

Supplemental Data:

Transcriptome integration analysis in hepatocellular carcinoma reveals discordant intronic miRNA-host gene pairs in expression

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SUPPLEMENTARY TABLES 1-6:

Supplementary Table 1. The primers used in qRT-PCR, 5-RACE and ChIP assays.

Purpose	Primers	Sequence (5' - 3')	
qRT-PCR	Primary mir-26b	Forward	AGTGGGCTCCTCCTCTAGGC
		Reverse	CCGAGCCAAGTAATGGAGAA
	Precursor mir-26b	Forward	ACCCAGTTCAAGTAATTCAGG
		Reverse	CAAGTAATGGAGAACAGGCTG
	U6	Forward	CTCGCTTCGGCAGCACA
		Reverse	AACGCTTCACGAATTTGCGT
	Primary CTDSP1	Forward	TTCCTCGAGGTCGGTGGAAAT
		Reverse	TCCCGCCTGAAGTTTTTCGTA
	18S	Forward	GACTCAACACGGGAAACCTC
		Reverse	AGCATGCCAGAGTCTCGTTC
5' RACE	Reverse GSP Primer 3	CACACCCTCTCTGGGCCTCTGACATT	
	Reverse GSP nested Primer 3	CCTAGGGTCTGGAGGCAGATGCCAAG	
ChIP	Amplicon 1	Forward	GTGGACCTCAGGATCTGGAC
		Reverse	AGTGGCCATCTGTTTGCCCT
	Amplicon 2	Forward	GCAGTGAGGACTTCGTACCC
		Reverse	TATTAAGGCGCCCACATAGG
	Amplicon 3	Forward	CAGGGGCGTTTCAGAGAAAGT
		Reverse	GCAGAAGAGTGAGTGGAGGAT
	Amplicon 4	Forward	GCCAGTGAACAACGCGGACT
		Reverse	GGTTCTGTGTGACTTTGGGA

Supplementary Table 2. The expression pattern of 59 intronic miRNAs with their host genes in LCS_HCC dataset.

miRNA/host gene pairs	miRNA		mRNA		Positive correlation*			
	FDR q-value	T vs. NT	FDR q-value	T vs. NT	NT		T	
					r-value	p-value	r-value	p-value
miR-10a /HOXB3	7.10E-22	0.46	5.30E-10	1.13	/	/	/	/
let-7g /WDR82	2.70E-28	0.49	9.60E-55	1.82	/	/	/	/
miR-126 /EGFL7	1.00E-21	0.52	1.00E-29	1.54	/	/	/	/
miR-26a-1 /CTDSPL	1.30E-16	0.56	1.10E-32	1.34	/	/	/	/
miR-26a-2 /CTDSP2	3.80E-14	0.56	1.20E-37	1.43	/	/	0.16	0.04
miR-139 /PDE2A	3.10E-14	0.58	6.60E-13	0.77	/	/	/	/
miR-26b /CTDSP1	2.80E-14	0.6	9.30E-16	1.29	/	/	/	/
miR-105-2 /GABRA3	6.10E-14	0.64	1.50E-19	1.17	/	/	/	/
miR-148b /COPZ1	4.40E-09	0.65	1.60E-78	2.49	0.15	0.04	/	/
miR-188 /CLCN5	2.30E-11	0.67	2.20E-01	1.05	/	/	/	/
miR-27b /C9orf3	5.50E-10	0.67	3.90E-02	0.91	/	/	0.22	0.003
miR-128-1 /R3HDM1	5.20E-19	0.70	1.60E-78	2.02	/	/	/	/
miR-152 /COPZ2	3.00E-12	0.70	4.30E-01	1.04	0.17	0.03	0.27	<0.001
Let-7f-2 /HUWE1	6.70E-18	0.72	3.40E-70	1.35	/	/	/	/
miR-98 /HUWE1	2.10E-12	0.72	3.40E-70	1.35	/	/	/	/
miR-93 /MCM7	4.80E-09	0.73	3.60E-77	4.12	/	/	/	/
miR-24-1 /C9orf3	5.20E-07	0.75	3.90E-02	0.91	/	/	/	/
miR-33 /SREBF2	3.40E-07	0.76	3.30E-52	2.16	/	/	/	/
miR-30c-1 /NFYC	1.30E-04	0.77	7.10E-53	1.80	0.26	0.001	0.33	<0.001
miR-23b /C9orf3	1.20E-04	0.80	3.90E-02	0.91	/	/	0.24	0.001
miR-153-1 /PTPRN	3.00E-02	0.81	2.10E-18	1.21	/	/	/	/
miR-342 /EVL	2.80E-05	0.82	6.60E-05	1.27	0.2	0.01	0.42	<0.001
miR-16-1 /DLEU2	8.90E-03	0.84	4.10E-50	1.52	/	/	/	/
miR-16-2 /SMC4	1.20E-02	0.86	8.30E-86	4.06	0.17	0.02	/	/
miR-208a /MYH6	1.10E-02	0.86	1.60E-24	1.17	/	/	/	/
miR-30e /NFYC	7.30E-03	0.86	7.10E-53	1.80	0.28	<0.001	0.41	<0.001
miR-181c /NANOS3	3.00E-02	0.88	7.90E-25	1.22	/	/	/	/
miR-140 /WWP2	2.20E-02	0.89	9.70E-63	1.59	/	/	/	/
miR-330 /EML2	1.30E-03	0.89	2.80E-54	1.33	/	/	/	/
miR-335 /MEST	1.90E-06	0.89	2.20E-04	1.27	/	/	0.23	0.002
miR-28 /LPP	4.10E-04	0.90	8.00E-30	1.49	/	/	/	/
miR-204 /TRPM3	5.40E-02	0.91	1.90E-46	1.26	0.17	0.03	/	/
miR-33b /SREBF1	2.50E-02	0.91	2.20E-19	1.81	/	/	/	/
miR-9-1 /C1orf61	4.90E-02	0.91	1.10E-28	1.22	/	/	/	/

