	DAB2IP	1.01E-60	-1.23
GPER1	5.21E-23	-1.54	LGALS7	4.7E-09	-1.23
STAT5A	1.22E-62	-1.54	PER2	4.96E-56	-1.23
DMBT1	1.02E-13	-1.53	PPM1L	8.98E-27	-1.23
FAT1	4.19E-28	-1.52	ASS1	1.75E-12	-1.22
ZDHHC2	5.00E-34	-1.52	GLI1	2.63E-15	-1.22
EFNA5	6.80E-17	-1.49	MIA2	3.31E-27	-1.22
BIN1	5.16E-36	-1.48	PPP2R1B	2.07E-66	-1.22
CSN2	5.96E-23	-1.47	CLU	2.35E-16	-1.21
AIFM2	6.76E-60	-1.45	VWA5A	6.53E-26	-1.2
LRMP	8.74E-29	-1.45	TIMP3	3.56E-22	-1.19
DKK3	1.21E-34	-1.44	BMP4	2.47E-12	-1.18

EZH1	3.11E-101	-1.43	ERRFI1	1.74E-31	-1.18
KLF5	4.11E-17	-1.43	MXI1	2.89E-47	-1.17
EDA2R	1.56E-30	-1.42	RASL10B	1.48E-16	-1.17
ETS2	8.23E-60	-1.42	RPS6KA2	1.82E-40	-1.16
KLF6	4.47E-64	-1.42	IRF4	1.89E-09	-1.15
PDGFRL	6.13E-28	-1.42	MCC	4.96E-26	-1.15
RASL11A	2.28E-30	-1.42	SOX15	2.82E-12	-1.14
RARB	2.33E-32	-1.41	FOXO4	4.67E-57	-1.13
VIM	9.01E-49	-1.4	TFAP2B	0.003786231	-1.13
NFATC2	5.44E-17	-1.39	THRA	1.02E-38	-1.12
ZFP36L2	1.25E-48	-1.39	ALOX15B	0.0000605	-1.11
CYGB	1.33E-36	-1.38	CDKN2C	2.32E-32	-1.11
EPHA2	1.46E-44	-1.38	DAPK2	1.14E-30	-1.11
SOCS3	4.36E-29	-1.38	DCD	0.000375002	-1.11
MRVI1	3.75E-40	-1.37	FBLN1	5.00E-19	-1.11
PTGDR	1.55E-25	-1.37	SHPRH	1.16E-21	-1.11
GALR1	6.74E-78	-1.36	DAB2	1.48E-34	-1.1
MAP3K8	5.22E-35	-1.36	TDGF1	9.79E-21	-1.1
TCF7L2	8.96E-47	-1.36	CDK6	2.09E-15	-1.09
PGR	0.0000428	-1.34	FBXW7	1.88E-83	-1.09
VSNL1	1.14E-12	-1.33	TANK	1.67E-72	-1.08
PDLIM4	5.72E-21	-1.32	CTNNA3	3.29E-26	-1.07
UNC5C	8.01E-16	-1.32	LATS2	1.08E-41	-1.07
PLA2G16	1.01E-23	-1.31	TCF4	2.97E-27	-1.07
ITGB3	1.03E-22	-1.3	DCUN1D3	1.34E-74	-1.06
YAP1	1.85E-55	-1.3	DFNA5	7.93E-36	-1.05
EYA4	9.05E-12	-1.27	PRDM11	2.34E-33	-1.05
AFAP1L2	1.57E-26	-1.26	RASSF3	1.17E-18	-1.04
PLCE1	5.94E-16	-1.26	AJAP1	3.57E-14	-1
SFRP5	8.86E-17	-1.25	ANKRD30A	0.011597573	-1
AXIN2	7.11E-19	-1	SFRP4	0.0000108	-0.82
NDRG4	1.81E-13	-1	SIK1	7.41E-12	-0.82
ARHGAP29	5.49E-21	-0.99	CCNDBP1	9.14E-40	-0.81
GSTP1	6.98E-11	-0.98	EPHA3	0.00000238	-0.81
ZBTB4	1.99E-60	-0.98	LATS1	9.68E-13	-0.81

