

Supplementary information

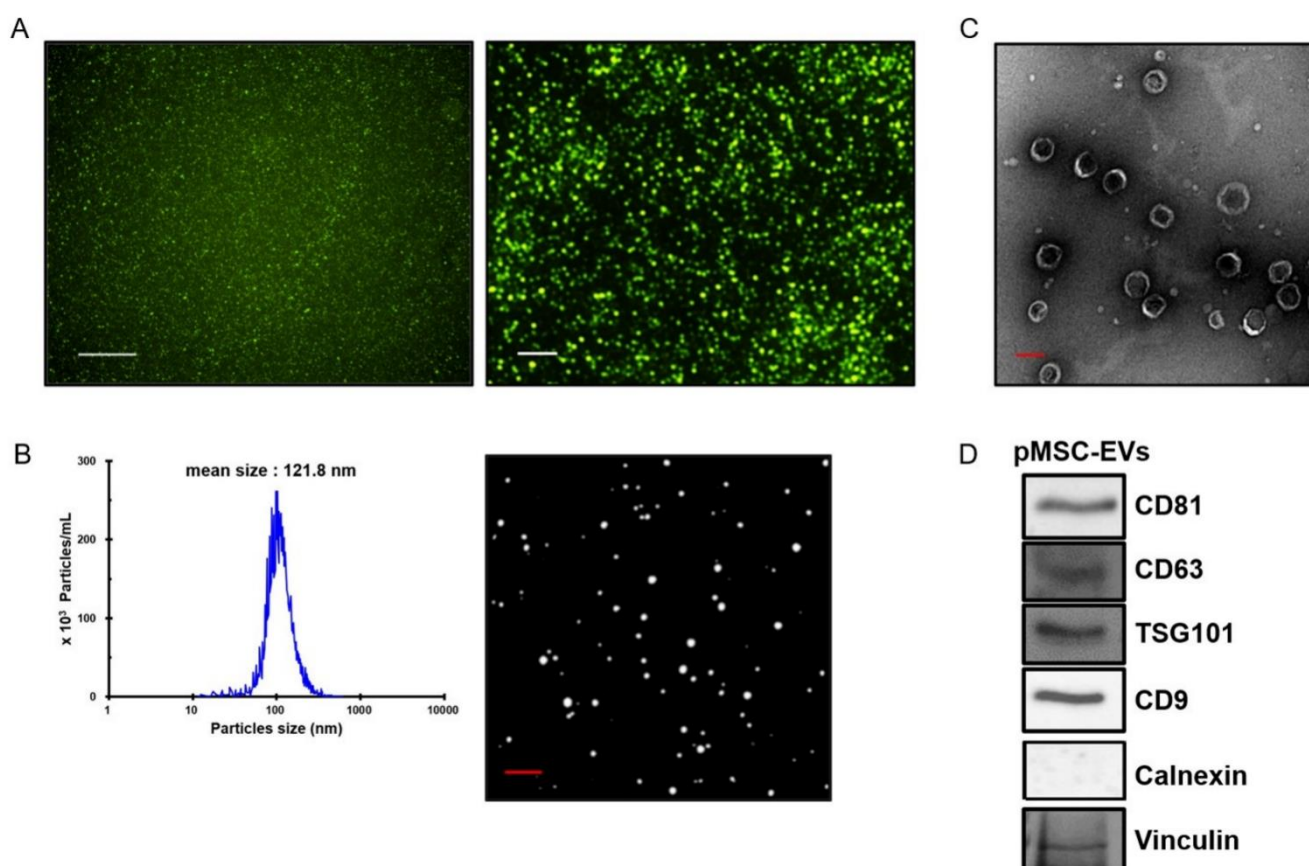


Figure S1. Characterization of human placenta derived mesenchymal stem cells-EVs. (A) Fluorescence microscopy images of EVs. EVs were stained for CD63, the common EV marker and Alexa 488 (green). Scale bar: 50 μ m (left), 4 μ m (right). (B) The average size of EVs is 121.8 nm in diameter measured by nanoparticle tracking analysis (NTA) and (C) transmission electron microscopy (TEM). Scale bar: 0.1 μ m. (D) Western blotting detected typical EV markers, including CD81, CD63, TSG101, CD9, and Calnexin, a negative marker.

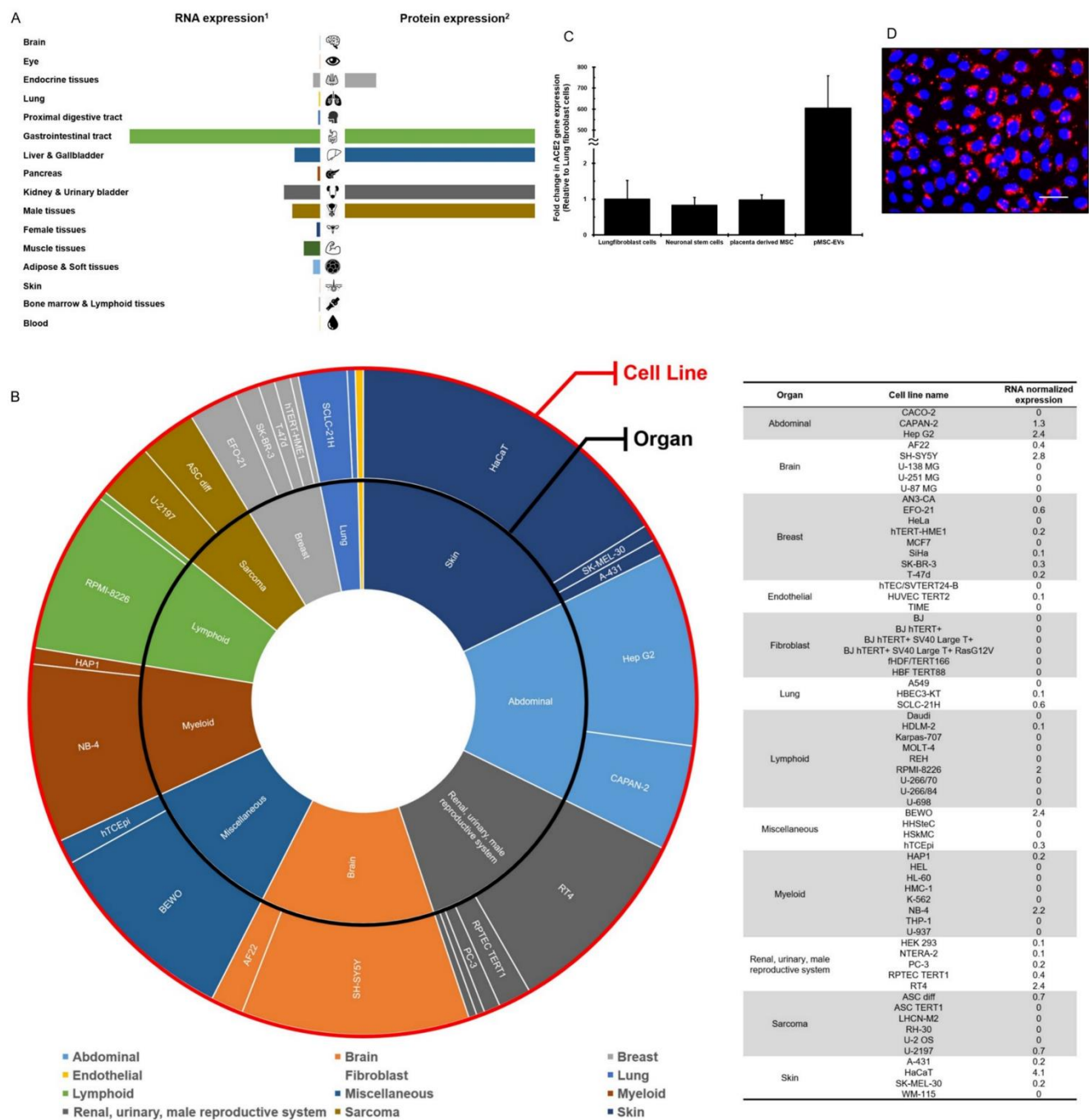


Figure S2. Organs expressing ACE2 receptors. (A) Summarization of ACE2 gene expression level of ACE2 receptor in various human tissues. Data were obtained from Human Protein Atlas (HPA). (1 indicates ACE2 RNA expression measured by RNA sequencing; 2 indicates ACE2 protein expression measured by in situ hybridization.) (B) Summarization of ACE2 expression in human cell lines. Expression data were acquired from HPA. (C) Gene expression levels of ACE2 in human lung fibroblasts (LL24), neuronal stem cells (NSCs), pMSCs, and pMSC-EVs. (D) Uptake of EVs of PKH26 labelled EVs by Beas-2B cells observed for 24 h after EV treatment.