miR-15a /DLEU2	1.40E-01	0.92	4.10E-50	1.52	/	/	/	/
miR-190 /TLN2	1.10E-01	0.93	3.00E-31	1.37	/	/	/	/
miR-326 /ARRB1	6.70E-02	0.93	5.40E-23	1.26	/	/	/	/
miR-196a-1 /HOXB7	1.00E-01	0.94	1.20E-31	1.32	/	/	/	/
miR-211 /TRPM1	1.90E-01	0.95	3.30E-24	1.22	/	/	0.16	0.04
miR-151a /PTK2	6.80E-01	1.00	8.50E-66	2.99	/	/	0.3	<0.001
miR-218-2 /SLIT3	8.90E-01	1.00	5.40E-15	1.15	/	/	0.17	0.03
miR-340 /RNF130	2.20E-01	1.03	1.20E-07	1.14	/	/	0.3	<0.001
miR-7-1 /HNRNPK	3.00E-01	1.05	4.60E-47	1.72	0.16	0.04	/	/
miR-32 /C9orf5	2.80E-01	1.07	5.30E-21	1.64	/	/	0.23	0.002
miR-101b /RCL1	4.00E-01	1.07	1.10E-49	0.27	/	/	/	/
miR-105-1 /GABRA3	8.40E-02	1.08	1.50E-19	1.17	/	/	/	/
miR-149 /GPC1	2.00E-02	1.09	1.00E-07	1.11	/	/	/	/
miR-103-1 /PANK3	4.80E-03	1.15	2.10E-33	1.81	/	/	/	/
miR-95 /ABLIM2	7.40E-03	1.16	3.10E-03	1.07	/	/	/	/
miR-25 /MCM7	9.80E-03	1.17	3.60E-77	4.12	0.19	0.01	0.23	0.002
miR-103-2 /PANK2	1.80E-03	1.18	7.30E-66	2.12	/	/	/	/
miR-135a-2 /RMST	5.20E-04	1.18	1.00E-21	1.35	/	/	/	/
miR-191 /DALRD3	4.60E-06	1.23	7.00E-89	1.97	/	/	0.24	0.002
miR-218-1 /SLIT2	8.50E-06	1.24	1.80E-07	1.22	/	/	/	/
miR-338 /AATK	9.50E-09	1.28	6.00E-24	1.32	/	/	/	/
miR-106b /MCM7	3.70E-09	1.35	3.60E-77	4.12	/	/	0.32	<0.001
miR-128-2 /ARPP21	2.00E-09	1.50	3.10E-11	1.13	/	/	/	/
miR-15b /SMC4	1.50E-06	1.50	8.30E-86	4.06	0.21	0.03	/	/
miR-224 /GABRE	8.20E-28	2.37	1.40E-38	3.76	0.26	0.001	0.29	<0.001

*Only significant positive correlation values were listed. “/” refers to no-significance.

Supplementary Table 3. Expression pattern of seven intronic miRNA clusters in LCS_HCC dataset.

miR clusters	T		NT		T vs. NT	
	r-value	p-value	r-value	p-value	1 st miR	2 nd miR
miR-15b-16-2						
miR15b/miR-16-2	0.58	<0.001	0.55	<0.001	up	down
miR-30c-1-30e						
miR-30c-1/miR-30e	0.86	<0.001	0.74	<0.001	down	down
miR-23b-27b-24-1						
miR-23b/miR-27b	0.67	<0.001	0.47	<0.001	down	down
miR-23b/miR-24-1	0.63	<0.001	0.52	<0.001	down	down
miR-27b/miR-24-1	0.60	<0.001	0.47	<0.001	down	down
miR-15a-16-1						
miR-15a/miR-16-1	0.79	<0.001	0.63	<0.001	down	down
miR-105-1-105-2						
miR-105-1/miR-105-2	-0.07	0.40	-0.34	<0.001	up	down
miR-106b-93-25						
miR-106b/miR-93	0.34	<0.001	0.31	<0.001	up	down
miR-106b/miR-25	0.57	<0.001	0.19	0.01	up	up
miR-93/miR-25	0.33	<0.001	0.33	<0.001	down	up
let-7f-2-miR-98						
let-7f-2/miR-98	0.08	0.31	0.14	0.08	down	down

Supplementary Table 4. The expression pattern analysis in tumor, non-tumor and the comparison of tumor vs. non-tumor tissues in TCGA_LIHA and TCGA_BRCA datasets.