SOD2	4.68E-24	-0.97	MAL	0.0000057	-0.8
AHR	1.69E-21	-0.95	PHLPP1	1.02E-22	-0.8
MTUS1	1.34E-23	-0.94	TBRG1	7.32E-56	-0.8
RASSF8	1.21E-15	-0.94	EPB41L3	5.35E-13	-0.79
TNFSF12	9.39E-37	-0.94	ING3	3.26E-42	-0.79
BTG2	9.67E-13	-0.93	EHF	0.000710106	-0.78
CDH17	3.80E-18	-0.92	RBL2	1.37E-29	-0.77
CITED2	2.34E-23	-0.92	SSBP2	6.61E-18	-0.76
STARD13	4.17E-25	-0.92	IFI16	8.45E-14	-0.74
ADPRH	9.09E-39	-0.91	PTEN	1.07E-28	-0.74
GPC5	3.67E-14	-0.91	PTENP1	3.91E-24	-0.74
HIPK2	8.90E-17	-0.91	USP12	7.02E-12	-0.74
NUAK1	1.28E-20	-0.9	ALOX15	0.001932497	-0.73
PRKAA1	1.39E-28	-0.9	KIF1B	7.29E-26	-0.73
TMEFF2	1.08E-42	-0.9	RASAL1	0.002957746	-0.73
HIC1	9.62E-16	-0.89	ATM	8.65E-21	-0.72
PTPRT	0.004588064	-0.89	EEF1A1	6.47E-36	-0.72
TSC22D1	9.85E-45	-0.89	ROBO1	1.16E-10	-0.72
FAM172A	7.10E-44	-0.88	RPL5	8.00E-29	-0.72
IQGAP2	1.58E-09	-0.88	BLCAP	1.75E-41	-0.71
DUSP22	7.49E-51	-0.87	DUSP26	0.000000587	-0.71
FBXO31	1.45E-61	-0.87	FLNA	3.8E-14	-0.71
FBXO32	8.82E-14	-0.87	CTDSPL	4.12E-30	-0.7
LIMA1	6.09E-25	-0.87	LRIG1	2.16E-12	-0.7
OSGIN1	1.76E-11	-0.87	RASSF10	0.00208321	-0.7
CEBPD	1.8E-11	-0.86	BMPR1A	1.84E-24	-0.69
ESRRB	6.41E-11	-0.86	GLTSCR2	4.9E-14	-0.69
FAS	3.33E-17	-0.86	HACE1	2.23E-21	-0.69
LSAMP	0.000000586	-0.86	PLCD1	1.34E-18	-0.69
PCDHGC3	7.68E-26	-0.86	PRKCE	4.89E-14	-0.69
SMARCA2	1.11E-40	-0.86	ST5	1.53E-18	-0.69
ERBB4	0.002736371	-0.84	PHLDA3	4.09E-10	-0.68
SH3GLB1	9.92E-69	-0.84	S100A2	0.007300953	-0.68
SMYD4	8.09E-70	-0.84	SCUBE2	0.018003547	-0.68
TBX5	2.32E-10	-0.84	ACSM1	0.00169842	-0.67

BNIP3L	1.95E-32	-0.83	ADARB1	5.04E-25	-0.67
BCL6B	9.53E-22	-0.82	CTGF	0.000000396	-0.67
IGFBP3	2.09E-16	-0.82	ITGB1	9.73E-28	-0.67
PTPN13	8.49E-10	-0.82	PTPN11	2.09E-27	-0.67
UNC5D	0.000000046	-0.67	NR2C2	7.94E-15	-0.63
EXTL2	1.09E-27	-0.66	CACNA2D3	0.0000644	-0.62
FHIT	1.85E-08	-0.66	NEDD4	3.71E-13	-0.62
RNF144A	5.79E-11	-0.66	RPL11	1.05E-20	-0.62
DCC	8.62E-13	-0.65	SDHD	2.41E-34	-0.62
NFATC1	2.66E-12	-0.65	DDX3X	9.60E-41	-0.61
AKR1B1	5.57E-13	-0.64	LZTS1	3.24E-10	-0.61
CBL	2.59E-21	-0.64	JDP2	3.06E-13	-0.6
GLIPR1	3.02E-12	-0.64	NEDD4L	2.12E-11	-0.6
HBP1	1.68E-42	-0.64	ZBTB7C	0.000340151	-0.6
NOTCH1	3.46E-14	-0.64	APC	4.40E-17	-0.59
PRKAA2	0.001869145	-0.64	EHD3	7.75E-13	-0.59
RTN4	1.67E-36	-0.64	HECA	4.20E-28	-0.59
SMAD4	7.65E-34	-0.64	NDRG1	0.00000295	-0.59
VTCN1	0.024513818	-0.64	PF4	4.91E-25	-0.59
KIF7	2.26E-08	-0.63	TOM1L2	1.65E-14	-0.59