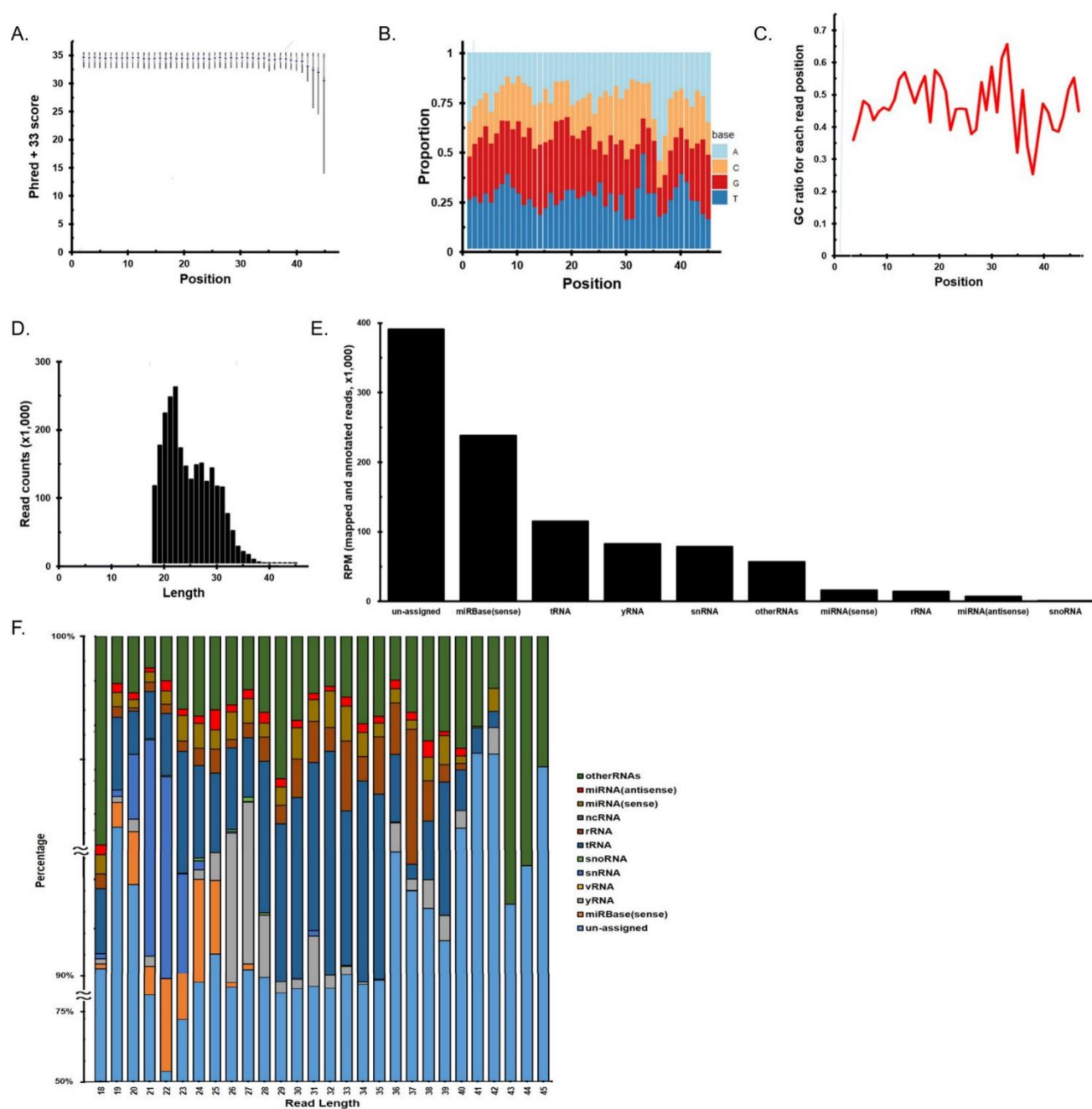
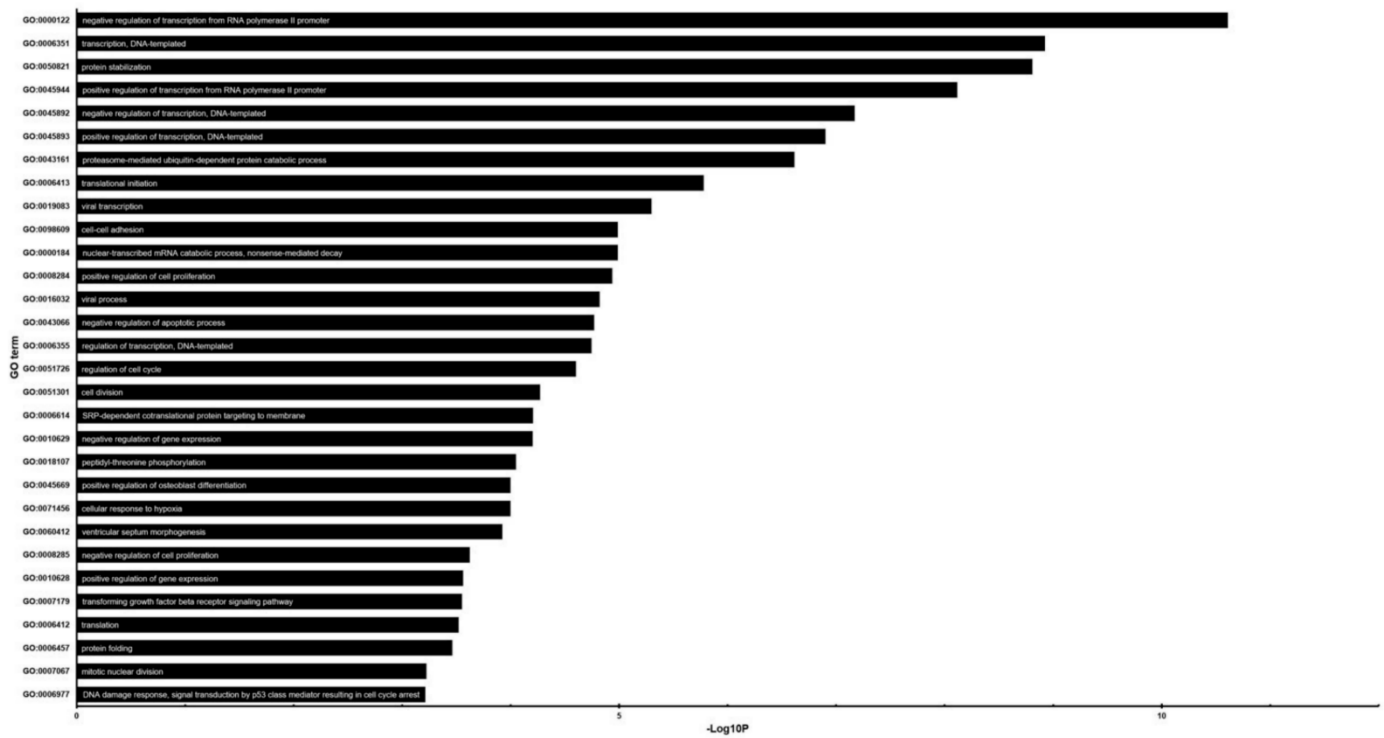
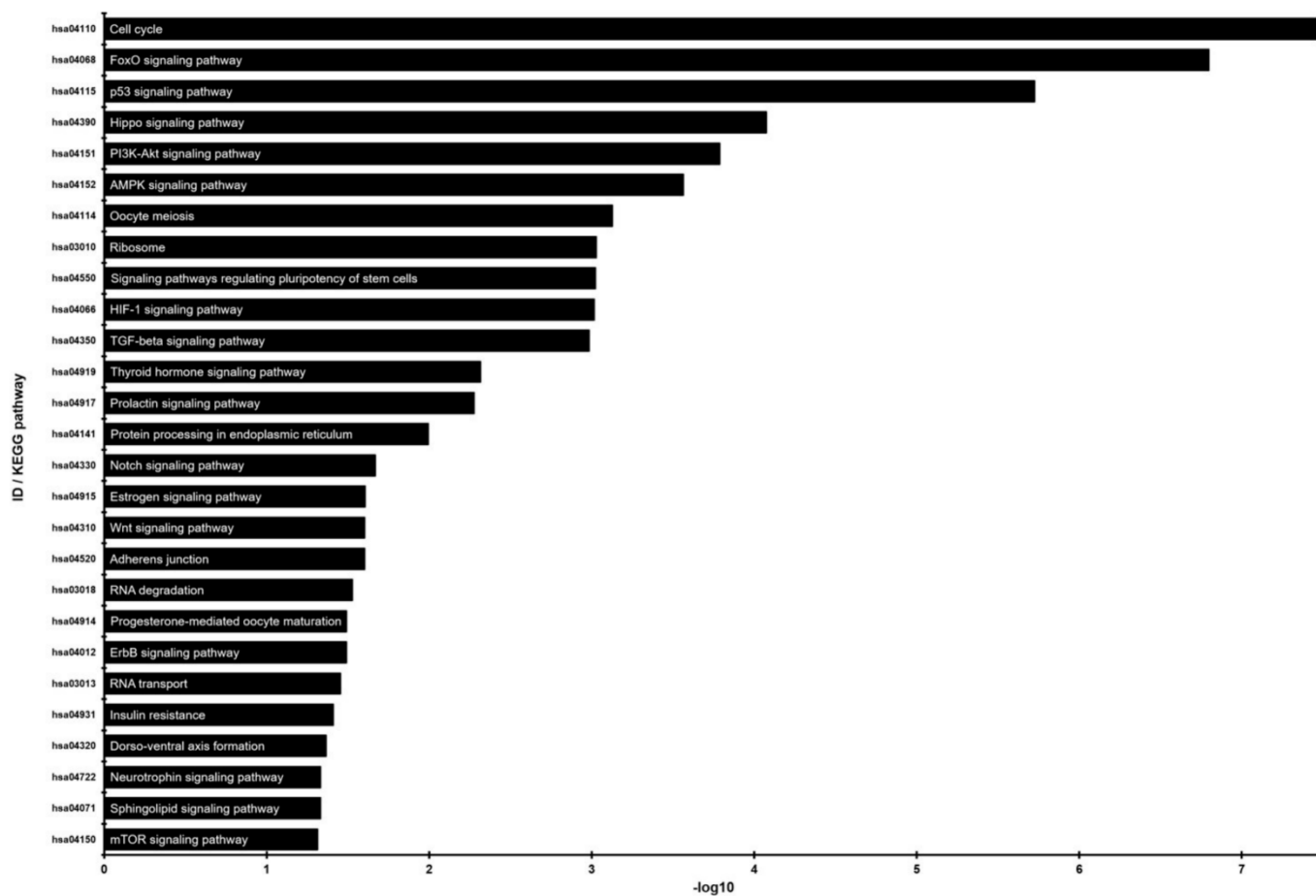