Category		Non-tumor	Tumor	Tumor/non-tumor
<i>TCGA_LIHC Dataset</i>				
Discordant pairs_n(%)		323 (85.0)	161 (42.4)	209 (55.0)
	All	57 (15.0)	219 (57.6)	171 (45.0)
Concordant pairs_n(%)	$r \leq 0.3$	10 (2.6)	89 (23.4)	-
	$r > 0.3$	47 (12.4)	130 (34.2)	-
<i>TCGA_BRCA Dataset</i>				
Discordant pairs_n(%)		303 (79.7)	163 (42.9)	232 (61.2)
	All	77 (20.3)	217 (57.1)	148 (38.9)
Concordant pairs_n(%)	$r \leq 0.3$	29 (7.6)	112 (29.5)	-
	$r > 0.3$	48 (12.6)	105 (27.6)	-

Supplementary Table 5. Quadratic weighted inter-rater agreement (kappa) test of IPA Upstream regulators for each miRNA-host gene pair

miRNA/host gene pairs	Upstream regulators from Positive correlated surrogates		Upstream regulators from Negative correlated surrogates	
	Kappa-value	95% CI	Kappa-value	95% CI
<i>Tumor-related intronic miRNA-host gene pairs</i>				
let-7g/WDR82	-0.32	(-0.38, -0.26)	-0.47	(-0.51, -0.42)
miR-105-2/GABRA3	-0.38	(-0.48, -0.29)	-0.51	(-0.56, -0.46)
miR-10a/HOXB3	-0.36	(-0.44, -0.28)	-0.36	(-0.49, -0.24)
miR-126/EGFL7	-0.33	(-0.40, -0.27)	0.02	(-0.09, 0.13)
miR-148b/COPZ1	-0.21	(-0.31, -0.11)	-0.41	(-0.46, -0.36)
miR-26a-1/CTDSPL	-0.18	(-0.29, -0.07)	-0.35	(-0.42, -0.27)
miR-26a-2/CTDSP2	-0.29	(-0.37, -0.22)	-0.15	(-0.20, -0.11)
miR-26b/CTDSP1	-0.32	(-0.39, -0.25)	-0.37	(-0.42, -0.33)
miR-188/CLCN5	-0.12	(-0.15, -0.09)	-0.47	(-0.52, -0.42)
miR-15b/SMC4	-0.27	(-0.37, -0.18)	-0.42	(-0.46, -0.37)
miR-224/GABRE	-0.56	(-0.68, -0.45)	-0.51	(-0.60, -0.41)
miR-128-2/ARPP21	-0.33	(-0.37, -0.29)	-0.44	(-0.49, -0.38)
miR-139/PDE2A	-0.08	(-0.14, -0.01)	-0.27	(-0.33, -0.21)
miR-27b/C9orf3	-0.39	(-0.48, -0.29)	-0.24	(-0.29, -0.19)
<i>Representative intronic miRNA-miRNA pairs in clusters</i>				
miR-106b/miR-93	0.02	(-0.07, 0.10)	0.24	(0.17, 0.31)
miR-30c-1/miR-30e	0.09	(-0.02, 0.20)	0.19	(0.08, 0.29)

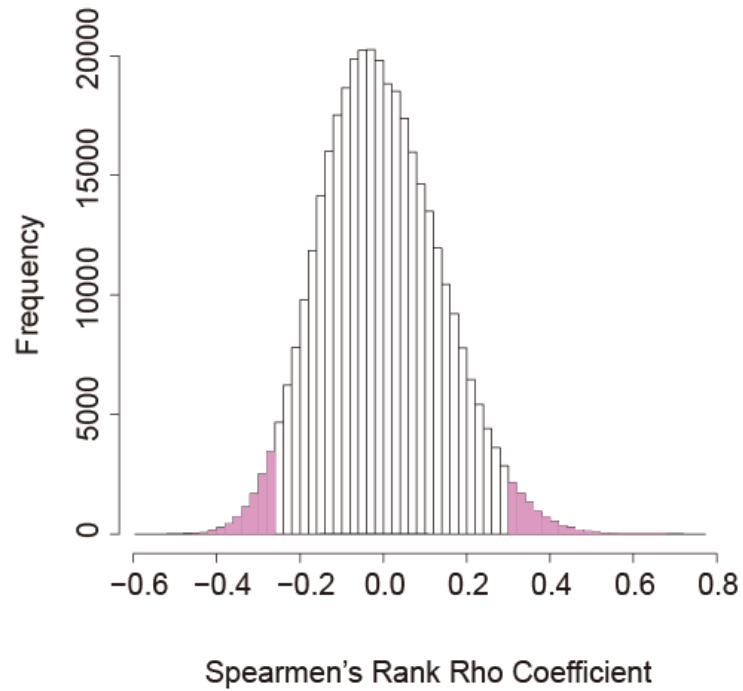
Supplementary Table 6. The promoter activity annotation of intronic miRNAs in ENCODE database