Supplemental Table 3. 45 TSGs with a significant difference enrichment of H3K27ac marker between breast cancer and normal tissue.

45 TSGs with a significant difference enrichment of H3K27ac marker			
LTF	SPRY2	ZBTB16	ERBB4
FOXC1	PGR	SYNM	NOTCH1
ANKRD30A	EFNA5	NTRK3	MTUS1
RASSF3	AIFM2	PPP1R1B	PRKAA2
CSRNP1	KANK1	AGTR1	FAS
TGFBR3	AFAP1L2	LRIG1	GPBR1
KLF5	PLCE1	NDRG1	SOD2
PLD1	PTCH1	IQGAP2	ZBTB7C
PLA2G16	ADAMTS8	BNIP3L	SCUBE2
IL17RD	CDK6	BTG2	PTPRT
LRIG3	ASS1	HECA	PHLDA3
RASSF10			

Supplemental Table 4. A list of NamiRNA candidates in breast cancer based on text mining.

NamiRNAs	Expression levels	NamiRNAs	Expression levels
hsa-miR-107	up	hsa-miR-762	up
hsa-miR-1245a	up	hsa-miR-765	up
hsa-miR-1323	up	hsa-miR-1246	down
hsa-miR-137	up	hsa-miR-1248	down
hsa-miR-151b	up	hsa-miR-362	down
hsa-miR-184	up	hsa-miR-1258	down
hsa-miR-190b	up	hsa-miR-1275	down
hsa-miR-320b	up	hsa-miR-1290	down
hsa-miR-3646	up	hsa-miR-1469	down
hsa-miR-3648	up	hsa-miR-1471	down
hsa-miR-3687	up	hsa-miR-18a	down
hsa-miR-375	up	hsa-miR-320d	down
hsa-miR-421	up	hsa-miR-326	down
hsa-miR-4257	up	hsa-miR-320e	down
hsa-miR-429	up	hsa-miR-339	down
hsa-miR-4306	up	hsa-miR-376	down
hsa-miR-449a	up	hsa-miR-3923	down
hsa-miR-484	up	hsa-miR-448	down
hsa-miR-492	up	hsa-miR-451a	down
hsa-miR-562	up	hsa-miR-4521	down
hsa-miR-573	up	hsa-miR-4634	down
hsa-miR-575	up	hsa-miR-496	down
hsa-miR-578	up	hsa-miR-520b	down
hsa-miR-592	up	hsa-miR-520h	down
hsa-miR-603	up	hsa-miR-564	down
hsa-miR-608	up	hsa-miR-567	down
hsa-miR-618	up	hsa-miR-568	down
hsa-miR-630	up	hsa-miR-613	down
hsa-miR-632	up	hsa-miR-621	down
hsa-miR-638	up	hsa-miR-676	down

hsa-miR-661	up	hsa-miR-718	down
hsa-miR-663a	up	hsa-miR-802	down
hsa-miR-760	up	hsa-miR-892a	down
hsa-miR-762	up	hsa-miR-892b	down
hsa-miR-765	up	hsa-miR-95	down

Supplemental Table 5. 332 potential targeted TSGs positively regulated by miR-339 in breast cancer.