Figure S3. Quality control information for the small RNA sequencing library. (A) The Phred + 33 score for each read position. Total number of reads in the library, 24,834,367; average Phred score, 34.8. (B) The ratio of A, T, G, and C for each read position. (C) The GC ratio for each read position. (D) Histogram showing read length distribution. Read length ranged from 18 to 45. Most reads were 18–23 bases in length, corresponding to the size of miRNAs. (E) Table showing small miRNA library reads mapped on to the human genome. Unassigned reads were most common, followed by miRNAs, and tRNAs. (F) Classification of RNA versus read length. Reads of 20–24 bases, the size of most miRNAs, mapped mainly to miRNAs.

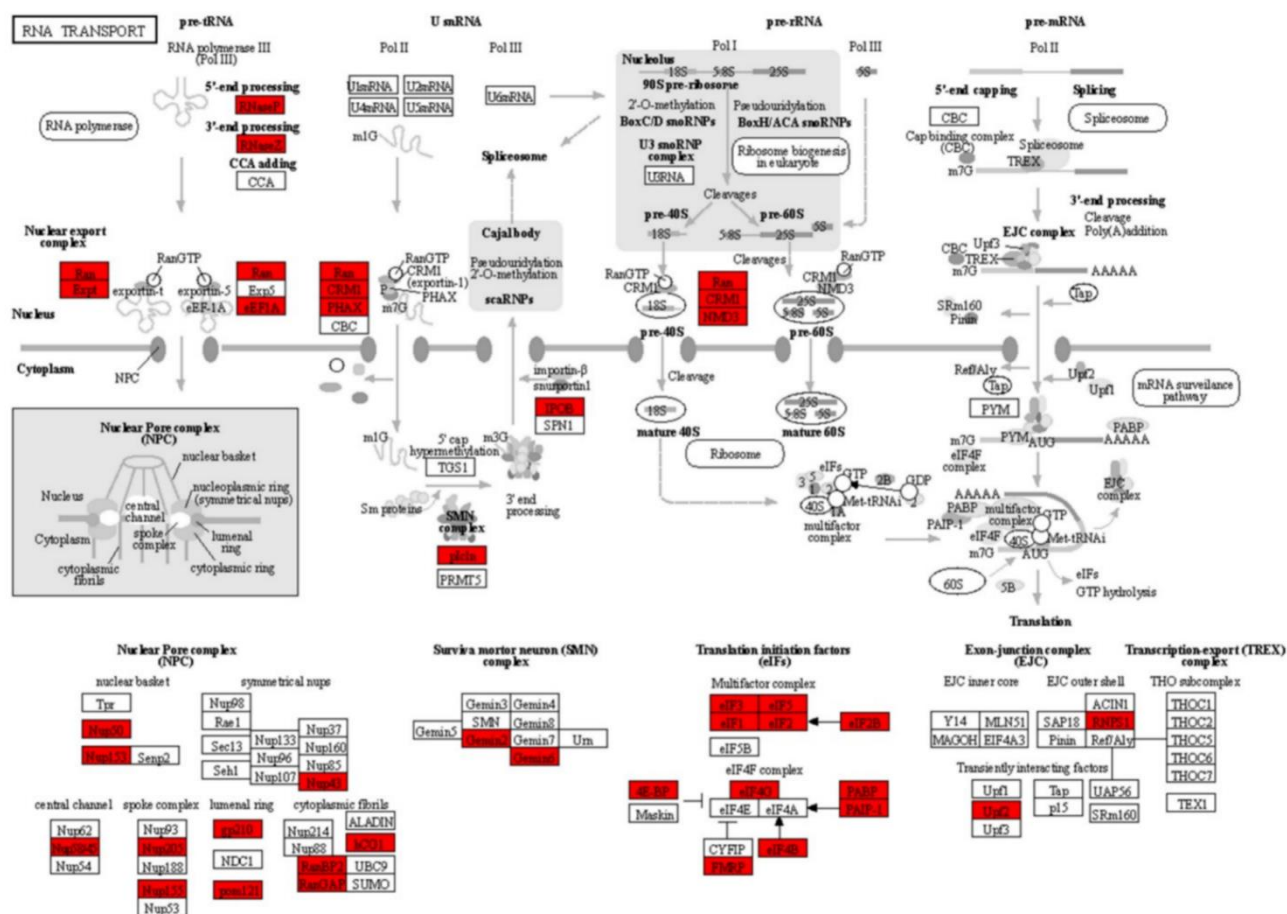
A.



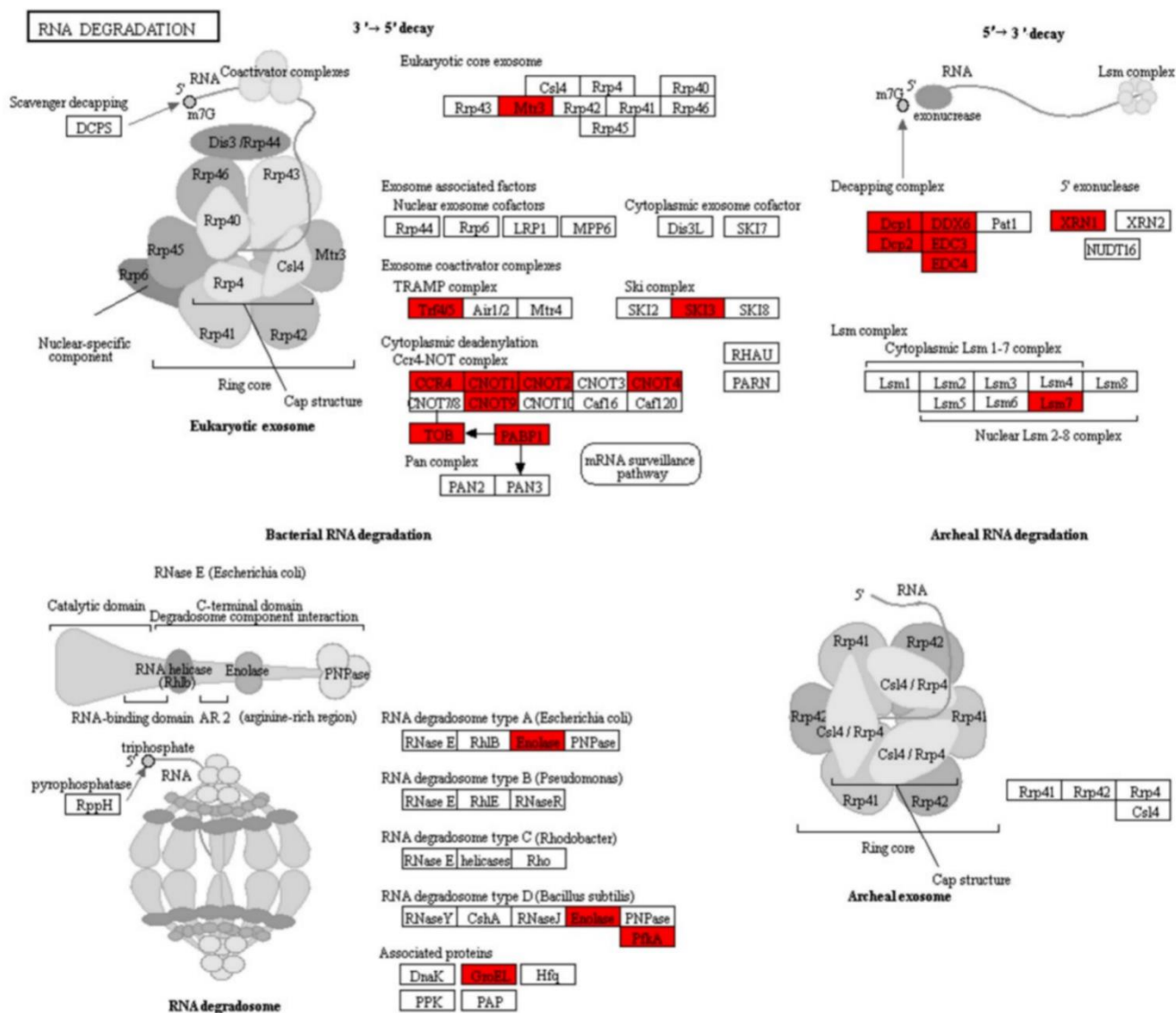
B.



C.