miRNAs		Host gene		miRNA location in host gene	Distance [#] (bp)	H3K4me3 signal				literature evidences
Name	Chromosome Location	Name	Chromosome Location			0-2.5kb of miRNA upstream	2.5-5kb of miRNA upstream	5-7.5kb of miRNA upstream	>7.5kb of miRNA upstream to 0.5kb of host gene TSS downstream	
let-7g	chr3: 52302294- 52302377 [-]	WDR82	chr3: 52,288,438- 52,312,659 [-]	intron 2	10282	weak promoter in GM12878	weak promoter in GM12878 and NHLF	weak promoter in GM12878, NHLF, HUVEC, HMEC, HSMM, NHEK, K562, H1-hESC,	weak and strong promoter in all 9 cell lines	-
mir-105-2	chrX: 151562884- 151562964 [-]	GABRA3	chrX: 151,335,634- 151,619,831 [-]	intron 1	56867	no signal	no signal	no signal	weak signal for H1-hESC	-
mir-10a	chr17: 46657200- 46657309 [-]	HOXB3	chr17: 46,626,232- 46,667,631 [-]	intron 1	10322	strong promoter in GM12878, K562, HUVEC, HSMM, NHLF; poised promoter in H1-hESC, NHEK	strong promoter in NHLF; weak promoter in HMEC and HSMM	strong promoter in NHLF, HSMM, HMEC, K562 and HUVEC; weak promoter in GM12878, K562, HMEC, HSMM and NHEK; poised promoter in H1-hESC, HepG2 and NHEK	no signal	-
mir-126	chr9: 139,565,054- 139,565,138 [+]	EGFL7	chr9: 139,557,379- 139,567,130 [+]	intron 7	7675	strong promoter in HUVEC	strong promoter in HUVEC; weak promoter in GM12878, H1-hESC, K562, HepG2, HMEC and HSMM; poised promoter in NHEK and NHLF	overlap with promoter of EGFL7; strong promoter in K562 and HUVEC; poised promoter in GM12878 and HepG2	-	Experimentally proved independent promoter
mir-148b	chr12: 54731000- 54731098 [+]	COPZ1	chr12: 54,718,874- 54,745,635 [+]	intron 1	12126	strong insulator in GM12878, HUVEC, HMEC, HSMM, NHEK and NHLF; weak promoter in K562	no signal	no signal	-	-
mir-26a-1	chr3: 38010895- 38010971 [+]	CTDSP1	chr3: 37,903,669- 38,025,960 [+]	intron 5	107226	very weak promoter signal in HSMM; strong insulator in GM12878, H1-hESC, K562, HUVEC, NHEK and NHLF	no signal	no signal	weak promoter in GM12878, K562, HepG2, HMEC, HSMM, NHEK, NHLF	-
mir-26a-2	chr12: 58218392- 58218475 [-]	CTDSP2	chr12: 58,213,710- 58,240,747 [-]	intron 5	22272	no signal	no signal	weak promoter in HMEC	weak promoter in K562, GM12878, HepG2, HSMM, NHEK, NHLF;	-

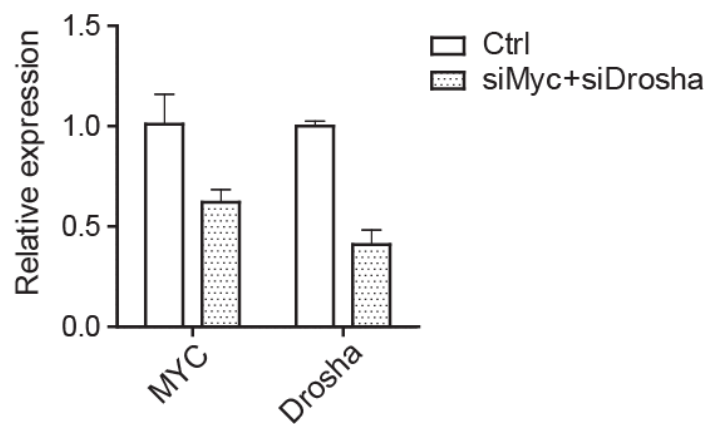
										strong promoter in the downstream 1.2kb of CTDSP2 in all 9 cells	
mir-26b	chr2: 219267369- 219267445 [+]	CTDSP1	chr2: 219,264,478- 219,270,664 [+]	intron 4	2891	strong promoter in GM12878, K562, HepG2, HUVEC, HMEC, HSMM, NHEK, NHLF; weak promoter in H1-hESC	-	-	-	-	-
mir-188	chrX: 49768109- 49768194 [+]	CLCN5	chrX: 49,687,225- 49,863,892 [+]	intron 3	80884	no signal	no signal	no signal	weak promoter in HSMM	-	-
mir-15b	chr3: 160122376- 160122473 [+]	SMC4	chr3: 160,118,347- 160,152,741 [+]	intron 5	4029	strong promoter in GM12878, K562, HepG2, HUVEC, HMEC, HSMM, NHEK; weak promoter in H1-hESC and NHLF; poised promoter in H1-hESC, NHEK	strong promoter in GM12787, H1-hESC, K562, HepG2, HUVEC, HMEC, HSMM, NHEK and NHLF	-	-	-	-
mir-224	chrX: 151127050- 151127130 [-]	GABRE	chrX: 151,121,596- 151,143,151 [-]	intron 6	16021	no signal	no signal	no signal	weak promoter in K562, HepG2, HUVEC, HMEC, NHEK; strong or weak promoter in the downstream 1kb of GABRE in K562, HepG2, HUVEC, HSMM, NHEK, NHLF	-	-
mir-128-2	chr3: 35785968- 35786051 [+]	ARPP21	chr3: 35,721,279- 35,835,988 [+]	intron 18	64689	no signal	no signal	no signal	no signal	Experimentally proved Pol III-binding independent promoter	-
mir-139	chr11: 72326107- 72326174 [-]	PDE2A	chr11: 72,287,184- 72,385,497 [-]	intron 2	59323	poised promoter in NHLF	no signal	no signal	weak promoter in HepG2; alternative splicing PDE2A promoter region had signals in K562, HepG2, HUVEC, HMEC, HSMM, NHEK, NHLF	-	-
mir-27b	chr9: 97847727- 97847823 [+]	C9orf3	chr9: 97,521,931- 97,849,500 [+]	intron 5	325796	no signal	no signal	no signal	no signal (There are promoters for some types of alternative splicing of c9orf3)	-	-

It refers to the distance from the first nucleotide of precursor miRNA to the transcriptional start site of host gene.