Potential targeted TSGs of miR-339			
ABCG2	EI24	MAP3K8	RPL5
ABI2	EIF3F	MARCKS	RTN4
ACHE	EMP1	MARVELD1	RUNX3
ADAMTS8	EPAS1	MCC	S100A2
ADARB1	EPB41	MIA	SAA1
ADIPOQ	EPHA2	MIA2	SASH1
AFAP1L2	EPHB6	MLH3	SCUBE2
AGTR1	ESR2	MRVI1	SDHD
AHCYL1	ETS2	MT1M	SEMA3B
AHNAK	EXTL2	MT2A	SEMA3G
AHR	EZH1	MTUS1	SEPT4
AIF1	FABP3	MXI1	SHISA3
AKAP12	FAS	NAPEPLD	SIAH1
AKR1B15	FAT1	NCOA4	SIK1
ALOX15	FBLN1	NDRG1	SIRT1
ALOX15B	FBXO25	NDRG2	SIRT2
ANAPC1	FBXO31	NDRG4	SIRT3
ANGPTL4	FBXO32	NEDD4	SIRT4
ANXA1	FHL1	NEDD4L	SLIT2
APAF1	FLNA	NF1	SMAD2
ARHGEF12	FOXC1	NF2	SMARCA2
ARNTL	G0S2	NFATC1	SMCHD1
ATF3	GABARAP	NFATC2	SOCS3
ATMIN	GADD45A	NGFR	SOD2
ATR	GALR1	NKX3-1	SOX15
AZGP1	GKN1	NNAT	SOX7
BCL10	GLI1	NOTCH2	SPRY2
BCL6B	GLIPR1	NPAS2	SPRY4
BCORL1	GLTSCR2	NR4A1	SRPX
BCR	GNB2L1	NR4A3	SSBP2

BHLHE41	GPC5	NRF1	ST5
BIN1	GPER1	NUMB	STAC2
BLCAP	GPIHBP1	NUP98	STARD13
BMP4	GSN	OSGIN1	STAT3
BMPR1A	GSTP1	OXTR	STAT5A
BNIP3L	HBP1	PAIP2	SUFU
BTG2	HEPACAM	PBRM1	SYNM
BTG3	HIC1	PCDHGC3	SYNPO2
CABLES1	HIPK2	PDCD4	TAGLN
CAMTA1	HIRA	PDLIM4	TANK
CAV1	HIVEP1	PF4	TAT
CBL	HIVEP3	PGRMC2	TCEAL7
CCDC136	HSPB7	PHLDA3	TCEB3
CCNDBP1	ID4	PHLPP2	TCF7L2
CD300LG	IGFBP3	PIWIL2	TDGF1
CD82	IGFBP4	PKD1	TET2
CDH17	IKZF2	PLA2G16	TFPI2
CDH5	IL17RD	PLCD1	THBD
CDKN1A	ING3	PLCE1	THRA
CDKN1C	ING4	PLD1	THRB
CDO1	ING5	PML	THSD1
CIDEC	INPP4B	PPARA	TIMP3
CITED2	IQGAP2	PPARG	TMEFF2
CIZ1	IRF4	PPP1R1B	TNFAIP3
CLDN1	ITGA7	PPP2R1B	TNFRSF10A
CLDN23	ITGB1	PPP2R5C	TNFRSF10B
CLU	ITGB3	PRDM2	TOM1L2
CNN1	KANK1	PRKAA1	TOPORS
CTNNBIP1	KAT5	PRKAR1A	TRIM13
CTNND1	KCNRG	PRODH	TRIM35
CUL1	KDM3A	PTCH1	TSC22D1
CYB5A	KDM5A	PTCH2	TTF1
CYGB	KIF7	PTEN	TUSC5
DAB2IP	KLF10	PTPN11	TXNIP
DDB2	KLF5	PTPRK	UHRF2

DDR2	KLF6	RAP1A	USP12
DDX3X	KRIT1	RASAL1	UVRAG
DFFA	KRT17	RASAL2	VIM
DFNA5	LATS1	RASL10A	VSNL1
DKK3	LATS2	RASSF1	WISP3
DLC1	LEFTY2	RASSF4	WNT11
DLEC1	LGALS7	RB1CC1	YAP1
DLK1	LHX6	RBBP8	YPEL3
DMBT1	LIFR	RBM5	ZBTB4
DMTF1	LIMA1	RBM6	ZBTB7C
DNAJB4	LITAF	RBMS3	ZFHX3
DPH1	LLGL1	RBP7	ZFP36
DPP4	LRRC4	RCHY1	ZFP36L2
DUSP1	LTF	RHOB	ZHX2
DUSP6	LXN	RNASEL	ZNF185
EDNRB	LZTS1	RND3	ZNF292
EEF1A1	MAB21L1	RPA1	ZNF366
EGR1	MAL	RPL10	ZYX

Supplemental Table 6. 127 upregulated genes after transfecting miR-339 in breast cancer cells.