Eukaryotic RNA degradation



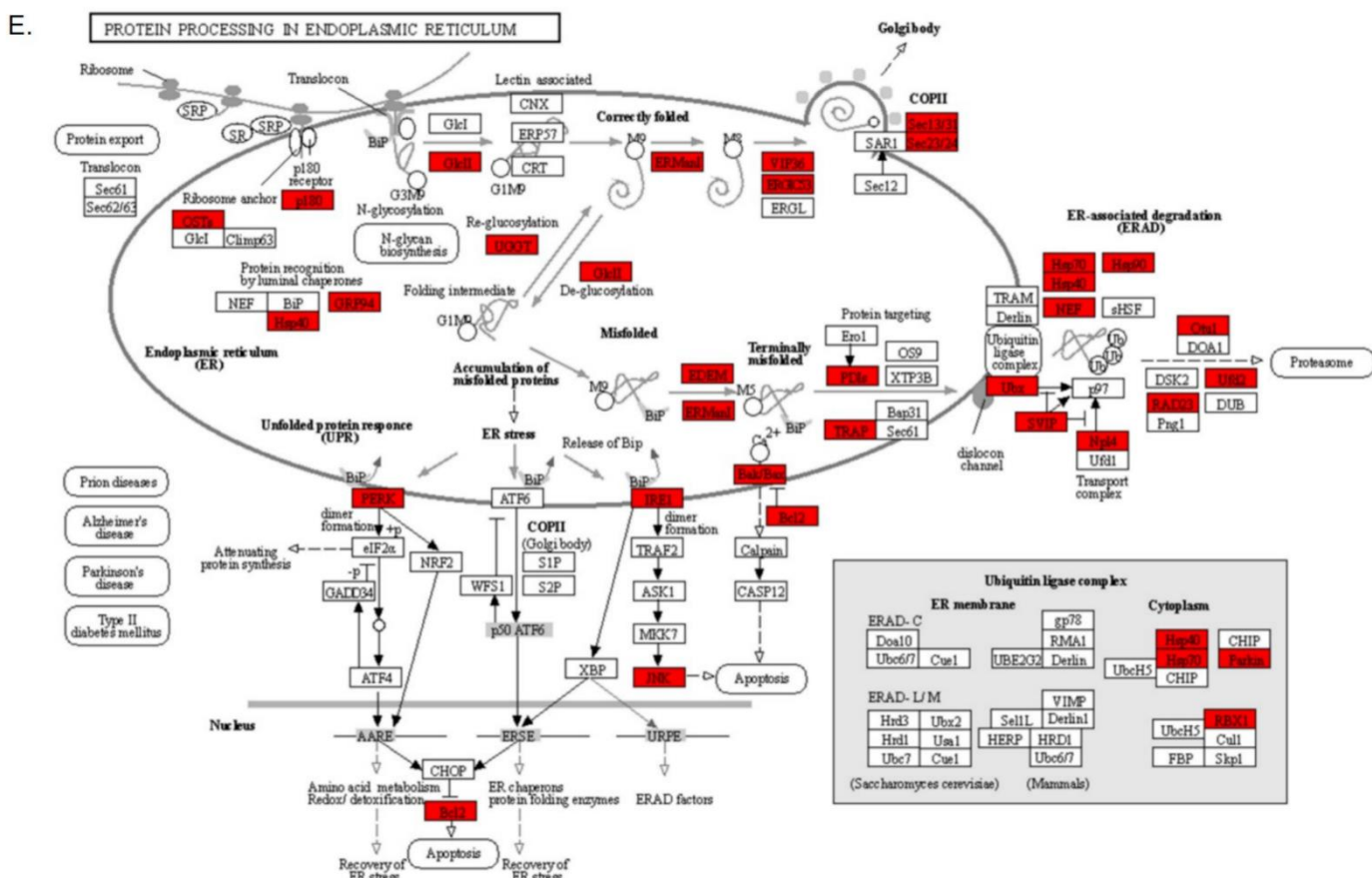
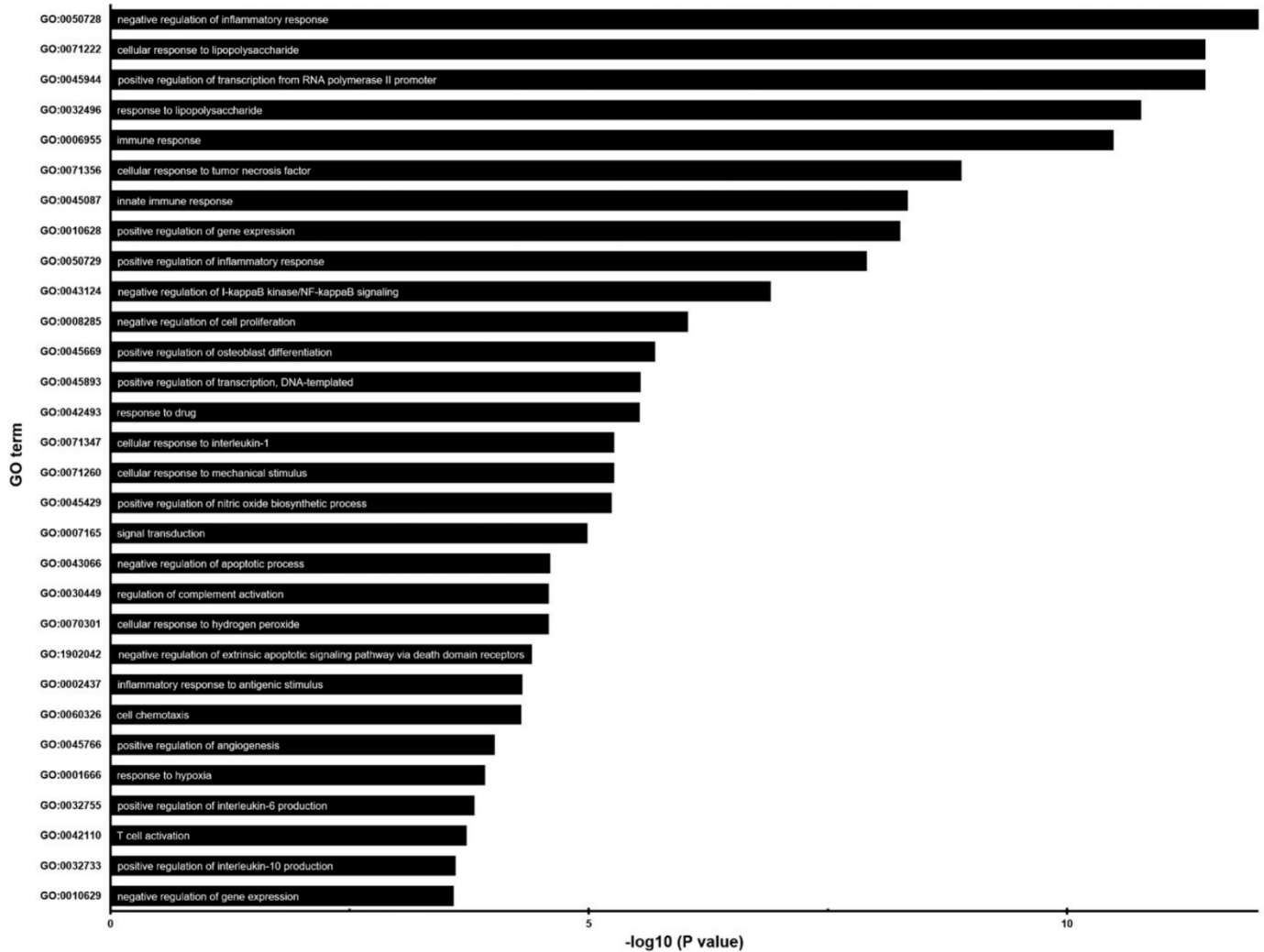
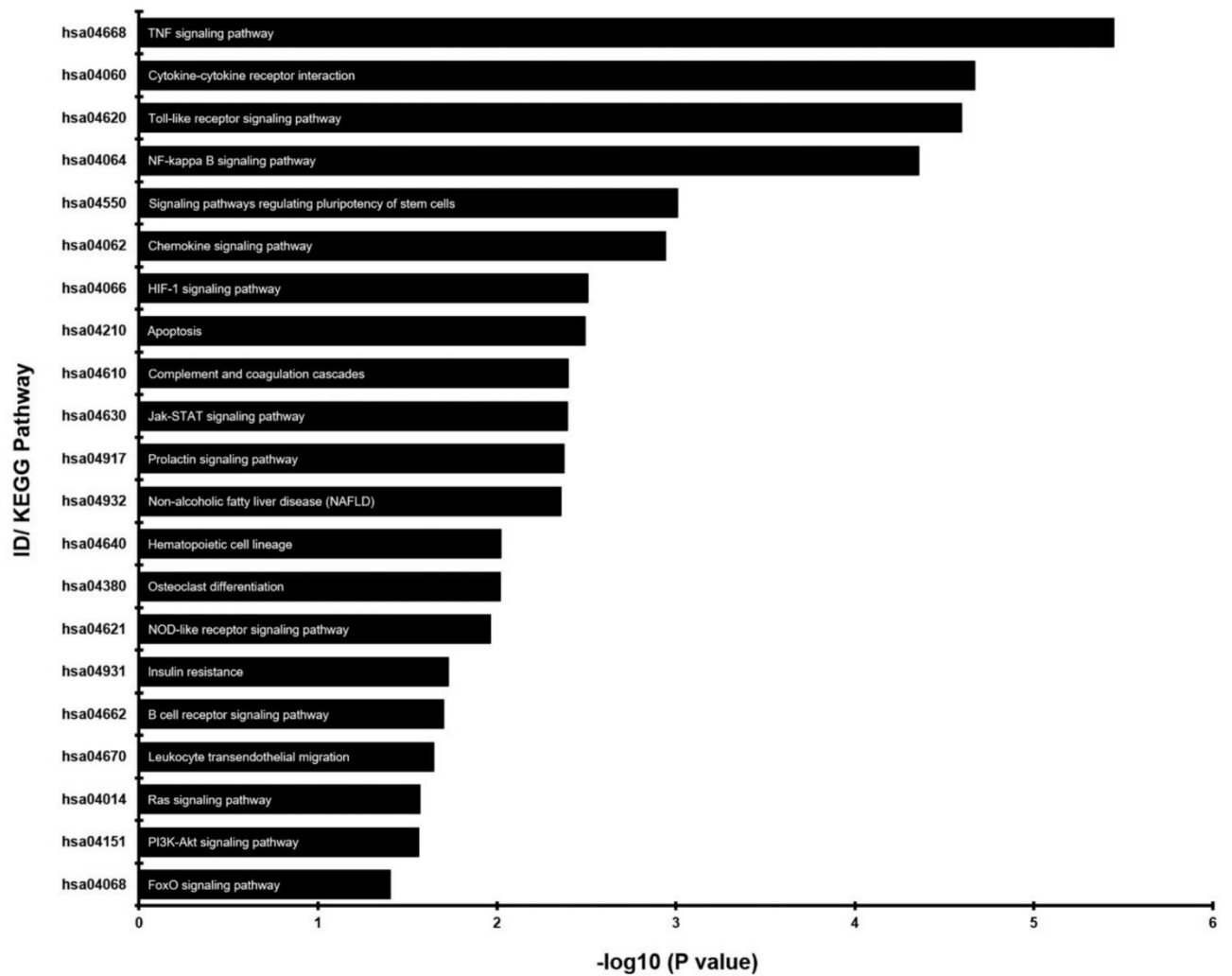