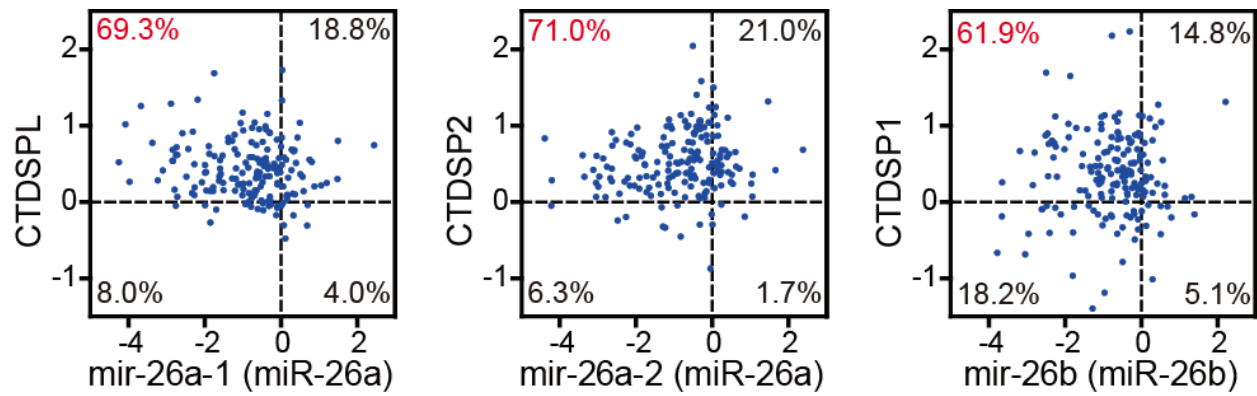
SUPPLEMENTARY FIGURES 1-4:



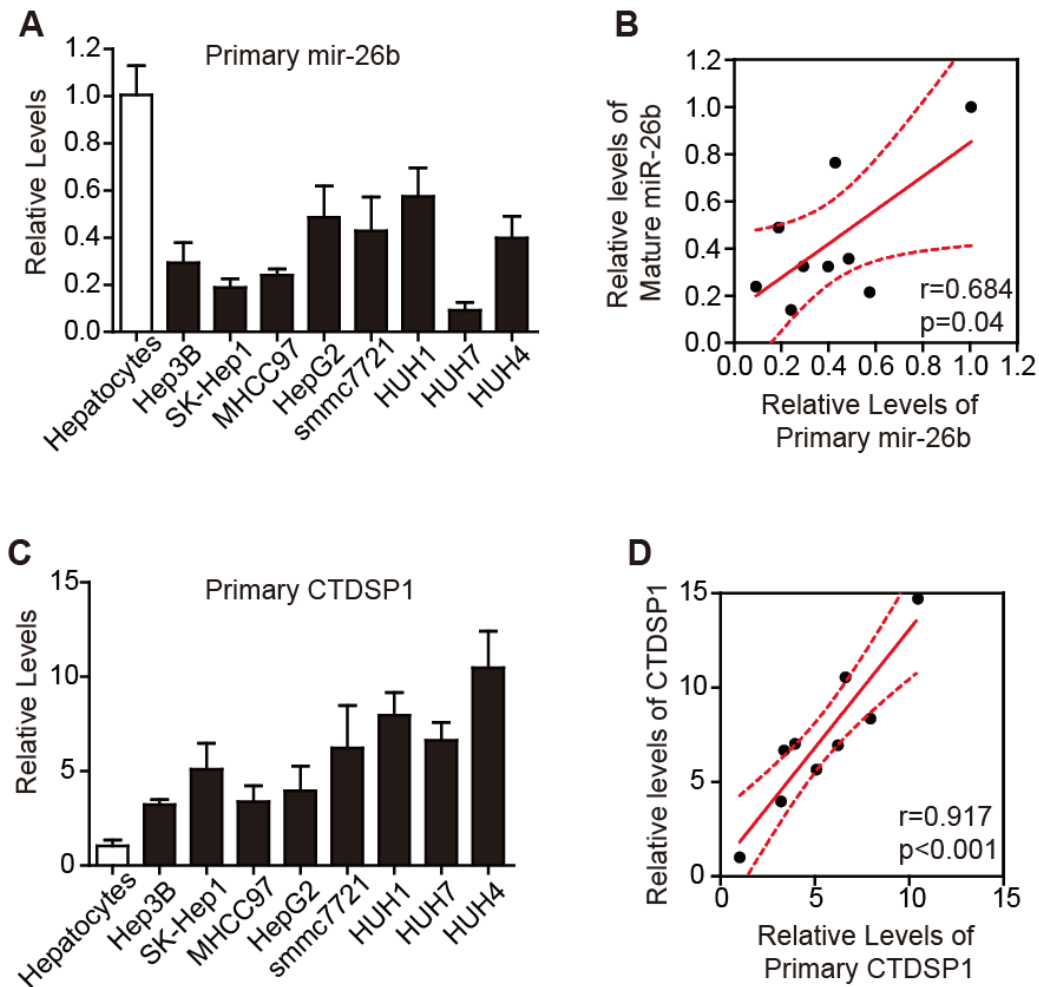
Supplementary Fig. 1. The histogram distribution of the Spearman's rank correlation coefficients between 14 tumor-related intronic miRNA/ 14 host gene pairs and 13101 mRNA genes.