Gene	Log2(Fold change)	P-value	Gene	Log2(Fold change)	P-value
CDIPT-AS1	4.16	4.36E-02	KREMEN1	0.88	5.00E-02
LOC101929140	4.07	1.22E-02	PIK3IP1	0.88	2.90E-03
MIR6732	3.71	1.05E-02	POMZP3	0.87	1.53E-02
FPR1	3.54	2.61E-02	SMPD3	0.85	9.76E-03
UPK3B	3.47	1.73E-02	SAA2	0.85	5.06E-03
SLC30A3	3.15	8.77E-03	CA2	0.84	4.37E-02
FBXO2	2.67	6.73E-03	MDP1	0.82	4.81E-02
SLC14A1	2.63	4.62E-02	WFDC2	0.82	2.23E-02
PRSS30P	2.43	2.60E-02	IL32	0.82	7.58E-03
MB	2.07	1.39E-03	HLA-F	0.81	7.66E-03
ATP6V1B1	1.89	1.84E-02	HSH2D	0.79	4.65E-02
SERPING1	1.68	1.68E-02	PTPRH	0.78	7.35E-03
GLI1	1.66	1.21E-02	LLGL2	0.77	1.87E-02
EAF2	1.63	6.73E-03	PLXNB1	0.77	1.82E-02
HLA-DQB1	1.57	4.60E-02	DDIT4	0.77	2.32E-02
CCL2	1.55	4.50E-02	LYL1	0.76	4.54E-03
ARL9	1.49	4.93E-02	LRRC26	0.76	2.24E-02
GPC2	1.43	3.33E-02	MAP3K8	0.75	3.14E-03
CSF2	1.43	5.52E-19	CDKN2D	0.75	8.78E-04
GP6	1.43	4.56E-02	TRAF1	0.75	1.90E-07
GHRL	1.42	3.39E-02	CORO1A	0.74	1.09E-02
IL6	1.39	2.61E-10	ASNS	0.73	1.10E-06
DMBT1	1.34	1.14E-02	TNK1	0.73	1.76E-02
CCL20	1.32	2.80E-06	HSD17B8	0.72	1.06E-02
CXCL3	1.31	8.43E-15	VWA1	0.72	1.68E-04
F13A1	1.27	1.12E-02	SLC6A9	0.72	1.24E-02
MUC6	1.23	1.73E-04	BOLA1	0.72	3.32E-02
SLPI	1.23	1.32E-03	VIPR1	0.72	3.23E-02
SPINT1	1.18	1.53E-03	RAB3D	0.71	2.42E-02
TMPRSS2	1.18	2.87E-02	GALNT2	0.71	6.94E-04