Figure S4. Function of mRNAs targeted by the five miRNAs. (A) Statistical enrichment analysis of GO terms for the target genes of the miRNAs. The plot shows the top 30 GO terms. The x axis shows minus log10 transformed adjusted p-values and the y axis shows the GO terms. (B) Statistical enrichment analysis of 83 inflammatory associated genes in KEGG pathways. The pathway showing adjusted p-values < 0.05 is presented in the plot. The x axis shows minus log10 transformed and adjusted p-values, and the y axis shows the names of the KEGG pathway i.e., RNA transport (C), RNA degradation (D), protein processing in endoplasmic reticulum (E), and TGF-BETA signaling pathway (F). The red box in each pathway indicates the gene targeted directly by miRNAs.

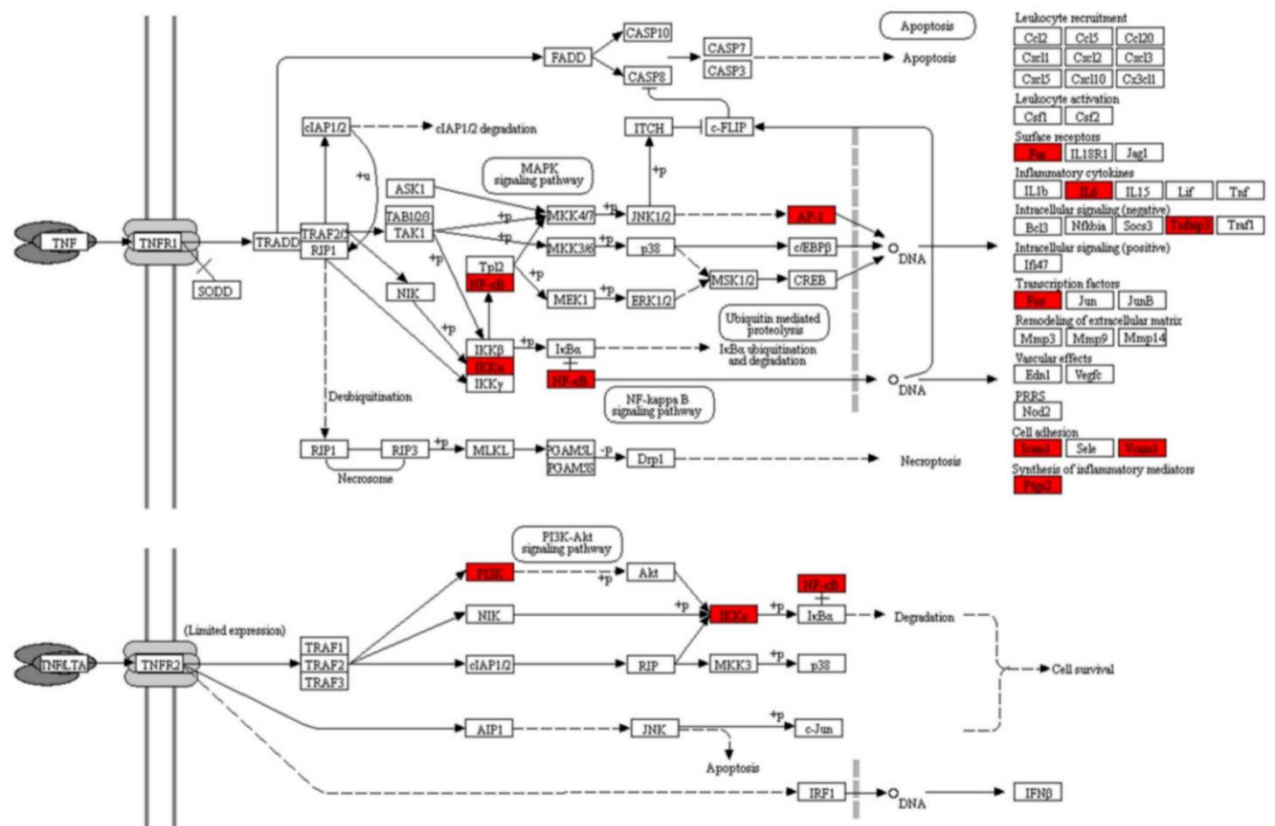
A.