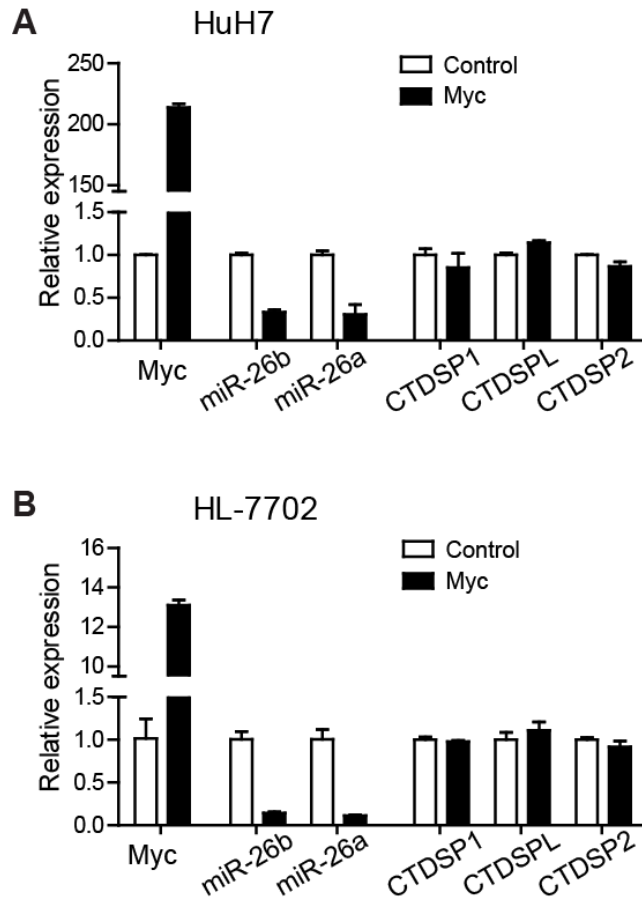
Supplementary Fig. 2. Myc and Drosha levels were measured by qRT-PCR in HuH7 cells at two days after the transfection of Myc and Drosha siRNAs.



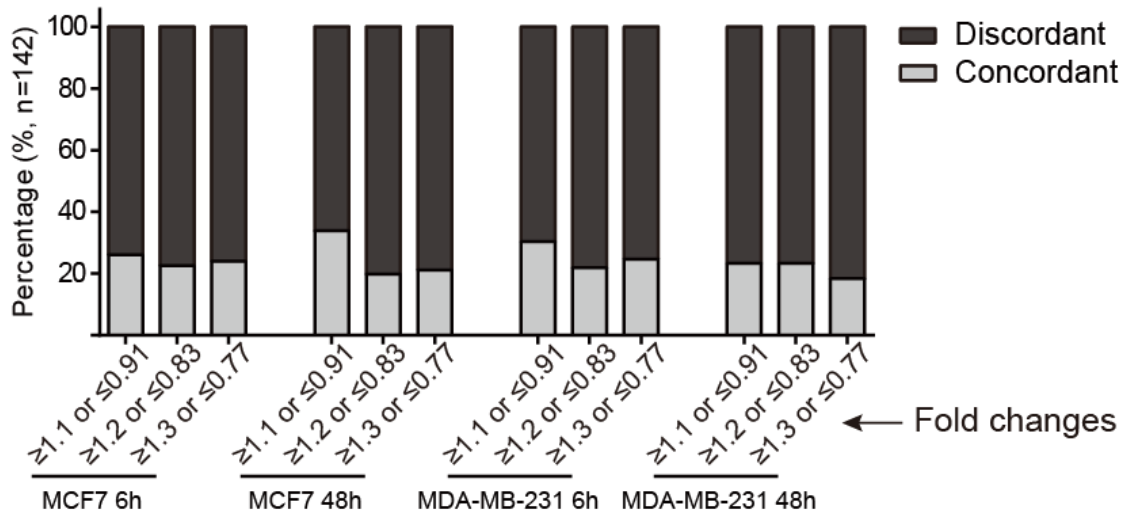
Supplementary Fig. 3. The discordant expression of miR-26s and their host genes in 176 HCC tissues. The expression of CTDSPs and miR-26s in paired tumor and non-tumor tissues from 176 patients with HCC.



Supplementary Fig. 5. The expression of primary mir-26b and primary CTDSP1 in HCC cell lines. (A) qRT-PCR analysis of primary mir-26b in hepatocytes and eight HCC cell lines. (B) Linear regression analysis between the level of primary mir-26b and the level of mature miR-26b. (C) qRT-PCR analysis of primary CTDSP1 in hepatocytes and eight HCC cell lines. (D) Linear regression analysis between the level of primary CTDSP1 and the level of mature messenger RNA CTDSP1. (A, C) The experiments were performed in triplicates and results were shown as mean \pm standard deviation.