ERBB3	1.15	1.31E-02	CPE	0.71	2.06E-02
TCF4	1.14	4.39E-02	LPAR2	0.70	1.23E-02
ICOSLG	1.13	1.26E-02	LINC00116	0.70	1.38E-03
LCN2	1.12	4.37E-09	AKR1B1	0.69	4.13E-03
PARTICL	1.12	2.06E-02	SLC43A2	0.68	4.50E-02
SUSD2	1.10	1.68E-02	PTGFRN	0.68	1.44E-02
LOC1019297 05	1.09	2.78E-02	MYO1D	0.67	4.65E-02
IL20RB	1.06	4.17E-02	WNK4	0.67	3.53E-02
LOC113230	1.05	2.59E-02	PTPN6	0.67	4.02E-02
GPER1	1.05	1.39E-02	JUNB	0.67	7.53E-07
ADAP2	1.04	4.28E-02	SH3BP1	0.65	1.41E-02
GIPR	1.04	3.96E-02	ZG16B	0.65	2.39E-03
HIST2H2BE	1.03	1.61E-02	LSR	0.65	2.79E-02
PI3	1.03	4.31E-03	HLA-DPA1	0.65	7.45E-03
SPNS3	1.02	2.95E-02	C9orf16	0.64	5.65E-04
TAF12	1.00	1.43E-03	TRIB3	0.64	2.20E-02
MALAT1	1.00	7.56E-03	ZNF385A	0.63	3.03E-03
CXCL2	1.00	9.59E-09	TMEM53	0.63	3.75E-02
ODF3B	0.99	9.09E-03	MMP15	0.63	3.86E-02
LYPD3	0.99	7.96E-03	ST14	0.62	4.27E-02
LIN7B	0.99	1.85E-03	MEF2BNB	0.62	4.20E-02
VEGFA	0.99	1.54E-05	DHRS7	0.62	6.47E-03
IL411	0.97	2.10E-02	G0S2	0.61	4.33E-06
CXCL8	0.97	1.12E-04	PCK2	0.61	1.05E-03
PDZK1IP1	0.95	5.48E-03	HID1	0.61	4.82E-02
MXD3	0.94	6.92E-04	UNC119	0.61	2.07E-03
CXCL1	0.94	1.27E-03	S100A3	0.60	2.72E-02
PTGS2	0.93	1.10E-02	DHRS4L2	0.60	4.98E-02
SAA1	0.93	1.67E-05	TTC9	0.60	2.60E-02
TFEB	0.91	3.31E-03	ARHGAP33	0.60	3.01E-02
TAGLN	0.89	4.31E-04	RRAD	0.59	6.88E-04
MIR1914	0.89	4.18E-02	WIBG	0.59	5.08E-03
CX3CL1	0.89	4.58E-03	SOD2	0.59	2.91E-02
GRB7	0.89	1.07E-04			

Supplemental Table 7. 91 upregulated genes modulated by miR-339 through targeting enhancer and their targeting sites on enhancer in breast cancer cells.

Upregulated target_gene	miR339 _target _num	enhancer_ chr	enhancer_start	enhancer_end	log2Fold Change
GPER1	4	chr7	1066826	1085232	1.05
IL32	4	chr16	3069540	3074918	0.82
IL32	4	chr16	3108653	3110211	0.82
MUC6	4	chr11	1059960	1074107	1.23
PRSS30P	4	chr16	2917269	2919101	2.43
PTPN6	4	chr12	7026068	7054839	0.67
SLC43A2	4	chr17	1546736	1552353	0.68
TNK1	4	chr17	7253008	7267590	0.73
TNK1	4	chr17	7303186	7309418	0.73
TRIB3	4	chr20	326469	330075	0.64
ZG16B	4	chr16	2917269	2919101	0.65
ZG16B	4	chr16	2885027	2897659	0.65
IL32	3	chr16	3155959	3156760	0.82
PTPN6	3	chr12	7097504	7105013	0.67
TRIB3	3	chr20	396023	396829	0.64
VWA1	3	chr1	1409842	1410778	0.72
ADAP2	2	chr17	29232358	29234947	1.04
ARHGAP33	2	chr19	36247415	36250236	0.60
ARL9	2	chr4	57331303	57335414	1.49
ARL9	2	chr4	57410849	57411618	1.49
ARL9	2	chr4	57396642	57397388	1.49
ATP6V1B1	2	chr2	71203490	71206278	1.89
BOLA1	2	chr1	149902917	149912765	0.72
BOLA1	2	chr1	149855373	149861669	0.72
BOLA1	2	chr1	149819694	149827045	0.72
BOLA1	2	chr1	149830185	149835266	0.72
CCL20	2	chr2	228681910	228684969	1.32
CCL20	2	chr2	228726924	228747807	1.32
CDKN2D	2	chr19	10725994	10730369	0.75
CORO1A	2	chr16	30203328	30221731	0.74
CX3CL1	2	chr16	57450592	57452140	0.89
CXCL2	2	chr4	74969030	74984221	1.00
DHRS4L2	2	chr14	24475454	24476783	0.60
DMBT1	2	chr10	124325098	124359538	1.34
ERBB3	2	chr12	56513325	56524007	1.15
ERBB3	2	chr12	56497061	56500541	1.15
FPR1	2	chr19	52206587	52208952	3.54
FPR1	2	chr19	52210488	52212474	3.54