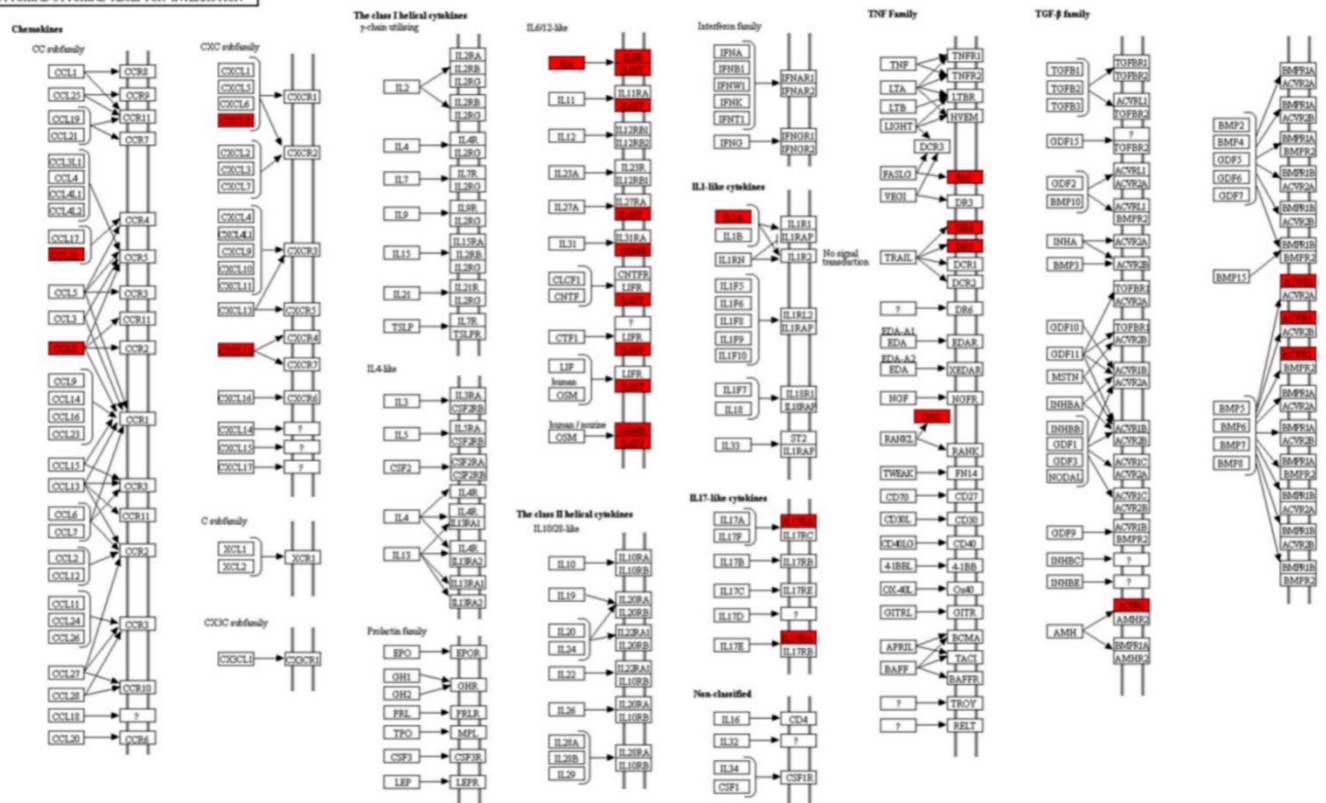
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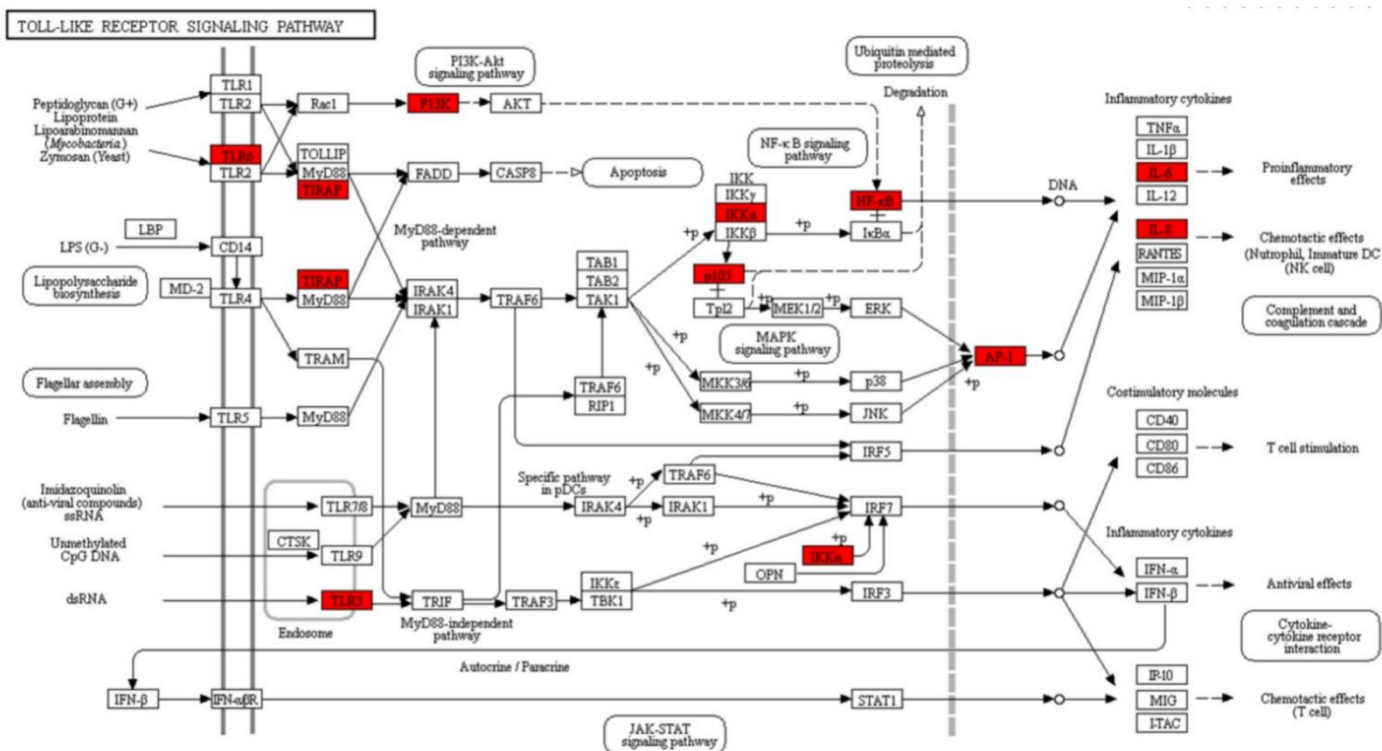
C. TNF SIGNALING PATHWAY



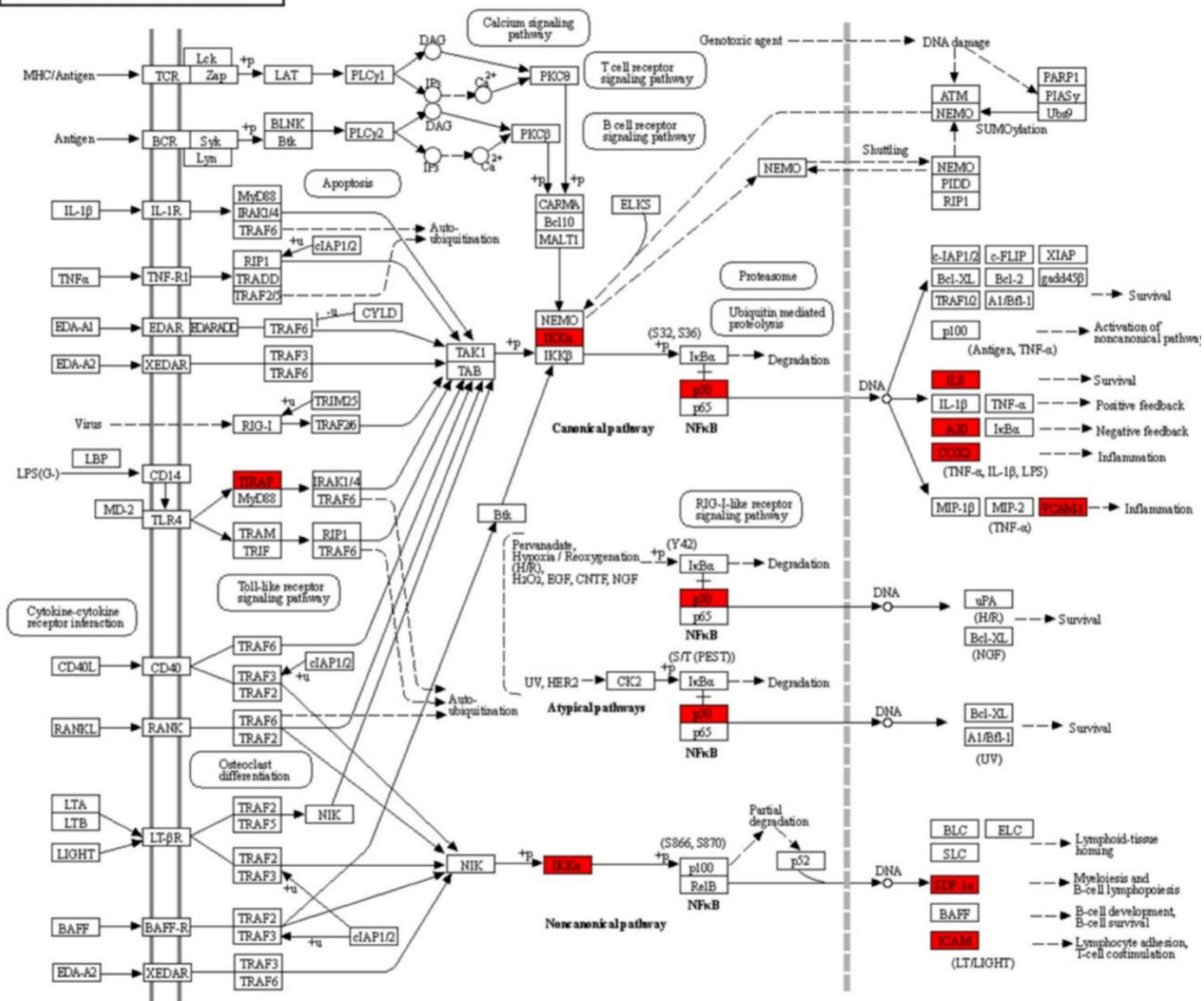
D. CYTOKINE-CYTOKINE RECEPTOR INTERACTION