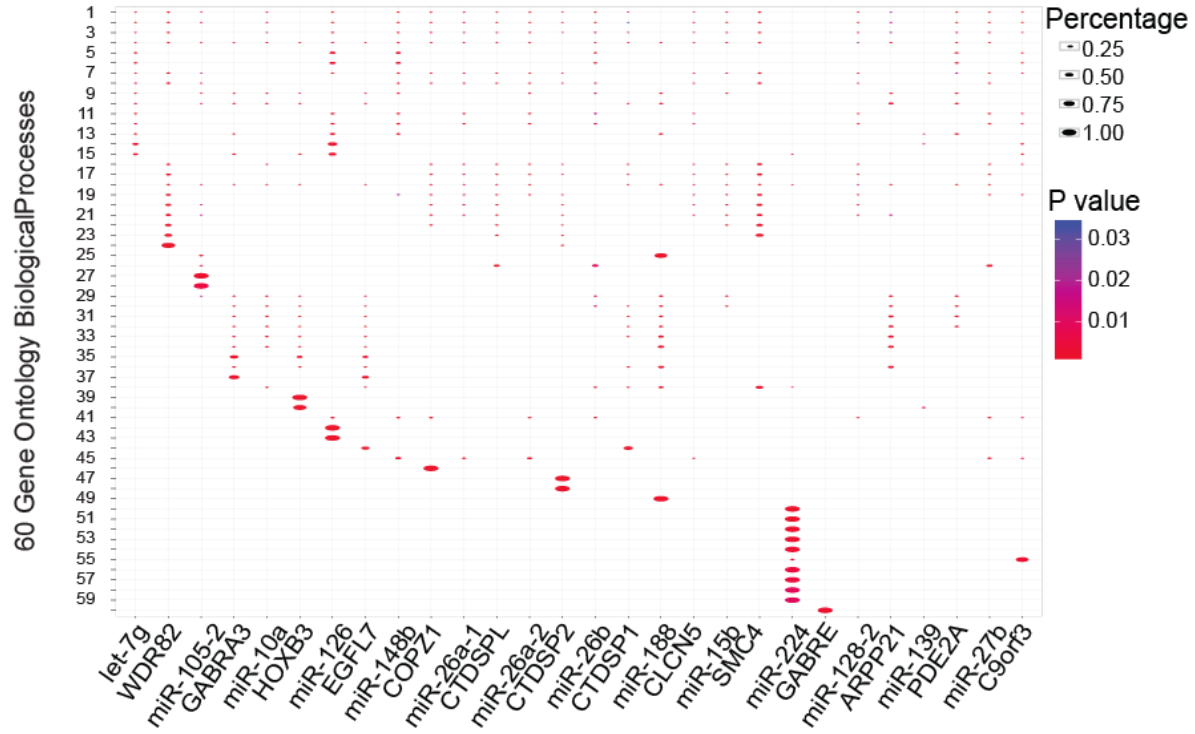


Supplementary Fig. 6. The expression of mature miR-26s and CTDSPs in HuH7 and HL-7702 cells with over-expressed Myc. (A) HuH7 cells were transfected with plasmids of Myc-PT3EF1a (Myc) or control PT3EF1a (control). 48 hours after transfection, the expression of Myc, miR-26s, CTDSPs were measured by qRT-PCR. (B) HL-7702 cells were transfected with plasmids of Myc-PT3EF1a or control PT3EF1a. 48 hours after transfection, the expression of Myc, miR-26s, CTDSPs were measured by qRT-PCR. The experiments were performed in triplicates and results were shown as mean \pm standard deviation.

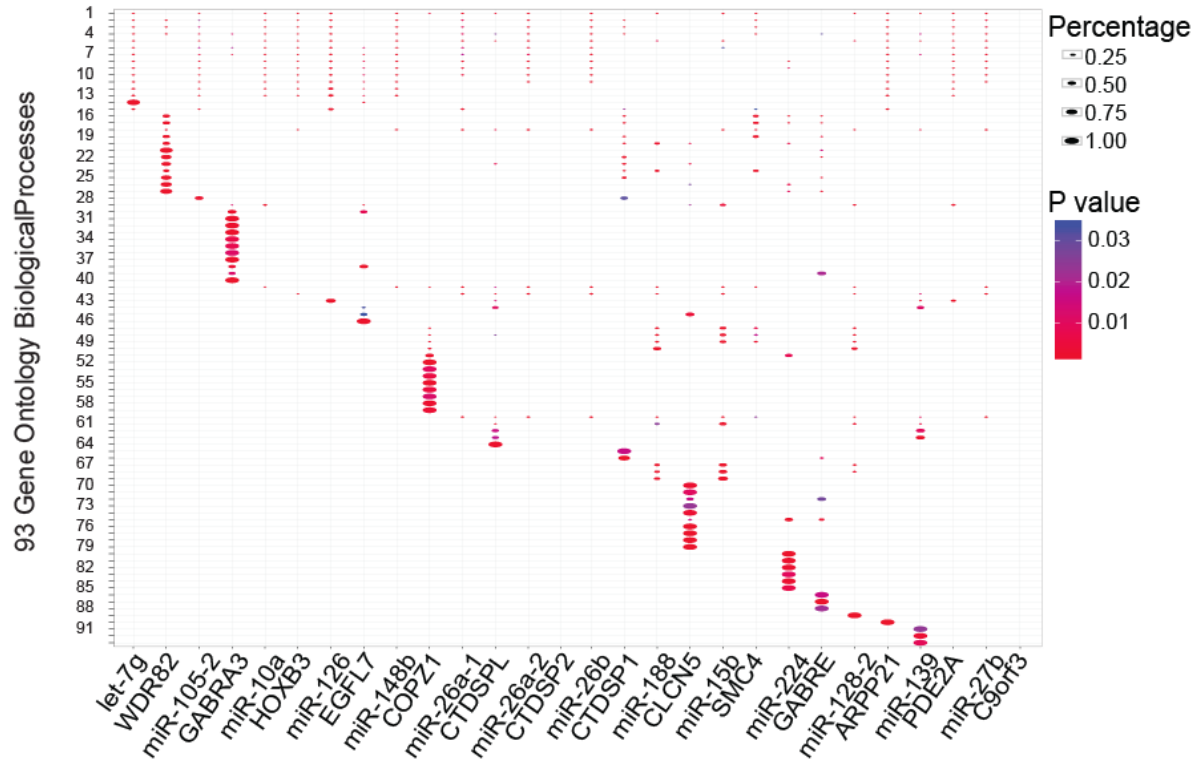


Supplementary Fig. 7. The expression pattern analysis of intronic miRNAs/host gene pairs in MCF7 and MDA-MB-231 breast cancer cells treated with ATAR for 6 hours and 48 hours (GSE18693). A total of 142 mature intronic miRNAs and their respective host genes were included. The miRNA or mRNA alteration was calculated using the expression intensity at 6 hours or 48 hours divided by that at 0 hour (untreated). Three different thresholds such as 1.1-fold, 1.2-fold and 1.3-fold were used to define the change of miRNA and mRNA. The percentage of concordant and discordant expression at different cell type and time point was shown.