FPR1	2	chr19	52280380	52312573	3.54
G0S2	2	chr1	209817889	209841963	0.61
G0S2	2	chr1	209861563	209866588	0.61
GIPR	2	chr19	46132731	46146784	1.42
GIPR	2	chr19	46219311	46228601	1.42
GLI1	2	chr12	57822952	57825827	1.66
GP6	2	chr19	55517018	55518162	1.43
GP6	2	chr19	55582631	55583499	1.43
GPC2	2	chr7	99745527	99757386	1.43
HIST2H2BE	2	chr1	149809900	149816844	1.03
HIST2H2BE	2	chr1	149902917	149912765	1.03
HIST2H2BE	2	chr1	149819694	149827045	1.03
HIST2H2BE	2	chr1	149830185	149835266	1.03
HLA-F	2	chr6	29719383	29721364	0.81
HSD17B8	2	chr6	33215501	33218839	0.72
HSD17B8	2	chr6	33180621	33181862	0.72
HSD17B8	2	chr6	33122993	33130716	0.72
HSH2D	2	chr19	16270619	16274747	0.79
HSH2D	2	chr19	16291600	16310179	0.79
ICOSLG	2	chr21	45668432	45672520	1.13
IL20RB	2	chr3	136673199	136675755	1.06
IL4I1	2	chr19	50378341	50382384	0.97
IL4I1	2	chr19	50368679	50374249	0.97
IL4I1	2	chr19	50361288	50363758	0.97
IL4I1	2	chr19	50350985	50352724	0.97
JUNB	2	chr19	12868006	12868581	0.67
KREMEN1	2	chr22	29424561	29441935	0.88
LCN2	2	chr9	130952452	130956555	1.12
LCN2	2	chr9	130921129	130923361	1.12
LCN2	2	chr9	130898931	130900234	1.12
LIN7B	2	chr19	49587561	49590545	0.99
LIN7B	2	chr19	49630779	49631400	0.99
LIN7B	2	chr19	49645833	49654301	0.99
LLGL2	2	chr17	73510522	73513638	0.77
LOC113230	2	chr19	14128606	14135128	1.05
LOC113230	2	chr19	14228812	14231094	1.05
LPAR2	2	chr19	19783111	19784401	0.70
LPAR2	2	chr19	19701046	19729785	0.70
LRRC26	2	chr9	140072174	140085208	0.76
LRRC26	2	chr9	140043962	140057894	0.76
LRRC26	2	chr9	140015944	140025575	0.76
LRRC26	2	chr9	140111364	140114037	0.76
LYL1	2	chr19	13259332	13267351	0.76
LYL1	2	chr19	13226311	13230407	0.76

LYL1	2	chr19	13123166	13172894	0.76
LYL1	2	chr19	13253134	13255766	0.76
LYL1	2	chr19	13250950	13252287	0.76
LYL1	2	chr19	13241928	13244475	0.76
MALAT1	2	chr11	65237796	65242559	1.00
MALAT1	2	chr11	65211761	65216222	1.00
MALAT1	2	chr11	65220022	65225691	1.00
MALAT1	2	chr11	65313477	65314300	1.00
MALAT1	2	chr11	65307402	65309453	1.00
MAP3K8	2	chr10	30675338	30677851	0.75
MB	2	chr22	35957489	35966634	2.07
MB	2	chr22	36042195	36046587	2.07
MB	2	chr22	36017332	36026276	2.07
MDP1	2	chr14	24715766	24722016	0.82
MIR1914	2	chr20	62525175	62543306	0.89
MIR1914	2	chr20	62579989	62589817	0.89
MIR1914	2	chr20	62608147	62613767	0.89
MMP15	2	chr16	58018096	58039372	0.63
ODF3B	2	chr22	51001385	51002198	0.99
PDZK1IP1	2	chr1	47644518	47645909	0.95
PIK3IP1	2	chr22	31636597	31641041	0.88
PLXNB1	2	chr3	48511509	48515640	0.77
PLXNB1	2	chr3	48442865	48444331	0.77
POMZP3	2	chr7	76196940	76249732	0.87
PTPRH	2	chr19	55762160	55772120	0.78
PTPRH	2	chr19	55657110	55679136	0.78
RAB3D	2	chr19	11454003	11455400	0.71
RAB3D	2	chr19	11484671	11492129	0.71
RRAD	2	chr16	66981474	66982354	0.59
RRAD	2	chr16	66906398	66934725	0.59
RRAD	2	chr16	66958607	66962881	0.59
S100A3	2	chr1	153535651	153541942	0.60
S100A3	2	chr1	153504085	153510374	0.60
S100A3	2	chr1	153478833	153480236	0.60
S100A3	2	chr1	153526320	153527273	0.60
S100A3	2	chr1	153510764	153511912	0.60
S100A3	2	chr1	153569190	153586597	0.60
SAA1	2	chr11	18266626	18270419	0.93
SAA1	2	chr11	18333666	18351686	0.93
SAA1	2	chr11	18287572	18291258	0.93
SAA2	2	chr11	18287572	18291258	0.85
SERPING1	2	chr11	57404767	57407522	1.68
SERPING1	2	chr11	57332904	57336286	1.68
SH3BP1	2	chr22	38069631	38074959	0.65