TOLL-LIKE RECEPTOR SIGNALING PATHWAY



F. **NF-KAPPA B SIGNALING PATHWAY**



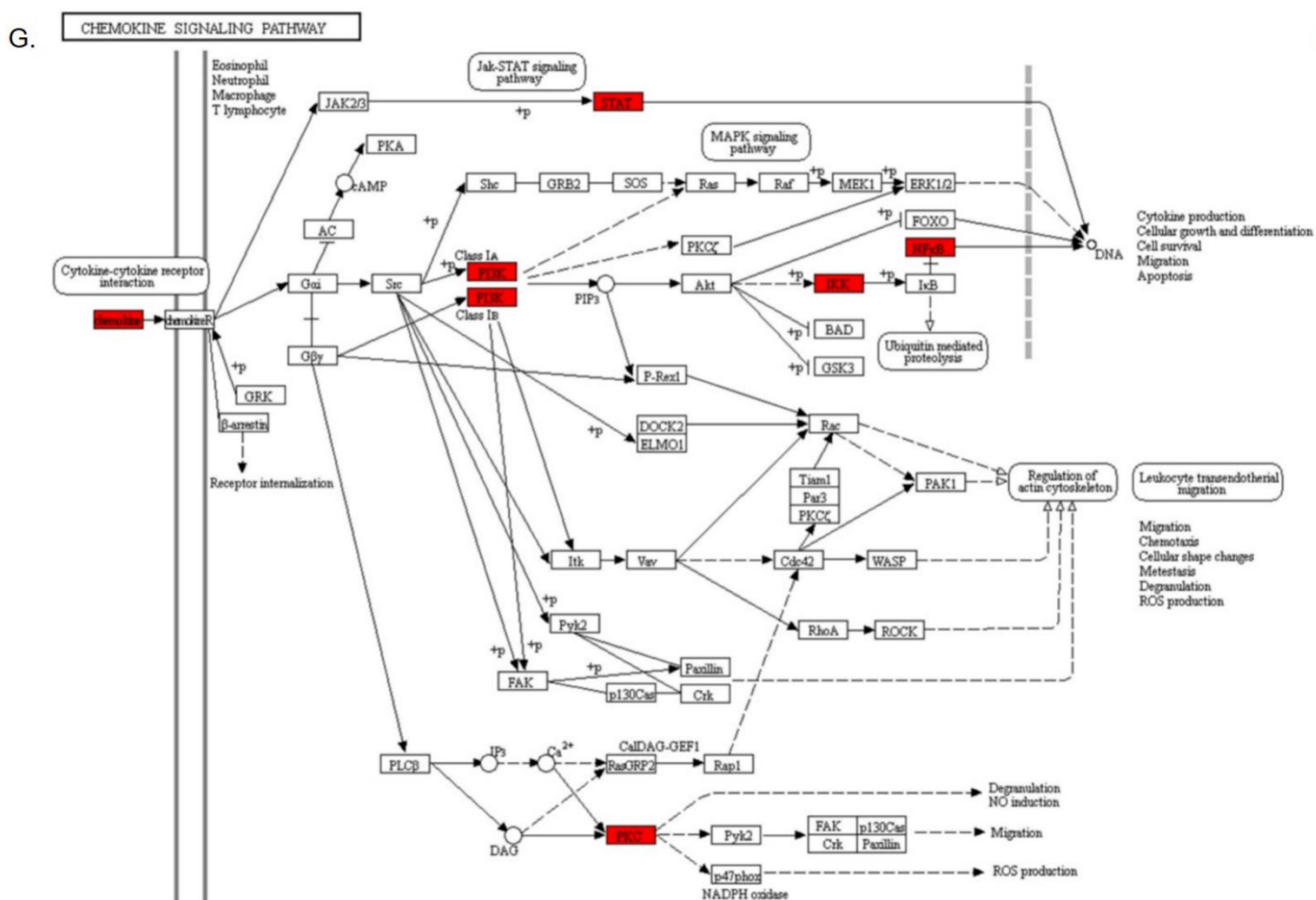


Figure S5. Significant inflammatory KEGG pathways regulating by the targets of the five miRNAs. (A) Statistical enrichment analysis of GO terms for 83 inflammatory associated genes. The plot shows the top 30 GO terms. The X axis shows minus log₁₀ transformed and adjusted p-values and the y axis shows the GO terms. (B) Significant pathways involving the 83 genes targeted by the five miRNAs. The 83 genes are predicted to be involved in inflammatory responses through pathways such as TNF signaling (C), Toll-like receptor signaling (D), cytokine-cytokine interactions (E), NF-kAPPAB signaling (F), and chemokine signaling (G). The red box in each pathway indicates the gene targeted directly by the miRNAs.

Table S1. The expression levels of 84 common miRNAs present in EVs derived from eight MSCs cultured under various conditions and six PD-EVs.