A. With positive correlated gene surrogates



B. With negative correlated gene surrogates



Supplementary Fig. 8. The top 15 of enriched Gene Ontology biological process of 14

tumor-related intronic miRNA-host gene pairs. (A) The BP Ontology Enrichment Analysis based on positive correlated gene surrogates of 14 intronic miRNA-host gene pairs. The top 15 biological process were used for this figure and there were a total of 60 biological processes. These 60 biological processes from 1 to 60 were: organic substance metabolic process (5167); cellular metabolic process (4944); primary metabolic process (4945); single-organism cellular process (5607); single-organism metabolic process (1178); small molecule metabolic process (1050); nitrogen compound metabolic process (2851); organic cyclic compound metabolic process (2289); cellular response to stimulus (1746); single-multicellular organism process (1387); biosynthetic process (1268); organic substance biosynthetic process (1240); response to chemical stimulus (884); regulation of biological quality (320); transport (450); macromolecule metabolic process (2639); cellular macromolecule metabolic process (2322); regulation of cellular process (3539); cellular nitrogen compound metabolic process (2143); heterocycle metabolic process (1613); cellular aromatic compound metabolic process (1776); nucleobase-containing compound metabolic process (1327); nucleic acid metabolic process (974); gene expression (412); response to stress (225); regulation of metabolic process (416); regulation of macromolecule metabolic process (37); regulation of primary metabolic process (35); single organism signaling (1257); cell communication (1269); multicellular organismal development (935); anatomical structure development (927); system development (704); signal transduction (678); cellular developmental process (166); signal-organism developmental process (569); cell differentiation (118); cellular component organization (905); system process (43); organ development (50); protein metabolic process (1035); catabolic process (188); organic acid metabolic process (180); anatomical structure morphogenesis (86); cellular biosynthetic process (677); cellular protein metabolic process (150); RNA metabolic process (36); macromolecule biosynthetic process (34); regulation of response to stimulus (164); cellular membrane organization (6); membrane organization (6); organic substance transport (8); lipid metabolic process (6); intracellular transport (6); single-organism transport (46); establishment of localization in cell (7); macromolecule localization (7); cellular localization (7); protein localization (6); cellular response to stress (6). (B) The analysis based on negative correlated gene surrogates of 14 intronic miRNA-host gene pairs. The top 15 biological process were used for this figure and there were a total of 93 biological processes. These 93 biological processes from 1 to 93 were: single-organism cellular process (5032); organic substance metabolic process

(4010); primary metabolic process (3895); cellular metabolic process (4017); regulation of cellular process (3782); macromolecule metabolic process (3089); cellular macromolecule metabolic process (2709); nitrogen compound metabolic process (2464); cellular nitrogen compound metabolic process (2345); organic cyclic compound metabolic process (2280); cellular aromatic compound metabolic process (2056); nucleobase-containing compound metabolic process (1367); heterocycle metabolic process (1380); nucleic acid metabolic process (235); biosynthetic process (1153); single-organism metabolic process (520); small molecule metabolic process (461); cellular response to stimulus (1900); response to chemical stimulus (338); transport (320); catabolic process (141); organic acid metabolic process (178); response to stress (201); regulation of biological quality (360); oxoacid metabolic process (176); single-organism transport (164); carboxylic acid metabolic process (143); cellular biosynthetic process (103); cellular component organization (494); organelle organization (23); cellular component assembly (11); cellular component biogenesis (11); macromolecular complex subunit organization (10); positive regulation of macromolecule metabolic process (10); positive regulation of cellular metabolic process (10); positive regulation of metabolic process (10); macromolecular complex assembly (9); cell cycle (20); cellular catabolic process (21); cellular macromolecular complex assembly (8); single-multicellular organism process (2254); cell communication (1495); regulation of metabolic process (476); regulation of macromolecule metabolic process (63); cellular protein metabolic process (26); cell cycle process (9); multicellular organismal development (564); anatomical structure development (580); system development (515); organ development (161); system process (41); cell adhesion (21); nervous system development (19); cell development (18); neurological system process (17); cellular component movement (17); cellular component morphogenesis (13); transmission of nerve impulse (12); multicellular organismal signaling (12); single organism signaling (1517); signal transduction (388); regulation of primary metabolic process (51); regulation of cellular metabolic process (54); positive regulation of cellular process (20); organic substance biosynthetic process (49); lipid metabolic process (52); single-organism developmental process (357); cellular developmental process (290); cell differentiation (229); protein metabolic process (17); establishment of localization in cell (10); response to organic substance (23); cellular localization (10); carbohydrate derivative metabolic process (9); organonitrogen compound metabolic process (48); cellular membrane organization (8); membrane organization (8); symbiosis,

encompassing mutualism through parasitism (8); interspecies interaction between organisms (8); ion transport (17); cation transport (12); organonitrogen compound biosynthetic process (11); transmembrane transport (11); metal ion transport (10); G-protein coupled receptor signaling pathway (10); cellular response to chemical stimulus (13); response to inorganic substance (9); response to endogenous stimulus (9); anatomical structure morphogenesis (52); gene expression (190); macromolecule biosynthetic process (27); regulation of nitrogen compound metabolic process (26); regulation of cellular biosynthetic process (24).