SH3BP1	2	chr22	38028705	38032705	0.65
SLC14A1	2	chr18	43354594	43356226	2.63
SLC30A3	2	chr2	27515916	27526602	3.15
SLC6A9	2	chr1	44489784	44517654	0.72
SLC6A9	2	chr1	44443904	44446943	0.72
SLC6A9	2	chr1	44537407	44551791	0.72
SLPI	2	chr20	43921672	43922746	1.23
SOD2	2	chr6	160136690	160150793	0.59
SPINT1	2	chr15	41117482	41119073	1.18
SPINT1	2	chr15	41060748	41086722	1.18
SPINT1	2	chr15	41158131	41158861	1.18
ST14	2	chr11	129990092	129995471	0.62
SUSD2	2	chr22	24541384	24553819	1.10
TAF12	2	chr1	28927488	28929607	1.00
TAGLN	2	chr11	117092034	117093057	0.89
TAGLN	2	chr11	117076481	117078695	0.89
TFEB	2	chr6	41753318	41757437	0.91
TMEM53	2	chr1	45172065	45209732	0.63
TMEM53	2	chr1	45094043	45098973	0.63
TRAF1	2	chr9	123686026	123708942	0.75
TRAF1	2	chr9	123654168	123655985	0.75
TRAF1	2	chr9	123630057	123640849	0.75
UPK3B	2	chr7	76049723	76100123	3.47
VEGFA	2	chr6	43692239	43693775	0.99
VEGFA	2	chr6	43737116	43743665	0.99
VEGFA	2	chr6	43765787	43767267	0.99
VIPR1	2	chr3	42512852	42539768	0.72
WFDC2	2	chr20	44064964	44065911	0.82
WFDC2	2	chr20	44046755	44049142	0.82
WIBG	2	chr12	56364208	56375128	0.59
WNK4	2	chr17	40965765	40971520	0.67
ZNF385A	2	chr12	54772517	54773742	0.63
ZNF385A	2	chr12	54751489	54755011	0.63
ZNF385A	2	chr12	54804644	54826328	0.63
CX3CL1	1	chr16	57374914	57375690	0.89
CXCL2	1	chr4	74999482	75000209	1.00
FPR1	1	chr19	52209063	52210053	3.54
GHRL	1	chr3	10283668	10284208	1.42
GPC2	1	chr7	99814403	99815923	1.43
HIST2H2BE	1	chr1	149818748	149819685	1.03
IL6	1	chr7	22735332	22736848	1.39
MALAT1	1	chr11	65277556	65278370	1.00
MXD3	1	chr5	176726433	176728810	0.94
MXD3	1	chr5	176752513	176753833	0.94

PLXNB1	1	chr3	48475430	48476007	0.77
POMZP3	1	chr7	76262477	76263352	0.87
RAB3D	1	chr19	11403833	11404646	0.71
S100A3	1	chr1	153544391	153546358	0.60
S100A3	1	chr1	153524728	153525485	0.60
SH3BP1	1	chr22	37985671	37987628	0.65
SMPD3	1	chr16	68485709	68486751	0.85
TMPRSS2	1	chr21	42926255	42927180	1.18
UNC119	1	chr17	26889970	26891339	0.61
VIPR1	1	chr3	42492444	42494105	0.72