miRNA	ID	MSC1-EVs	MSC2-EVs	MSC3-EVs	MSC4-EVs	MSC5-EVs	MSC6-EVs	MSC7-EVs	MSC8-EVs	PD1-EVs	PD2-EVs	PD3-EVs	PD4-EVs	PD5-EVs	PD6-EVs
hsa-let-7a-5p	MIMAT0000062	94794.5	174629.0	46080.8	143994.2	150493.2	149839.8	85700.1	143439.6	144317.8	61717.9	162406.0	183726.9	107008.0	44679.7
hsa-let-7b-5p	MIMAT0000063	24148.8	27689.1	27639.8	36074.7	40177.1	42825.4	30255.1	41274.1	6056.7	22314.1	67574.5	66459.6	60121.6	126851.1
hsa-let-7c-5p	MIMAT0000064	12691.4	15227.9	7272.3	2232.5	1315.5	1350.5	1631.8	1597.7	292.5	5093.9	4038.8	4228.7	22756.9	2550.9
hsa-let-7d-3p	MIMAT0004484	2471.4	2467.9	2261.5	1311.6	3020.3	4473.8	5158.8	4006.1	101.5	475.9	4799.9	3327.8	998.0	464.7
hsa-let-7d-5p	MIMAT0000065	6419.2	5729.5	4334.5	6996.3	7653.0	8463.9	5703.0	8485.1	7587.0	7381.3	9765.3	17322.6	14850.8	4868.8
hsa-let-7e-5p	MIMAT0000066	1135.1	12220.7	940.4	6093.1	4536.5	2901.6	27.4	2320.5	203.8	87.5	783.8	12.4	207.4	175.0
hsa-let-7f-5p	MIMAT0000067	28077.8	31777.1	8165.9	17125.9	29276.5	19973.1	9935.5	19680.1	105722.7	31636.4	7414.8	10400.3	33481.6	51633.5
hsa-let-7g-5p	MIMAT0000414	8550.7	6416.1	5405.9	6606.7	8709.1	8111.8	7245.7	8316.0	121519.6	25982.6	22060.0	23165.7	22722.5	21268.4
hsa-let-7f-5p	MIMAT0000415	8767.2	13644.8	8980.2	21659.4	18630.5	15206.3	11782.9	15445.5	25622.5	12732.9	42426.7	30302.2	10657.1	10663.7
hsa-miR-1-3p	MIMAT0000416	288.2	153.7	678.5	319.9	61.9	968.3	1539.6	218.1	74.5	346.4	7.6	1894.7	138.6	348.8
hsa-miR-100-5p	MIMAT0000098	1695.1	20479.4	6424.4	5349.3	13293.7	9368.7	5170.4	3067.4	192.2	2849.6	531.9	1576.6	11035.3	1276.0
hsa-miR-103a-3p	MIMAT0000101	2316.2	789.5	1370.3	3897.2	1116.2	3332.8	3476.3	2741.9	2594.7	1123.3	9689.5	4620.3	963.6	1507.8
hsa-miR-10a-5p	MIMAT0000253	3666.6	27949.7	6109.7	3047.1	9902.0	13208.4	7132.7	2501.0	198.0	173.8	1130.6	828.6	3163.6	522.7
hsa-miR-122-5p	MIMAT0000421	45289.8	516.1	55547.5	319.9	6919.5	6690.0	4346.4	4788.4	124.6	2633.8	3602.2	2717.5	19938.2	3478.1
hsa-miR-1249-3p	MIMAT0005901	504.6	147.4	226.9	461.6	480.1	1205.7	242.1	505.9	39.7	130.6	2169.1	2154.2	35.5	117.0
hsa-miR-125a-5p	MIMAT0000443	2565.5	5061.9	2266.3	5012.8	2991.7	2434.7	2421.2	3323.2	323.4	303.3	1605.3	1689.0	619.9	812.4
hsa-miR-125b-5p	MIMAT0000423	1408.0	6206.3	4464.3	4127.4	3153.4	3309.4	3372.6	14521.7	182.5	1209.6	1548.8	1634.8	3713.6	580.6
hsa-miR-126-3p	MIMAT0000445	21598.6	6784.8	9588.0	6211.0	7023.1	3131.1	2828.5	3064.0	37417.1	24601.5	5921.0	1312.5	26022.4	18486.8
hsa-miR-127-3p	MIMAT0000446	7350.9	20358.6	8350.9	82260.1	49057.5	25435.2	17224.4	30016.3	2847.5	57617.8	1205.7	5.2	11344.6	2782.7
hsa-miR-1307-3p	MIMAT0005951	697.5	471.6	1118.1	1966.9	967.0	1149.9	1202.2	1055.2	487.4	260.1	2090.7	4295.6	860.5	175.0
hsa-miR-139-5p	MIMAT0000250	1968.0	605.1	1048.5	178.2	1024.2	1263.6	1169.4	1609.1	1402.1	5352.8	2183.8	1688.6	25094.3	4810.9
hsa-miR-143-3p	MIMAT0000435	8767.2	6638.6	5756.6	1205.4	1094.8	948.3	1254.4	657.8	582.0	303.3	2629.4	2070.9	8010.3	232.9
hsa-miR-146a-5p	MIMAT0000449	3657.2	4642.3	2254.3	7757.7	6247.6	5165.7	2908.8	4931.2	29598.3	7251.8	2091.5	2200.1	4401.0	6085.8
hsa-miR-149-5p	MIMAT0000450	749.3	1794.0	1653.8	2887.7	1982.9	1738.3	1551.1	2198.3	120.8	1036.9	2609.6	2981.8	6291.6	1334.0
hsa-miR-150-5p	MIMAT0000451	15764.0	2137.3	4882.2	2144.0	5126.2	11390.0	7149.6	8240.7	64757.9	27191.0	19599.2	18110.1	9969.7	19240.2
hsa-miR-151a-5p	MIMAT0004697	1742.1	3764.9	849.1	1347.0	1031.3	827.9	1212.6	347.2	6137.8	5180.2	1323.5	4.0	4022.9	3420.1
hsa-miR-155-5p	MIMAT0000646	565.8	1997.5	798.6	2108.5	1289.6	1424.1	324.5	961.6	4516.8	1598.0	1065.2	2594.3	757.4	36045.3
hsa-miR-15a-5p	MIMAT0000068	255.2	121.9	472.0	54.3	332.6	121.5	135.1	270.7	825.1	303.3	351.1	1290.7	138.6	348.8
hsa-miR-15b-5p	MIMAT0000417	1233.9	541.6	1202.2	1010.6	797.2	2024.6	1101.3	1142.0	4954.8	1641.2	1821.6	1604.1	860.5	1276.0
hsa-miR-16-5p	MIMAT0000069	16262.7	6072.8	9131.6	4676.4	8425.9	7943.6	5346.5	19177.6	27641.0	23997.3	13269.7	21690.8	13304.0	9562.7
hsa-miR-181a-5p	MIMAT0000256	38622.4	37384.6	46899.9	47674.2	34659.8	59005.5	48244.7	46861.9	54427.9	52740.9	181180.1	151561.2	47575.0	35581.7
hsa-miR-181b-5p	MIMAT0000257	5021.7	6009.2	5992.0	10874.6	5509.5	7197.0	7362.1	6471.7	5335.0	4230.7	19837.8	18473.0	12513.3	2666.8
hsa-miR-185-5p	MIMAT0000455	890.4	83.8	560.8	89.7	247.7	1112.1	606.2	2126.4	796.2	432.7	1223.3	1576.8	413.6	232.9
hsa-miR-191-5p	MIMAT0000440	7854.3	4979.2	8999.4	7137.9	5204.9	8330.2	7966.4	8069.4	19065.2	12603.4	18059.0	24612.9	14507.1	8519.6
hsa-miR-193a-5p	MIMAT0004614	95.3	312.7	452.7	2391.9	1490.6	558.3	656.6	430.5	35.9	44.3	986.1	3699.4	35.5	59.1
hsa-miR-196b-5p	MIMAT0001080	330.5	662.3	447.9	426.2	354.1	236.3	677.8	174.7	377.4	260.1	586.9	894.9	207.4	175.0
hsa-miR-197-3p	MIMAT0000227	706.9	579.7	1161.4	390.7	2565.5	869.2	1844.3	5083.0	475.9	648.5	6307.7	6515.3	551.1	522.7
hsa-miR-199a-3p	MIMAT0000232	20154.0	21414.0	8197.1	7970.3	17506.5	16835.3	5591.0	11069.4	10462.3	6345.5	11332.8	15199.8	3301.1	44505.8
hsa-miR-199b-3p	MIMAT00004563	10079.9	10701.2	4101.5	3985.7	8753.8	8418.2	2796.1	5535.3	5242.4	3194.9	5665.9	7600.5	1651.1	22253.5
hsa-miR-204-5p	MIMAT0000265	979.9	2328.1	443.1	249.1	480.1	327.6	648.3	125.6	53.2	475.9	29.5	2284.0	7494.7	24861.2
hsa-miR-21-5p	MIMAT0000076	36683.8	87400.9	15146.4	23324.1	16188.6	7478.9	6596.4	10455.0	64767.5	41044.9	11959.5	11079.1	21381.9	77420.8
hsa-miR-22-3p	MIMAT0000077	1117.4	6803.9	5634.1	2037.7	2467.2	3484.3	1946.5	2900.7	3696.6	23695.2	5624.6	4788.7	20591.3	333091.0
hsa-miR-221-3p	MIMAT0000278	14174.4	2181.8	863.5	11795.4	1471.8	756.6	745.2	342.6	2035.1	1598.0	2757.3	16123.3	13417.7	986.3
hsa-miR-222-3p	MIMAT0000279	6480.4	14147.1	5773.4	67419.8	26264.5	4853.7	11204.6	8859.6	1627.9	993.8	978.9	3166.3	5672.9	1102.2
hsa-miR-223-3p	MIMAT0000280	3930.1	605.1	1151.8	443.9	2502.9	1292.6	1355.9	1924.3	26253.5	11783.4	3377.9	4427.8	5776.0	7013.0
hsa-miR-23a-3p	MIMAT0000078	6706.2	12951.8	4783.7	8289.0	7572.6	8400.4	5572.6	6467.1	22322.6	10531.8	11721.2	9163.4	7735.3	8635.5
hsa-miR-23b-3p	MIMAT0000418	1144.5	1088.3	640.1	72.0	237.9	431.2	256.5	19.4	2259.0	648.5	674.9	664.4	688.6	1102.2
hsa-miR-24-3p	MIMAT0000080	16709.7	18057.1	25213.7	19251.0	16459.3	20199.3	14589.4	15524.3	24858.3	17523.5	45282.8	53489.2	17532.0	12286.3
hsa-miR-25-3p	MIMAT0000081	1012.8	732.3	1317.5	1701.2	1637.1	609.5	905.4	1352.1	2982.6	950.6	2785.4	2615.2	3816.7	638.6
hsa-miR-26a-5p	MIMAT0000082	40749.2	39953.1	14889.4	13708.0	14638.0	10542.0	13273.9	11473.7	112982.4	77945.5	28227.5	26250.9	35578.4	50648.4
hsa-miR-26b-5p	MIMAT0000083	2932.6	2582.4	753.0	1293.9	1775.6	1823.0	685.7	733.2	23453.4	8546.5	1967.5	521.9	2613.6	3883.7
hsa-miR-27a-3p	MIMAT0000084	5172.3	2728.6	2741.9	1701.2	2083.9	2636.4	3046.0	1674.2	13573.1	7036.0	5823.6	6933.1	2648.0	5158.6
hsa-miR-27b-3p	MIMAT0000419	2495.0	1183.7	995.6	213.7	949.1	962.7	998.0	1190.0	3021.2	2935.9	1305.2	3133.6	1823.0	1334.0
hsa-miR-29a-3p	MIMAT0000086	725.8	910.3	584.9	691.8	125.3	692.0	507.1	331.2	3304.9	907.5	563.9	255.7	448.0	812.4
hsa-miR-30d-5p	MIMAT0000245	2297.3	2391.7	2064.6	868.9	1520.1	2240.8	2100.3	3278.7	7878.4	3669.6	4158.8	909.3	3301.1	3362.2
hsa-miR-320a-3p	MIMAT0000510	5106.4	5061.9	7125.8	28743.1	11980.2	7795.4	8351.0	10351.1	2056.3	35175.4	14461.6	19816.5	1857.4	45433.0
hsa-miR-320c	MIMAT00005793	245.8	274.5	584.9	1293.9	297.8	414.5	1020.3	475.1	57.1	44.3	27.4	1192.9	241.8	348.8
hsa-miR-328-3p	MIMAT0000752	1229.2	630.6	1310.3	1081.4	1281.5	1659.2	1572.7	1534.8	113.1	1080.1	4023.7	2477.8	1101.1	1160.1
hsa-miR-342-3p	MIMAT0000753	2029.1	795.9	558.4	922.0	675.7	583.9	741.9	561.9	10618.6	4662.3	1017.7	2870.8	5260.4	2435.0
hsa-miR-345-5p	MIMAT0000772	307.0	312.7	1161.4	638.7	222.7	1161.1	2080.9	862.2	255.9	173.8	5287.1	745.6	104.3	290.9
hsa-miR-34a-5p	MIMAT0000255	6936.8	18336.8	7572.6	11476.7	12203.6	11298.6	2931.5	5980.6	446.9	5050.7	1017.4	2124.7	14678.9	10779.6
hsa-miR-369-5p	MIMAT0001621	1116.3	3625.1	2167.8	1506.4	2730.8	3746.2	2147.1	2216.6	400.6	821.2	4.7	632.4	1169.9	348.8
hsa-miR-378a-3p	MIMAT0000732	3986.5	3542.4	5192.1	2374.2	3916.4	8655.6	4833.6	4402.4	1423.4	9323.4	20153.7	15699.4	688.6	232.9
hsa-miR-411-5p	MIMAT0003329	862.2	2226.4	798.6	1453.3	1269.0	539.3	267.6	402.0	298.3	216.9	90			

Table S2. miRNAs matched to the coding region binding sites of SARS-CoV-2.

miRNA	Expression (%) ¹	Score ²
hsa-miR-181a-5p	4.69	70
hsa-miR-26a-5p	1.58	68
hsa-miR-199a-3p	1.31	69
hsa-miR-320a-3p	1.15	73
hsa-miR-16-5p	0.78	99
hsa-miR-23a-3p	0.74	79
hsa-miR-181b-5p	0.73	70
hsa-miR-199b-3p	0.65	69
hsa-miR-122-5p	0.64	67
hsa-miR-378a-3p	0.49	55
hsa-miR-27a-3p	0.29	67
hsa-miR-103a-3p	0.26	85
hsa-miR-197-3p	0.25	82
hsa-miR-30d-5p	0.20	95
hsa-miR-26b-5p	0.14	68
hsa-miR-139-5p	0.12	83
hsa-miR-27b-3p	0.11	67
hsa-miR-15b-5p	0.11	99
hsa-miR-532-5p	0.10	61
hsa-miR-155-5p	0.09	51
hsa-miR-1-3p	0.09	54
hsa-miR-411-5p	0.09	88
hsa-miR-320c	0.07	73
hsa-miR-424-5p	0.07	98
hsa-miR-196b-5p	0.06	52
hsa-miR-29a-3p	0.04	91
hsa-miR-23b-3p	0.03	79

1 indicates “Percentage of miRNAs in EVs”.

2 indicates the prediction score or the miRDB method. According to miRDB, a predicted target with score > 80 is most likely to be real.